Exposure to Gestational Diabetes Is a Stronger Predictor of Dysmetabolic Traits in Children Than Size at Birth

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Context and Objective: Being born small or large for gestational age and intrauterine exposure to gestational diabetes (GDM) increase the risk of type 2 diabetes in the offspring. However, the potential combined deleterious effects of size at birth and GDM exposure remains unknown. We examined the independent effect of size at birth and the influence of GDM exposure *in utero* on cardiometabolic traits, body composition, and puberty status in children.

Design, Participants, and Methods: The present study was a longitudinal birth cohort study. We used clinical data from 490 offspring of mothers with GDM and 527 control offspring aged 9 to 16 years, born singleton at term from the Danish National Birth Cohort with available birthweight data.

Results: We found no evidence of a U-shaped association between size at birth (expressed as birthweight, sex, and gestational age adjusted z-score) and cardiometabolic traits. Body size in childhood and adolescence reflected the size at birth but was not reflected in any metabolic outcome. No synergistic adverse effect of being born small or large for gestational age and exposure to GDM was shown. However, GDM was associated with an adverse metabolic profile and earlier onset of female puberty in childhood and adolescence independently of size at birth.

Conclusion: In childhood and adolescence, we found GDM was a stronger predictor of dysmetabolic traits than size at birth. The combination of being born small or large and exposed to GDM does not exacerbate the metabolic profile in the offspring. **(*J Clin Endocrinol Metab* 104: 1766–1776, 2019)**

Because the prevalence of type 2 diabetes (T2D) has increased dramatically in the past decade (1), the early identification of individuals with an increased risk of T2D is of high importance. In 1991, Hales *et al.* (2) proposed that early fetal development, as expressed by reduced growth, was associated with an increased risk of developing T2D in adulthood. This association was subsequently confirmed in a large number of studies during the past three decades (3, 4), with an increased abdominal fat distribution, increased fasting blood

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Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; BW, birthweight; DEXA, dual-energy X-ray absorptiometry; DNBC, Danish National Birth Cohort; GA, gestational age; GDM, gestational diabetes mellitus; LBW, low birthweight; LGA, large for gestational age; SGA, small for gestational age; T2D, type 2 diabetes; WC, waist circumference.

glucose level, reduced muscle mass (5, 6), and hepatic insulin resistance (7) representing some of the adult metabolic abnormalities present in individuals born small at birth.

However, the shape of the association in the relationship between birthweight (BW) and T2D has been inconsistent across studies, including findings of both a decreased (inverse association) (3, 8) and an increased risk of developing T2D with an increased birthweight (3). In addition, a large meta-analysis of adult white subjects reported that a high birthweight (>4000 g) was associated with an increased risk of developing T2D to the same extent as low birthweight (LBW) (<2500 g) compared with normal birthweight (2500 to 4000 g), indicating a U-shaped association between BW and a later risk of T2D (9).

The increased risk of metabolic disease at the high end of the BW spectrum has been suggested to be strongly influenced by the exposure to gestational diabetes mellitus (GDM) in fetal life (3, 10). Previous studies have reported that offspring of women with GDM are more likely to be overall and centrally obese and to exhibit insulin resistance and glucose intolerance in early adulthood (10–13). Recently, we showed that the adolescent offspring of women with GDM have an adverse metabolic and body compositional profile compared with offspring born to control mothers (14). Additionally, an earlier onset of puberty has been linked to an increased risk of cardiovascular and metabolic disease later in life (15), and both size at birth (16) and fetal exposure to GDM (14, 17) are thought to affect pubertal maturation. As such, the effect of being born of a mother with GDM seems similar to those effects seen among individuals born with a LBW or high BW.

However, to the best our knowledge, only a few studies have investigated the potential joint association of BW and GDM on childhood health in a general population (18–20). Two longitudinal studies showed a combined deleterious effect of being born large for gestational age (LGA) and exposed to GDM on the development of metabolic syndrome (18) and obesity (19) in childhood. A prospective cohort study reported an increased risk of overweight in adolescents with increasing BW and further reported an adverse effect from exposure to GDM. However, the effect of GDM in the latter study was mainly explained by the BW, indicating that BW is a more essential risk marker for being overweight in adolescence compared with GDM exposure *in utero*. Therefore, the evidence of a potential combined adverse effect of being born small or large and exposed to GDM *in utero* seems conflicting. Previous studies addressing this were limited by excluding children born small for gestational age (SGA) (18, 19), including self-reported measures on anthropometrics (20), by not exploring the potential effect on puberty onset, and by lack of advanced measures of body composition (19, 20).

In the present study, we examined the associations between size at birth and GDM exposure in fetal life on cardiometabolic traits, body composition, and puberty status in Danish children aged 9 to 16 years.

Methods

Study population and design

The present study was based on clinical data from a subcohort of children nested within the Danish National Birth Cohort (DNBC) (21). In brief, a total of 608 offspring of mothers with GDM and 626 randomly selected control offspring from the DNBC attended a clinical examination. Data collection was conducted nationwide in Denmark and included measures of anthropometry, body composition, puberty status, and cardiometabolic traits from boys and girls aged 9 to 16 years. The study design and method have previously been described in detail (14).

We included offspring born at term (between the 38th and 42nd gestational week) with available information on gestational age (GA) and BW (n = 1063). No twins or triplets (33 twins; 3 triplets) were included, and the analyses were confined to the first child enrolled for each woman to avoid correlated observations between siblings (35 siblings excluded). Offspring with type 1 diabetes (n = 3) and offspring born to mothers with type 1 diabetes (n = 8) were excluded. Our final study sample included 1017 offspring. The study was performed in accordance with the Declaration of Helsinki, and the Regional Scientific Ethics Committee of the municipalities of Copenhagen and Frederiksberg approved the protocol (approval nos. H-4-2001-045 and H-4-2013-129). Consent from both parents was given before the child's participation in the study.

