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Maternal gestational diabetes and childhood obesity at age 9–11: results of a multinational study

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Abstract

Aims/hypothesis The aim of this study was to examine the association between maternal gestational diabetes mellitus (GDM) and childhood obesity at age 9–11 years in 12 countries around the world.

Methods A multinational cross-sectional study of 4740 children aged 9–11 years was conducted. Maternal GDM was diagnosed according to the ADA or WHO criteria. Height and waist circumference were measured using standardised methods. Weight and body fat were measured using a portable Tanita SC-240 Body Composition Analyzer. Multilevel modelling was used to account for the nested nature of the data.

Results The prevalence of reported maternal GDM was 4.3%. The overall prevalence of childhood obesity, central obesity and high body fat were 12.3%, 9.9% and 8.1%, respectively. The multivariable-adjusted (maternal age at delivery, education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex and birthweight) odds ratios among children of GDM mothers compared with children of non-GDM mothers were 1.53

A list of members of the ISCOLE Research Group is given in the electronic supplementary material (ESM).

Electronic supplementary material The online version of this article (doi:10.1007/s00125-016-4062-9) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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(95% CI 1.03, 2.27) for obesity, 1.73 (95% CI 1.14, 2.62) for central obesity and 1.42 (95% CI 0.90, 2.26) for high body fat. The positive association was still statistically significant for central obesity after additional adjustment for current maternal BMI but was no longer significant for obesity and high body fat.

Conclusions/interpretation Maternal GDM was associated with increased odds of childhood obesity at 9–11 years old but this association was not fully independent of maternal BMI.

Keywords Children · Gestational diabetes · Obesity

Abbreviations

FFQ	Food frequency questionnaire
GDM	Gestational diabetes mellitus
ISCOLE	International Study of Childhood Obesity, Lifestyle and the Environment
NHANES	National Health and Nutrition Examination Survey

Introduction

Childhood obesity has increased dramatically in both developed and developing countries [1]. It has been suggested that prenatal, perinatal and postnatal environmental factors impact childhood obesity [2]. Some studies have found that intrauterine exposure to maternal gestational diabetes mellitus (GDM) places offspring at increased risk of long-term adverse outcomes, including obesity [3–12]. GDM, defined as any degree of glucose intolerance with onset or first recognition during pregnancy [3], is a common pregnancy complication affecting approximately 1–28% of pregnancies in a survey of 173 countries, based on uniform diagnostic criteria for GDM [4].

Early research from the Pima Indian Study and the Diabetes in Pregnancy Study at Northwestern University in the USA provided initial evidence of an association between maternal GDM and the risk of childhood obesity [5, 6]. However, other studies failed to find a clear association between maternal GDM and offspring obesity [7–12]. A recent literature review indicated that this difference may be due to the high type 2 diabetes mellitus risk in the unique Pima Indian population and the specialised clinical population in the Northwestern University study [2]. Furthermore, the majority of the previous studies are from high income countries, with limited data from low to middle income countries; thus studies that include children from multiple regions of the world are needed.

Indicators of central obesity, such as waist circumference, may better predict cardiovascular disease compared with adiposity measured by BMI [13]. However, limited data exist on the association between maternal GDM and different indicators of childhood obesity. The aim of the present study was to examine the association between self-reported maternal GDM and three indicators of childhood obesity (BMI, waist circumference and body fat) in children aged 9–11 years from 12 countries around the world.

Methods

Study design

The International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE) is a multinational cross-sectional study conducted at urban and suburban sites in 12 countries (Australia, Brazil, Canada, China, Colombia, Finland, India, Kenya, Portugal, South Africa, the UK and the USA) [14]. These countries are classified as low to high income countries according to the World Bank Classification (Table 1). More details on the study design and methods can be found elsewhere [14]. The Institutional Review Board at the Pennington Biomedical Research Center (coordinating centre) approved the overarching protocol, and the institutional/ethical review boards at each participating institution approved the local protocols. Written informed consent was obtained from parents or legal guardians, and child assent was also obtained as required by the local institutional/ethical review boards before participation in the study.

Participants

A total of 7372 children aged 9–11 years participated in ISCOLE. Of these children, 4740 remained after excluding participants who did not have valid data/information on accelerometer ($n = 1214$), maternal history of GDM ($n = 359$), BMI ($n = 5$), waist circumference ($n = 4$), percentage of body fat ($n = 58$), birthweight ($n = 383$), gestational age ($n = 101$), diet scores ($n = 82$), maternal age at child's birth ($n = 134$), maternal current BMI ($n = 216$) and other information (maternal education and infant feeding mode) ($n = 76$). Participants who were excluded did not differ in age or BMI z score but there was a higher proportion of boys compared with those who were included in the analysis. Data were collected from September 2011 to December 2013.

Measurements

Demographics and family health history Maternal education, current maternal body weight and height, maternal age at child's birth, child age, child sex, birthweight, infant feeding mode, gestational age and number of younger siblings were collected from parents or guardians by a demographic and family health history questionnaire. Maternal education was

Table 1 Prevalence of GDM and diagnostic criteria used at the 12 study sites, 1999–2004

Country (site)	World bank classification	Diagnostic criteria for GDM	No. of participants	GDM	
				No. of cases	Prevalence (%)
Australia (Adelaide)	High income	Modified WHO	386	20	5.2
Canada (Ottawa)	High income	ADA	443	14	3.2
Finland (Helsinki, Espoo and Vantaa)	High income	WHO	401	22	5.5
Portugal (Porto)	High income	Modified ADA	533	47	8.8
UK (Bath and NE Somerset)	High income	WHO	324	6	1.9
USA (Baton Rouge)	High income	ADA	363	21	5.8
Brazil (São Paulo)	Upper-middle income	WHO	354	11	3.1
China (Tianjin)	Upper-middle income	WHO	413	8	1.9
Colombia (Bogotá)	Upper-middle income	ADA	700	23	3.3
South Africa (Cape Town)	Upper-middle income	WHO	120	6	5.0
India (Bangalore)	Lower-middle income	Modified ADA	414	20	4.8
Kenya (Nairobi)	Low income	WHO	289	8	2.8
All sites			4740	206	4.3

classified into three categories: did not complete high school, completed high school or some college, and completed bachelor or postgraduate degree. The child's parents were asked whether the child was fed breast milk or not, age when completely stopped being fed breast milk, age when first fed formula and age when completely stopped drinking formula. These responses were classified into four categories: exclusive breast feeding, mixed feeding, weaned from breast feeding and exclusive formula feeding.

Maternal history of GDM Maternal history of GDM was recalled by parents or guardians and reported on the questionnaire. Maternal GDM was diagnosed between July 1999 and July 2004, inferred by the child's date of birth. The diagnostic criteria for GDM used in local maternity hospitals during this period were identified by each study site. Maternal GDM was diagnosed by the WHO or modified WHO criteria based on a 2 hr 75 g OGTT, or the ADA or modified ADA criteria based on 3 hr 100 g OGTT [15, 16]. The WHO criteria for GDM requires one plasma glucose test result of ≥7.0 mmol/l (fasting) or ≥7.8 mmol/l (2 h) [15]. The ADA criteria requires two plasma glucose test results of ≥5.3 mmol/l (fasting), ≥10.0 mmol/l (1 h), ≥8.6 mmol/l (2 h) or ≥7.8 mmol/l (3 h) [16].

Dietary pattern A food frequency questionnaire (FFQ) that was adapted from the Health Behavior in School-aged Children Survey (HBSC) and validated [17–19] was administered to all ISCOLE participants. The FFQ asked the participants about their 'usual' consumption of 23 food categories, with response options including: never, less than once per week, once per week, 2–4 days per week, 5–6 days per week, once a day every day, and more than once a day. Two diet pattern scores that represented an 'unhealthy diet pattern' (with positive loadings

for fast food, hamburgers, soft drinks, sweets, fried food, etc.) and a 'healthy diet pattern' (with positive loadings for vegetables, fruit, whole grains, low-fat milk, etc.) were obtained using principal components analyses [18, 19].