Exposure assessment

Birth measures

Information on BW and date of birth were extracted from the Danish Medical Birth Registry. GA at birth was determined by one or more of the following: (i) the expected due date, (ii) the mother's last menstrual period, and/or (iii) information derived from the Danish Medical Birth Registry (22).

The BW z-score was calculated as follows: (BW − normal BW for GA)/SD for normal BW. Subjects were classified into one of three categories of BW for GA: SGA (less than the 10th percentile), appropriate for gestational age (AGA) (10th to 90th percentile), or large for gestational age (LGA) (greater than the 90th percentile). Sex- and GA-specific BW standard curves produced from full-term singleton births from the entire DNBC population were used as the reference for normal BW to compute the variables for birth size.

GDM exposure and diagnosis

Identification of suspected GDM exposure *in utero* was determined using previously described GDM diagnosis criteria (23). In brief, women were classified as having a GDM diagnosis if in the index pregnancy they had had a documented

GDM diagnosis recorded in the Danish National Patient Registry (International Classification of Diseases, 10th edition, classifications 0244 and 0249) or a self-reported GDM diagnosis documented from the telephone interview conducted at 30 weeks of gestation or 6 months postpartum.

Clinical outcome measures

Anthropometric measurements, blood pressure at rest, fasting glucose, insulin, C-peptide, and lipid profiles were included. Sex- and age-specific z-scores for height, weight, and BMI were calculated according to Danish national reference curves based on the Least Mean Square (LMS) method (24). Because no Danish reference curves for waist circumference (WC) were available, we calculated the sex- and age-specific WC z-scores from British normal reference material [($WC_{measured}$ − mean WC)/SD for WC] (25). Crude measures and sex- and age-specific z-scores for weight, height, BMI, and WC were used to characterize the anthropometric measurements of the offspring. In contrast, only the z-scores for these variables were applied for the remaining analyses. Standard assays were applied for biomarker analysis as previously described (14). The homeostasis model assessment for estimated insulin resistance was evaluated and calculated as ([(fasting plasma insulin in pmol/L × fasting plasma glucose in mmol/L)/22.5] × 0.144). Puberty status was determined by Tanner score examination performed by educated staff. Breast development of Tanner B2 or greater for girls and testicle volume ≥4 mL for boys was considered the primary marker of pubertal onset (26–28). Additionally, pubic hair stage ≥2 in girls and boys and genital stage ≥2 in boys were considered secondary markers of onset of puberty. Information on body composition measured by dual-energy X-ray absorptiometry (DEXA) scanning (Lunar; Prodigy Scanex, Madison, WI), were available for a subset of the offspring (n = 556).

Covariates

Data on parental socio-occupational status (defined by the highest parental level of education and occupation: high proficiency, intermediate proficiency, skilled worker, unskilled worker, student, or unemployed), maternal parity (first, second, or third or later born), maternal smoking during pregnancy (nonsmoker or smoker), maternal height, and maternal prepregnancy body mass index (BMI) (<25, 25 to 29.9, or ≥30 kg/m^2) were derived from pregnancy interviews at gestational weeks 12 and 30. Information on maternal weight gain during pregnancy was obtained from interviews at 6 months postpartum. All information was self-reported.

Statistical analysis

To address potential differences in background characteristics, anthropometric data, body composition, and cardiometabolic traits between the SGA, AGA, and LGA offspring in the GDM-stratified analysis, one-way ANOVA was applied for normally distributed residuals, the Kruskal-Wallis test for skewed residuals, and the χ^2 test for categorical variables. Equality of variance between the BW groups was tested using the Levene test. In the case of variance heterogeneity ($P < 0.05$), the Welch test was applied instead of one-way ANOVA. Assumptions of normally distributed residuals were visually evaluated with histograms and QQ-plots. Data are presented as the mean ± SD for normally distributed variables, median and interquartile range for log-transformed or skewed variables, and numbers and percentages for categorical variables.

The shape of the association between the BW z-score and continuous outcome variables were visualized using scatterplots and tested by linear regression analyses by adding the explanatory variable as a linear and squared term (to allow for a U-shaped relation). Because no U-shaped associations were found ($P > 0.05$), linear regression analyses were applied to examine the effect of size at birth on childhood anthropometric data, metabolism, and body composition. The effect size was given in changes per increase in BW z-score. Because the effect of BW might be sex-dependent (29), the effect modification by sex was examined. No statistically significant interaction with sex was observed ($P > 0.05$). As such, we included sex as a potential confounding variable in our models. Subsequently, for variables that were statistically significant in our simple regression model, we applied multiple regression analysis with adjustment for confounding variables in three different steps. Model 1 was adjusted for age and sex. Model 2 was further adjusted for maternal prepregnancy BMI, maternal pregnancy weight gain, paternal social-occupational status, maternal smoking during pregnancy, and maternal parity. In model 3, maternal height was additionally adjusted for to account for genetic influence on offspring body size. For all regression models, the data were stratified by GDM exposure, and the variables were log-transformed when needed to meet the assumptions of the model.

To examine a potential additive adverse effect of GDM exposure *in utero* on the association between being born SGA or LGA compared with AGA on anthropometric data, cardiometabolic traits, and body composition, we applied an additive two-way ANOVA analysis with correction for multiple comparisons (Tukey-Kramer test), adding BW groups and GDM exposure as the explanatory variables. We calculated the β-coefficient and 95% CIs to estimate the mean differences for normally distributed residuals or the percentage of differences for log-transformed data. Additionally, an interaction analysis was conducted to test the potential interaction between BW groups and GDM exposure in relation to the metabolic profile in childhood.