Anthropometric measurements A battery of anthropometric measurements was taken according to standardised procedures across all study sites. Height was measured without shoes using a Seca 213 portable stadiometer (Seca, Hamburg, Germany), with the participant's head in the Frankfurt plane. Waist circumference was measured at the end of normal expiration with a non-elastic tape held midway between the lower rib margin and the iliac crest. Each measurement was repeated and the average was used for analysis (a third measurement was obtained if the difference between the first two measurements was >0.5 cm, then the average of the two closest measurements was used in the analyses) [14].

The participant's weight and percentage of body fat were measured using a portable Tanita SC-240 Body Composition Analyzer (Tanita, Arlington Heights, IL). All outer clothing, heavy pocket items, and shoes and socks were removed. Two measurements were obtained and the average was used in the analysis (a third measurement was obtained if the difference between the first two measurements was >0.5 kg or >2.0% for weight and percentage of body fat, respectively, then the average of the two closest measurements was used in the analyses)[14].

Maternal and childhood BMI were calculated by dividing weight in kilograms by the square of height in metres. Childhood BMI z scores were computed using age- and sex-specific reference data from the WHO. Waist circumference z scores were computed using age- and sex-specific reference data from the National Health and Nutrition Examination Survey III (NHANES III) from 1988 to 1994 [20]. Body fat z scores were

computed using the NHANES IV data from 1999 to 2004 [21]. Child obesity was defined as BMI z scores > +2 SD. Central obesity was defined as waist circumference ≥90th percentile of NHANES III reference [22]. High body fat was defined as body fat ≥90th percentile of NHANES IV reference [21]. Maternal overweight was defined as BMI ≥25 kg/m^2, based on self-reported maternal current height and weight.

Accelerometry An ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, FL, USA) was used to objectively measure moderate-to-vigorous physical activity, sedentary behaviour and sleeping time. The accelerometer was worn at the waist on an elasticated belt on the right mid-axillary line. Participants were encouraged to wear the accelerometer 24 h per day (removing it only for water-related activities) for at least 7 days including two weekend days (plus an initial familiarisation day and the morning of the final day)[14]. Nocturnal sleep duration was estimated from the accelerometer data using a fully automated algorithm for 24 h waist-worn accelerometers, which was recently validated for ISCOLE [23]. The weekly total sleep time averages were calculated using only days where valid sleep was accumulated (total sleep period time ≥ 160 min) and only for participants with at least three nights of valid sleep including one weekend day [24]. After exclusion of total sleep time and awake non-wear time (any sequence of ≥20 consecutive minutes of zero activity counts), moderate-to-vigorous physical activity was defined as all activity ≥574 counts per 15 s and total sedentary time was defined as all movement ≤25 counts per 15 s, consistent with the widely used Evenson cut-offs [25].

Statistical analysis

Variables were compared using a t test for means and a χ^2 test for proportions between women with and without GDM. Multilevel linear regression models were used to estimate the association between maternal GDM and z scores of childhood BMI, waist circumference and body fat. Multilevel logistic regression models were used to estimate the association between maternal GDM and the odds of childhood obesity, central obesity and high body fat. We defined child as level 1, school as level 2 and study site as level 3 for the multilevel analyses. Study site and school were considered to have random effects. The analyses were adjusted for maternal age at delivery (continuous variable), maternal current BMI (continuous variable), maternal education (categorical variable), infant feeding mode (categorical variable), birthweight (continuous variable), gestational age (continuous variable), number of younger siblings (continuous variable), child unhealthy diet pattern scores (continuous variable), moderate-to-vigorous physical activity (continuous variable), sleeping time (continuous variable), sedentary time (continuous variable), age (continuous variable) and sex (categorical variable). The criterion for statistical significance was $p < 0.05$. All statistical analyses were performed with SPSS for Windows, version 21.0 (Statistics 21, SPSS, IBM, USA) or SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