The onset of puberty was analyzed with logistic regression models, and we calculated ORs and 95% CIs with adjustment for offspring age and BMI in two subsequent models.

SAS, version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses. Two-tailed $P \leq 0.05$ was considered to indicate statistical significance.

Results

Parental, birth, and childhood characteristics for control and GDM offspring born SGA, AGA, or LGA

The median BW ranged from 2900 to 4500 g in control offspring and from 2816 to 4415 g in the GDM offspring (Table 1). Maternal weight gain during pregnancy was significantly different across BW groups, with the largest weight gain found among mothers who gave birth to a LGA offspring (control, $P = 0.02$; GDM, $P < 0.001$). The proportion of LGA births increased with maternal age and parity in offspring exposed to GDM *in utero* ($P = 0.05$ and $P = 0.0004$, respectively). The

Table 1. Unadjusted Measures of Parental and Birth Characteristics of Children Born SGA, AGA, or LGA

	Control Offspring				GDM Offspring			
Variable	**SGA**	**AGA**	**LGA**	***P* Value**	**SGA**	**AGA**	**LGA**	***P* Value**
Birth characteristics								
Subjects, n (%)	52 (10)	438 (83)	37 (7)		27 (6)	351 (72)	112 (23)	
BW, g	2900 (315)	3600 (520)	4500 (445)	$< 0.001^a$	2816 (360)	3670 (495)	4415 (518)	< 0.001
BW z-score[b]	−1.7 (0.5)	−0.1 (1.0)	1.6 (0.6)	< 0.001	−1.7 (0.7)	0.3 (1.0)	1.9 (1.0)	< 0.001
Male sex, n (%)[c]	29 (56)	219 (50)	20 (54)	0.68	18 (67)	171 (49)	64 (57)	0.08
Gestational age at birth, d	283 ± 12	281 ± 11	283 ± 10	0.19	276 ± 10	279 ± 13	277 ± 13	0.19
Parental characteristics								
Maternal prepregnancy BMI, n (%)								
<25.0 kg/m^2	44 (86)	349 (82)	29 (78)		11 (46)	147 (46)	38 (36)	
25.0–29.9 kg/m^2	6 (12)	54 (13)	5 (14)		7 (29)	93 (29)	35 (33)	
≥ 30.0 kg/m^2	1 (2)	25 (6)	3 (8)	0.75[d]	6 (25)	83 (26)	34 (32)	0.48[c]
Maternal pregnancy weight gain, kg	15.5 (4.6)	14.7 (5.5)	17.5 (6.0)	0.02	7.0 (11.1)	11.3 (8.5)	15.6 (9.1)	< 0.001
Maternal age, y	30.4 (4.6)	31.1 (4.2)	32.5 (4.0)	0.07	30.2 (5.2)	32.2 (4.4)	32.5 (4.3)	0.05
Parity, n (%)[c]								
First born	32 (63)	233 (54)	18 (49)		19 (73)	119 (36)	28 (26)	
Second born	15 (29)	133 (31)	10 (27)		4 (15)	124 (38)	50 (46)	
Third born or later	4 (8)	68 (16)	9 (24)	0.30	3 (12)	87 (26)	30 (28)	< 0.001
Maternal smoking in pregnancy, n (%)[c]	20 (39)	97 (22)	7 (19)	0.03	8 (30)	100 (29)	26 (23)	0.53
Parental socio-occupational status, n (%)[c]								
High proficiency	16 (31)	126 (29)	13 (35)		6 (23)	74 (23)	24 (23)	
Medium proficiency	15 (29)	148 (34)	14 (37)		8 (31)	99 (30)	32 (30)	
Skilled worker	13 (26)	98 (23)	8 (22)		8 (31)	96 (29)	31 (29)	
Unskilled worker	2 (4)	19 (4)	0 (0)		0 (0)	12 (4)	1 (1)	
Student	5 (10)	38 (9)	4 (5)		3 (12)	43 (13)	18 (17)	
Unemployed	0 (0)	4 (1)	0 (0)	0.94	1 (4)	4 (1)	1 (1)	0.87

Data presented as mean ± SD for normally distributed variables, median (interquartile range) for log-transformed or skewed variables, and n (%) for categorical variables.

Sex- and GA-specific BW standard curves produced from full-term singleton births offspring from the entire DNBC population were use as reference for normal BW to calculate BW z-scores and to categorize subjects as SGA (less than 10th percentile), AGA (10th to 90th percentile), or LGA (greater than 90th percentile) BW groups.

P values denote overall differences between BW categories stratified by GDM exposure; calculated using one-way ANOVA for continuous parametric variables, unless otherwise noted.

[a]Calculated using Welch test for continuous parametric variables

[b]Calculated using Kruskal-Wallis test for nonparametric continuous variables.

[c]Calculated using χ^2 test for categorical variables.

[d]Calculated using Fisher exact test for categorical variables.

proportion of mothers who smoked during pregnancy was almost twice as high for the offspring born SGA compared with the offspring born AGA or LGA among the control group ($P = 0.03$).

Among the control offspring, the BW groups were positively associated with z-scores for weight, height, BMI, and waist, as well as hip circumferences in childhood. In contrast, in children exposed to GDM *in utero*, the childhood z-score for weight and height were the only measures of anthropometry that were significantly related to size at birth. No associations between the size at birth and cardiometabolic health or body composition in childhood were seen in either GDM or control offspring (Table 2).

Shape of association and effect of size at birth

We found no U-shaped association between the BW z-score and anthropometric data, cardiometabolic traits, or any measures of body composition in offspring of control or GDM mothers ($P > 0.05$; data not shown).