Results

The prevalence of maternal GDM and the diagnostic criteria employed between 1999 and 2004 at the 12 study sites are presented in Table 1. The overall prevalence of self-reported maternal GDM was 4.3%, ranging from 1.9% in the UK and China to 8.8% in Portugal. Characteristics of study participants by maternal GDM status are presented in Table 2. GDM mothers had significantly older age at delivery than non-GDM mothers (29.9 years vs 28.3 years). Children of GDM mothers had significantly higher mean birthweight (3415 g vs 3274 g), and significantly higher prevalence of obesity (18.4% vs 12.0%), central obesity (16.0% vs 9.6%) and high body fat (12.1% vs 7.9%) at age 9–11 years compared with children of non-GDM mothers.

After adjustment for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex and birthweight, children of GDM mothers had significantly higher mean values for BMI z score (0.71 vs 0.54), waist circumference z score (0.06 vs −0.02) and body fat z score (0.17 vs 0.02) than children of non-GDM mothers (Table 3). These significant associations disappeared after additional adjustment for current maternal BMI.

Table 4 presents the association of maternal GDM with the risk of childhood obesity, central obesity and high body fat by all GDM mothers or GDM mothers with normal weight or overweight. The multivariable-adjusted odds ratios among children of GDM mothers compared with children of non-GDM mothers were 1.53 (95% CI 1.03, 2.27) for obesity, 1.73 (95% CI 1.14, 2.62) for central obesity and 1.42 (95% CI 0.90, 2.26) for high body fat (Table 4). The positive association between GDM and central obesity was still significant after additional adjustment for current maternal BMI, but not for general obesity or high body fat. In the multivariable-adjusted analyses, the positive association of maternal GDM with the odds of childhood obesity and central obesity were present among GDM mothers who were overweight but not among GDM mothers with normal weight.

When stratified by maternal GDM diagnostic criteria, sex of the child, level of moderate-to-vigorous physical activity, unhealthy diet scores, sleep time, breastfeeding status and the country's income classification, the positive association of maternal GDM with the odds of central obesity was only present in girls and in children of mothers whose GDM was diagnosed by the ADA criteria (Table 5). There were no significant interactions between maternal GDM and diagnostic criteria, the child's sex, level of moderate-to-vigorous physical activity, unhealthy diet pattern scores, sleep time, the

Table 2 Characteristics of study participants by maternal GDM status

Characteristic	Non-GDM ($n = 4534$)	GDM ($n = 206$)	p value
Maternal characteristics			
Age at delivery (years)	28.3 (5.7)	29.9 (5.8)	<0.001
Current BMI (kg/m²)	25.6 (4.9)	27.5 (5.0)	<0.001
Current overweight status, n (%)	2083 (45.9)	130 (63.1)	<0.001
Education, n (%)			0.54
Did not complete high school	997 (22.0)	52 (25.2)	
Completed high school/some college	2064 (45.5)	89 (43.2)	
Bachelor's or postgraduate degree	1473 (32.5)	65 (31.6)	
Offspring characteristics at birth or first year			
Boys, n (%)	2091 (46.1)	95 (46.1)	1.00
Birthweight (g)	3274 (576)	3415 (623)	0.001
Gestational age (weeks)	38.6 (2.2)	38.3 (2.1)	0.035
Infant breast feeding, n (%)			0.16
Exclusive breast feeding	1722 (38.0)	63 (30.6)	
Mixed feeding	2137 (47.1)	105 (51.0)	
Weaned from breast feeding	47 (1.0)	3 (1.5)	
Exclusive formula feeding	628 (13.9)	35 (17.0)	
Offspring characteristics at age 9–11 years			
Age (years)	10.4 (0.6)	10.4 (0.5)	0.76
Younger siblings[a]	0.60	0.55	0.39
BMI (kg/m²)	18.4 (3.4)	19.1 (3.6)	0.002
Waist circumference (cm)	64.2 (8.8)	66.3 (9.5)	0.001
Body fat (%)	20.8 (7.6)	22.4 (7.6)	0.002
Unhealthy diet pattern score	−0.15 (0.85)	−0.13 (0.93)	0.69
Moderate-to-vigorous physical activity (min/day)	59.6 (24.7)	59.0 (24.1)	0.71
Sedentary time (min/day)	518 (68)	520 (64)	0.63
Duration of night sleep (min/day)	528 (53)	521 (56)	0.051
General obesity, n (%)[b]	546 (12.0)	38 (18.4)	0.006
Central obesity, n (%)[c]	437 (9.6)	33 (16.0)	0.003
High body fat, n (%)[d]	359 (7.9)	25 (12.1)	0.030