The z-scores for weight, height, BMI, and waist, as well as hip measures, were positively associated with the BW z-score independently of offspring sex and age in both control and GDM offspring [$P < 0.05$; Table 3 (model 1) (30)]. Furthermore, in GDM offspring, the BW z-score was positively associated with high-density lipoprotein cholesterol and inversely associated with systolic blood pressure after adjustment for offspring sex and age [$P < 0.05$ (model 1) (30)].

Table 2. Unadjusted Measures of Anthropometry, Metabolic Markers, and Body Composition of Offspring Born SGA, AGA, or LGA of Mothers With GDM and Control Offspring

	Control Offspring				GDM Offspring			
Variable	**SGA**	**AGA**	**LGA**	***P* Value**	**SGA**	**AGA**	**LGA**	***P* Value**
Anthropometric characteristics, n	52–52	434–438	37		26–27	343–351	111–112	
Age, y	12.3 (2.1)	12.9 (2.3)	12.2 (2.6)	0.15	12.0 (1.4)	12.4 (2.3)	12.0 (2.4)	0.55
Weight, kg	41.7 (15.5)	45.3 (15.4)	48.5 (21.0)	0.002	43.7 (13.0)	46.9 (16.0)	48.2 (18.9)	0.07
Weight z-score	−0.4 ± 1.3	0.0 ± 1.1	0.6 ± 0.9	0.0002	0.2 ± 1.1	0.4 ± 1.1	0.7 ± 1.1	0.05
Height, cm	153.5 ± 9.5	159.8 ± 11.1	162.8 ± 14.5	0.0001[a]	152.6 ± 8.7	156.6 ± 11.3	158.6 ± 11.9	0.04
Height z-score	−0.3 ± 1.0	0.3 ± 1.1	0.8 ± 1.2	< 0.0001	−0.2 ± 1.0	0.3 ± 1.1	0.7 ± 1.2	< 0.0001[b]
BMI, kg/m^2	17.6 (3.2)	17.7 (3.3)	18.5 (3.2)	0.058	19.0 (5.4)	18.6 (4.1)	19.1 (4.1)	0.30
BMI z-score	−0.3 ± 1.2	−0.3 ± 1.1	0.2 ± 0.9	0.03	0.3 ± 1.4	0.3 ± 1.2	0.5 ± 1.3	0.27
Waist, cm	68.0 (9.4)	68.5 (10.3)	70.7 (9.9)	0.02	68.4 (19.6)	70.6 (12.8)	72.8 (13.5)	0.25
Waist z-score[b]	0.7 (1.8)	0.8 (1.5)	1.4 (1.2)	0.02	1.1 (3.2)	1.4 (2.4)	1.8 (2.5)	0.20
Hip, cm	79.6 ± 8.0	82.6 ± 9.3	85.0 ± 9.2	0.02	82.0 ± 8.7	83.3 ± 9.5	85.3 ± 9.4	0.09
Waist/hip ratio	0.85 ± 0.04	0.85 ± 0.05	0.86 ± 0.06	0.44	0.88 ± 0.07	0.87 ± 0.06	0.87 ± 0.05	0.65
Systolic blood pressure,[c] mm Hg	108.0 (10.5)	108.0 (11.0)	109.0 (11.0)	0.38	107.0 (8.0)	109.0 (11.0)	108.0 (12.0)	0.08
Diastolic blood pressure,[c] mm Hg	63.5 ± 7.0	62.7 ± 6.0	63.3 ± 6.4	0.52	63.0 ± 4.9	62.6 ± 6.1	62.4 ± 5.8	0.90
Metabolic characteristics, n	41-44	373-391	32-34		23-24	291-307	96-103	
Fasting plasma glucose, mmol/L	4.8 ± 0.6	4.8 ± 0.4	4.8 ± 0.5	0.93	4.9 ± 0.5	5.0 ± 0.6	5.0 ± 0.5	0.45
Fasting insulin, pmol/L	58.3 (37.8)	61.3 (34.7)	54.7 (24.8)	0.31	76.5 (40.1)	67.9 (48.9)	69.8 (39.4)	0.17
Fasting C-peptide, pmol/L	533.3 (198.7)	553.3 (225.2)	560.3 (197.5)	0.52	656.2 (223.4)	558.8 (265.3)	551.2 (245.6)	0.07
HOMA-IR	1.8 (1.0)	1.9 (1.1)	1.7 (1.0)	0.29	2.4 (1.4)	2.2 (1.7)	2.2 (1.3)	0.33
Triglycerides, mmol/L	0.6 (0.3)	0.7 (0.3)	0.7 (0.3)	0.86	0.8 (0.6)	0.8 (0.5)	0.7 (0.3)	0.15
HDL cholesterol, mmol/L	1.5 ± 0.5	1.6 ± 0.4	1.5 ± 0.5	0.29[a]	1.4 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	0.06
LDL cholesterol, mmol/L	2.3 (0.9)	2.3 (0.8)	2.4 (0.8)	0.37	2.3 (0.9)	2.3 (0.8)	2.3 (0.8)	0.48
Total cholesterol, mmol/L	4.2 ± 0.8	4.2 ± 0.7	4.3 ± 0.7	0.61	4.3 ± 0.8	4.3 ± 0.7	4.2 ± 0.7	0.92
Body composition measured by DEXA, n	39	328	26		10	124	29	
Total fat, %	27.8 ± 7.4	26.8 ± 6.8	26.1 ± 7.3	0.61	32.9 ± 9.8	31.1 ± 8.4	30.9 ± 5.5	0.78
Total lean mass, %	72.2 ± 7.4	73.2 ± 6.8	73.9 ± 7.3	0.62	67.1 ± 9.8	68.9 ± 8.4	69.1 ± 5.5	0.78
Android fat, %	21.7 (18.0)	19.0 (13.4)	17.5 (12.4)	0.44	27.6 (24.4)	25.3 (1.6)	24.7 (13.3)	0.69[a]
Gynoid fat, %	32.2 ± 8.4	31.0 ± 7.6	30.3 ± 8.6	0.58	36.1 ± 9.4	35.3 ± 8.7	35.7 ± 6.1	0.93

Data presented as mean ± SD for normally distributed variables and median (interquartile range) for log-transformed variables.

P values denote overall differences between BW categories stratified by GDM exposure; calculated using one-way ANOVA for continuous parametric variables, unless otherwise noted.

Sex- and GA-specific BW standard curves produced from full-term singleton births offspring from the entire DNBC population were use as reference for normal BW to calculate BW z-scores and to categorize subjects as SGA (less than 10th percentile), AGA (10th to 90th percentile), or LGA (greater than 90th percentile) BW groups.

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein.

[a]Calculated using Welch test for continuous parametric variables.

[b]Calculated using Kruskal-Wallis test for nonparametric continuous variables.

[c]Systolic and diastolic blood pressure adjusted for current offspring height.

When further adjusting for parental socio-occupational status and lifestyle factors, an increase in BW z-score was associated with an increase in the weight and height z-score of 0.2 (95% CI, 0.1 to 0.3; $P \leq 0.0001$) and a 0.8-cm (95% CI, 0.1 to 1.4 cm; $P = 0.02$) increased hip circumference in control offspring. Similar estimates were observed for GDM offspring in relation to the weight z-score (0.2; 95% CI, 0.1 to 0.3; $P = 0.0003$), the height z-score (0.2; 95% CI, 0.1 to 0.3; $P \leq 0.0001$), and hip circumference (0.9 cm; 95% CI, 0.1 to 1.8; $P = 0.04$) and was furthermore associated with an increase in the waist z-score of 0.2 (95% CI, 0.00 to 0.32; $P = 0.05$) and a reduction in systolic blood pressure of 1% (95% CI, −2% to 0%; $P = 0.02$) per increase in BW z-score (model 2) (30). The weight and height z-scores for GDM and control offspring and systolic blood pressure and hip circumference (for GDM offspring only) remained significantly associated with with the BW z-score after further adjustment for maternal height (model 3) (30). However, size at birth was not significantly related to the remaining cardiometabolic outcomes or measures of body composition by DEXA in offspring born of control or GDM mothers (Table 3).

Potential combined effect of BW and GDM exposure on cardiometabolic health in childhood

Examining the BW and GDM association on cardiometabolic health in a two-way ANOVA analysis showed that size at birth was significantly associated with size in childhood (for weight z-score and height z-score in SGA offspring and for weight z-score, BMI z-score, waist z-score, and hip circumferences in LGA offspring) independently of GDM exposure status (Table 4). However, size at birth was not significantly associated with any cardiometabolic or body compositional measure (Table 4). GDM exposure within the same BW categories was significantly associated with adverse anthropometric, metabolic, and body compositional

Table 3. Influence of BW z-Score on Unadjusted Measures of Childhood Anthropometric Data, Metabolism, and Body Composition

	Control Offspring		GDM Offspring	
Offspring Outcomes	**β Coefficient (95% CI)**	***P* Value**	**β Coefficient (95% CI)**	***P* Value**
Anthropometric characteristics, n	523–526		480–490	
Weight z-score	0.2 (0.2 to 0.3)	< 0.0001	0.2 (0.1 to 0.3)	< 0.0001
Height z-score	0.3 (0.2 to 0.4)	< 0.0001	0.2 (0.1 to 0.3)	< 0.0001
BMI z-score	0.1 (0.02 to 0.22)	0.02	0.1 (0.01 to 0.20)	0.03
Waist z-score	0.2 (0.1 to 0.3)	0.003	0.1 (0.0 to 0.3)	0.05
Hip, cm	1.3 (0.5 to 2.1)	0.002	0.8 (0.1 to 1.5)	0.02
Waist/hip ratio	0.0 (0.0 to 0.0)	0.91	0.0 (0.0 to 0.0)	0.74
Systolic blood pressure,[a] mm Hg	0% (−1% to 1%)	0.43	−1% (−1% to 0%)	0.02
Diastolic blood pressure,[a] mm Hg	−0.02 (−0.58 to 0.54)	0.94	−0.07 (-0.52 to 0.38)	0.76
Metabolic characteristics, n	446–467		410–434	
Fasting plasma glucose, mmol/L	−0.03 (−0.07 to 0.01)	0.21	0.00 (−0.04 to 0.05)	0.89
Fasting insulin, pmol/L	−3% (−7% to 2%)	0.24	−2% (−6% to 2%)	0.42
Fasting C-peptide, pmol/L	−1% (−4% to 3%)	0.70	−2% (−5% to 1%)	0.15
HOMA-IR	−3% (−8% to 1%)	0.14	−2% (−4% to 3%)	0.43
Triglycerides, mmol/L	0% (−3% to 4%)	0.91	−3% (−6% to 1%)	0.10
HDL cholesterol, mmol/L	0.02 (−0.02 to 0.06)	0.31	0.03 (0.00 to 0.06)	0.04
LDL cholesterol, mmol/L	0.03 (−0.03 to 0.09)	0.31	−0.01 (−0.07 to 0.04)	0.64
Total cholesterol, mmol/L	0.05 (−0.01 to 0.12)	0.11	0.01 (−0.05 to 0.06)	0.87
Body composition measured by DEXA, n	393		163	
Total fat, %	0.16 (−0.55 to 0.87)	0.66	−0.65 (−1.77 to 0.48)	0.26
Total lean mass, %	−0.16 (−0.87 to 0.55)	0.66	0.65 (−048 to 1.78)	0.26
Android fat, %	1% (−4% to 6%)	0.79	−2% (−9% to 5%)	0.50
Gynoid fat, %	0.24 (−0.56 to 1.04)	0.55	−0.48 (−1.64 to 0.67)	0.41

Data presented as mean changes per increase in BW z-score for normally distributed residuals or percentage of change (95% CI) for log-transformed data.

P values obtained by simple linear regression.

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein.

[a]Systolic and diastolic blood pressure adjusted for current offspring height.

outcomes (Table 4). We found no interaction between BW groups and GDM status in any of the outcomes ($P > 0.05$; data not shown).

Onset of puberty

The proportion of offspring who had reached puberty did not differ significantly across BW groups in the offspring exposed or not exposed to GDM (Table 5). In the age- and BMI-adjusted analyses, the size at birth was not significantly associated with puberty onset among males or females. However, among female offspring exposed to GDM, the odds of having reached puberty, as assessed by breast development, was more than two times greater compared with control offspring, independently of size at birth ($P = 0.04$; Table 6).

Discussion

In the present study, we found that being born SGA or LGA was associated with anthropometric measurements, including height, weight, BMI, waist, and hip circumference in childhood. However, no association was found with measures of cardiometabolic outcomes, body composition assessed by DEXA, or pubertal maturation. Our results do not support a U-shaped association between BW and adverse cardiometabolic traits in children at this young age. Interestingly, we found no adverse synergistic effect between being born SGA or LGA and exposed to GDM. In contrast, our results indicate that independently of size at birth, GDM exposure *in utero* is a strong predictor of a disadvantageous body composition, adverse cardiometabolic traits, and earlier onset of female puberty in childhood and adolescence.

Effect of BW and shape of association

In accordance with previous studies, we found that individuals born small were shorter and lighter at the follow-up examination. Individuals born LGA were heavier, with a higher BMI and larger waist and hip circumferences compared with children born AGA (Table 4).

An adverse fat distribution, in particular increased abdominal obesity, is a strong predictor of T2D (31). Also, WC, which is related to the intra-abdominal fat

Table 4. Effect of Size at Birth for GA and GDM Exposure in Fetal Life on Offspring Anthropometric, Cardiometabolic, and Body Compositional Outcomes in Children Aged 9 to 16 Years

	SGA vs AGA		LGA vs AGA		GDM exp.	
Offspring Outcomes	**Mean Difference or % Difference (95% CI)**	***P* Value**	**Mean Difference or % Difference (95% CI)**	***P* Value**	**Mean Difference or % Difference (95% CI)**	***P* Value[a]**
Birth characteristics						
BW, g	−812 (−906 to −718)	< 0.0001	876 (803 to 949)	< 0.0001	43 (−0.4 to 86)	0.05
Gestational age at birth, d	0 (−2 to 2)	1.00	0 (−2 to 1)	0.86	−3 (−4 to −2)	< 0.0001
Anthropometric characteristics						
Weight z-score	−0.3 (−0.6 to −0.01)	0.04	0.4 (0.2 to 0.7)	< 0.0001	0.4 (0.3 to 0.5)	< 0.0001
Height z-score	−0.6 (−0.9 to −0.3)	< 0.0001	0.04 (0.2 to 0.7)	< 0.0001	−0.02 (−0.2 to 0.1)	0.77
BMI z-score	−0.1 (−0.4 to 0.3)	0.93	0.3 (0.04 to 0.5)	0.02	0.5 (0.4 to 0.7)	< 0.0001
Waist z-score	−0.2 (−0.7 to 0.2)	0.54	0.3 (0.001 to 0.7)	0.05	0.7 (0.5 to 0.9)	< 0.0001
Hip, cm	−2.4 (−5 to 0.24)	0.08	2.1 (0.1 to 4.1)	0.04	0.8 (−0.3 to 2.0)	0.16
Waist/hip ratio	0.01 (−0.01 to 0.02)	0.52	0.00 (−0.01 to 0.01)	0.81	0.03 (0.02 to 0.03)	< 0.0001
Systolic blood pressure,[b,c] mm Hg	1% (−1% to 3%)	0.43	−1% (−8% to 1%)	0.31	1% (0% to 8%)	0.07
Diastolic blood pressure,[c] mm Hg	0.7 (−1.0 to 2.4)	0.61	0.0 (−1.3 to 1.3)	1.00	−0.2 (−1.0 to 0.6)	0.60
Metabolic characteristics						
Fasting plasma glucose, mmol/L	0.0 (−0.2 to 0.1)	0.92	0.0 (−0.2 to 0.1)	0.62	0.2 (0.2 to 0.3)	< 0.0001
Fasting insulin,[b] pmol/L	4% (−9% to 20%)	0.77	−3% (−13% to 8%)	0.79	14% (7% to 21%)	< 0.0001
Fasting C-peptide,[b] pmol/L	2% (−8% to 14%)	0.89	−2% (−10% to 6%)	0.79	6% (1% to 11%)	0.03
HOMA-IR[b]	3% (−12% to 20%)	0.90	−5% (−16% to 7%)	0.57	19% (11% to 27%)	< 0.0001
Triglycerides,[b] mmol/L	1% (−10% to 13%)	0.98	−7% (−15% to 2%)	0.16	6% (0% to 12%)	0.04
HDL cholesterol, mmol/L	−0.09 (−0.20 to 0.02)	0.15	0.04 (−0.04 to 0.13)	0.48	−0.06 (−0.11 to −0.01)	0.02
LDL cholesterol, mmol/L	0.11 (−0.08 to 0.30)	0.37	−0.02 (−0.17 to 0.12)	0.92	0.09 (0.01 to 0.18)	0.03
Total cholesterol, mmol/L	0.06 (−0.15 to 0.27)	0.79	0.02 (−0.15 to 0.18)	0.97	0.06 (−0.03 to 0.16)	0.19
Body composition measured by DEXA						
Total fat, %	1.12 (−1.45 to 3.70)	0.56	−0.50 (−2.98 to 1.97)	0.88	4.4 (3.1 to 5.8)	< 0.0001
Total lean mass, %	−1.12 (−3.69 to 1.46)	0.56	0.50 (−1.97 to 2.98)	0.88	−4.4 (−5.8 to −3.1)	< 0.0001
Android fat,[b] %	11% (−7% to 32%)	0.32	0% (−15% to 19%)	1.00	27% (16% to 39%)	< 0.0001
Gynoid fat, %	1.10 (−1.70 to 3.90)	0.63	−0.15 (−2.84 to 2.55)	0.99	4.4 (2.9 to 5.8)	< 0.0001

Data presented as mean differences for normally distributed variables; estimates and *P* values obtained using two-way ANOVA with correction for multiple comparisons (Tukey-Kramer).

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein.

[a] *P* values and estimates represent the additive effect of exposure to GDM within BW groups.

[b] Data presented as % differences (95% CI) for log-transformed variables.

[c] Systolic and diastolic blood pressure were adjusted for current offspring height.

mass, has been shown to be a valid measure of trunk fat mass in children aged 3 to 19 years (32). Our data showed a statistically significantly increased WC in children born LGA, independently of exposure to GDM (Table 4). These findings were confirmed in our linear regression models, with an increase in the WC z-score per increase in BW z-score in both exposed and unexposed children [Table 3 (30)]. However, after adjusting for maternal confounders, the association was attenuated and was no longer statistically significant (30).

It has previously been shown in a twin study with discordance for T2D that a nongenetic association exists between LBW and glucose intolerance and insulin resistance (33). Furthermore, we, and others, have documented several metabolic defects in young-adult SGA individuals, including decreased fat-free mass, increased abdominal obesity, and dysmetabolic traits (5–7). Such metabolic differences between SGA and AGA individuals were not apparent in our study population. The use of more advanced methods to study glucose metabolism in these studies could account for some of the discrepancies. Additionally, these studies of young adults showed that the differences between AGA and SGA were especially apparent when SGA individuals were subjected to metabolic challenges (*e.g.*, overfeeding, 36-hour fasting, or bed rest) (7, 34, 35). In the studies of discordant twins, the association between LBW and insulin resistance was only seen among elderly twins, suggesting an age-dependent effect (36). Finally, we did not see any evidence of a U-shaped relationship between BW and T2D risk, as previously reported (9). In contrast to these studies, we considered early markers of T2D in young healthy individuals. It is plausible that the detrimental metabolic effects of a low or high BW could be masked during puberty or could be more evident later in adolescence or adulthood.

No combined adverse health effect of size at birth and intrauterine GDM exposure

Both individuals born SGA and offspring exposed to GDM *in utero* have an increased long-term risk of developing T2D due to an adverse fetal environment. Data from Danish follow-up studies have strongly suggested that *in utero* exposure to diabetes could place the offspring at an increased risk of T2D that exceeds the magnitude recognized for those born SGA (4, 37, 38). In line with this, the

Table 5. Puberty Characteristics of Offspring Born SGA, AGA, or LGA of Mothers With or Without GDM

	Control Offspring				GDM Offspring			
Puberty Status	**SGA**	**AGA**	**LGA**	***P* Value[a]**	**SGA**	**AGA**	**LGA**	***P* Value[a]**
Girls								
Breast stage ≥2, n (%)	16 (89)	160 (84)	12 (86)	0.92[b]	8 (100)	128 (81)	40 (89)	0.25[b]
Pubic hair ≥2, n (%)	14 (74)	134 (77)	11 (73)	0.84[b]	4 (57)	98 (67)	33 (73)	0.52[b]
Boys								
Testicular size ≥4 mL, n (%)[b]	17 (81)	112 (86)	10 (91)	0.69	11 (85)	74 (72)	37 (82)	0.34
Pubic hair ≥2, n (%)[c]	10 (45)	83 (56)	9 (69)	0.38	6 (42)	62 (56)	22 (46)	0.39
Genital stage ≥2, n (%)	13 (61)	110 (76)	8 (73)	0.39[c]	11 (79)	77 (73)	38 (79)	0.73[b]

[a] *P* values denote differences across BW categories stratified by GDM exposure.

[b] P values calculated using Fischer exact test when expected counts were <5.

[c] *P* values calculated using χ^2 test.

results of the present study have demonstrated a substantial adverse effect of intrauterine exposure to GDM unrelated to the offspring's size at birth on body composition and metabolic traits. These findings indicate that *in utero* GDM exposure has a stronger effect on offspring health in childhood compared with the effect of BW and that the combination of being born SGA or LGA and exposed to GDM does not seem to exacerbate the adverse metabolic effects of GDM exposure *per se*. The results from a longitudinal prospective study of 4- to 7-year-old children born either AGA or LGA of GDM or control mothers showed an increased prevalence of obesity at age 7 years among children born LGA of GDM mothers compared with the other study groups (19). However, these differences were no longer evident at age 9 years (18) as in accordance with our results. At 11 years of age, LGA offspring had a 3.6-fold significantly greater cumulative risk of developing metabolic syndrome compared with children born AGA. This effect of BW only applied to offspring exposed to GDM in fetal life (18). A potential adverse synergistic effect of BW and GDM exposure on childhood metabolic health in SGA infants was not examined in their study.

Our analyses, stratified by GDM exposure, with and without adjustment for confounders, indicated a modest (1%), yet significant adverse effect of being born at the low end of the BW spectrum (BW z-score) and exposed to GDM on systolic blood pressure [Table 3 (30)]. A study investigating 14,881 offspring at the age of 9 to 14 years reported a protective effect of being born small on offspring adiposity, with a 30% increased risk of being overweight (BMI greater than the 95th percentile) for each 1-kg increment in BW. That study further showed that GDM exposure increased the risk of being overweight in childhood significantly (20). They did not detect any interaction between GDM and BW, similar to our results. However, they found that the association between GDM exposure and the later risk of being overweight was no longer statistically significant after adjustment for BW, suggesting that BW, rather than GDM exposure, is a superior risk marker of overweight in childhood (20). However, the use of self-reported measures of BW, GA, and anthropometric data in their study potentially increased the risk of recall and reporting biases.

Puberty onset

We found that the likelihood of having reached puberty using the Tanner stages for breast development, which is considered the reference standard for evaluating

Table 6. Age- and BMI-Adjusted Estimates for Onset of Puberty

		SGA vs AGA		LGA vs AGA		GDM Exposure	
Puberty Status	**Subjects, n**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value[a]**
Girls							
Breast stage ≥2	435	4.73 (0.89–25.28)	0.12	1.41 (0.50–3.94)	0.51	2.17 (1.03–4.60)	0.04
Pubic hair ≥2	406	1.08 (0.36–3.25)	0.90	1.01 (0.44–2.33)	0.95	1.49 (0.77–2.86)	0.23
Boys							
Testicular size ≥4 mL	323	1.67 (0.58–4.79)	0.90	3.19 (1.25–8.12)	0.08	0.63 (0.32–1.26)	0.19
Pubic hair ≥2	356	0.68 (0.29–1.58)	0.32	1.11 (0.55–2.25)	0.45	1.16 (0.67–2.00)	0.60
Genital stage ≥2	345	0.93 (0.40–2.16)	0.42	1.76 (0.80–3.85)	0.16	1.48 (0.82–2.68)	0.19

Age- and BMI-adjusted OR (95% CI) for onset of puberty comparing offspring born SGA or LGA with AGA offspring born of GDM or control mothers; breast development among girls and testicular size among boys was considered the primary outcome in defining puberty onset.

[a] *P* values and estimates represent the additive effect of exposure to GDM within BW groups.

puberty onset in girls (28), was increased among girls exposed to GDM, irrespective of their size at birth, age, or current BMI (Table 6). The association between GDM exposure and earlier onset of pubertal development shown in our study was consistent with previous findings (14, 17), and our results indicate that exposure to GDM *in utero* is a more important predictor for earlier onset of puberty among females than size at birth. However, this was not the case for boys, for whom testicular size was used to define the beginning of puberty, nor when other secondary sexual characteristics, which do not necessarily represent puberty onset, were applied.

Study strength and limitations

To the best of our knowledge, the present study is the largest of its kind to use objective measures of cardiometabolic outcomes, body composition, and puberty status to examine the effect of BW and GDM exposure. Recently, a validation study of self-assessed Tanner staging in boys and girls nested within the DNBC showed a substantial proportion of misclassification of Tanner stages (39), emphasizing the value of using clinical data of pubertal development. By including both SGA and LGA individuals of GDM and control mothers, we were able to study the effect of size at birth and GDM exposure in relation to childhood cardiometabolic health using objective data of BW obtained from reliable records.

However, the use of BW as a proxy for an adverse fetal environment has been debated, because BW is an unspecific marker of fetal growth. The association between BW and the risk of T2D could be confounded by a variety of factors, including genetic and nongenetic factors (4). Furthermore, a large variability in body composition for a given BW category has been shown (40), and fetal and infant body composition and growth might play an important role in the association between BW and childhood health. One limitation of our study was the lack of information on body composition at birth and genetic factors that could have affected BW and the later risk of T2D. However, we were able to control for several other covariates that have been associated with BW and/or the risk of T2D, including parental socio-occupational status (41, 42), maternal smoking during pregnancy (41), parity (8, 41), and maternal obesity (prepregnancy BMI and pregnancy weight gain) (18, 19, 43).

Conclusion

We have demonstrated that body size in childhood and adolescence reflects size at birth; however, the potentially deleterious metabolic effects from being born small or large were not apparent at the age of 9 to 16 years. Furthermore, the combination of being born SGA or LGA and exposed to GDM *in utero* did not increase the risk of adverse health outcomes in childhood or adolescence. However, we confirmed that exposure to GDM is a risk factor for detrimental cardiometabolic outcomes, disadvantageous body composition, and earlier onset of female puberty independently of the offspring's size at birth. From a health and prevention perspective, exposure to GDM could be a more important risk factor for the cardiometabolic health of children and adolescents compared with their size at birth.

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Author Contributions: S.F.O. and L.G.G. are the guarantors of this work, had full access to the data, and take responsibility for the integrity and contents of the data and the accuracy of the data analyses. F.B.K., AC.B.T., L.H., and L.G.G. collected the clinical data, together with the GDM/DNBC study team. The research question for the present study was designed in cooperation among F.B.K, AC.B.T, and L.G.G. F.B.K. was responsible for analyzing the data and drafting the report. AC.B.T., L.H., and L.G.G. assisted in the interpretation of the results. All authors reviewed the report and approved the final version.

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