Data are mean (SD) or number (%)

[a] Mean numbers of siblings per participant.

[b] General obesity was defined as BMI z score > +2 SD for age- and sex-specific distribution based on the WHO growth reference

[c] Central obesity was defined as waist circumference ≥90th percentile for age- and sex-specific distribution using NHANES III reference

[d] High body fat was defined as body fat ≥90th percentile for age- and sex-specific distribution using NHANES IV reference

breastfeeding status, or the country's income classification with the risk of childhood obesity, central obesity and high body fat (all p values for interactions are >0.05).

Discussion

In this multinational cross-sectional study, we found that maternal GDM was associated with increased odds of obesity and central obesity in children aged 9–11 years old in 12

countries; however, these associations were not fully independent of maternal BMI.

Early research in the Pima Indian Study demonstrated that the offspring of Pima Indian women with diabetes prior to pregnancy and GDM were heavier at birth and had much higher rates of obesity at age 5–19 years than the offspring of prediabetic or non-diabetic women [5, 26]. In the Northwestern University Diabetes in Pregnancy Study, diabetes during pregnancy, including both GDM and insulin-treated diabetes prior to pregnancy, was associated with increased BMI of the offspring

Table 3 Mean z scores for BMI, waist circumference and percentage body fat among offspring by maternal GDM status

Outcome	BMI z score			Waist circumference z score			Body fat z score		
	Non-GDM	GDM	p value	Non-GDM	GDM	p value	Non-GDM	GDM	p value
No. of participants	4534	206		4534	206		5434	206	
Model 1[a]	0.48 (0.08)	0.70 (0.12)	0.012	−0.04 (0.03)	0.06 (0.05)	0.006	−0.05 (0.09)	0.13 (0.12)	0.01
Model 2[b]	0.54 (0.08)	0.75 (0.11)	0.010	−0.03 (0.03)	0.07 (0.04)	0.006	0.02 (0.09)	0.20 (0.11)	0.009
Model 3[c]	0.54 (0.08)	0.71 (0.11)	0.045	−0.02 (0.03)	0.06 (0.04)	0.021	0.02 (0.09)	0.17 (0.11)	0.027
Model 4[d]	0.51 (0.08)	0.60 (0.11)	0.29	−0.04 (0.03)	0.01 (0.05)	0.14	−0.01 (0.09)	0.10 (0.11)	0.13

Data are mean (SE)

[a] Model 1 adjusted for child sex

[b] Model 2 adjusted for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time and sex

[c] Model 3 adjusted for variables in model 2 and birthweight

[d] Model 4 adjusted for variables in model 3 and current maternal BMI

at birth and after 5 years of age [27]. However, other studies failed to find a clear association between maternal GDM and obesity in children aged 5 years or older [7–11]. One study found that prenatal exposure to the metabolic effects of mild, diet-treated GDM did not increase the risk of childhood obesity [7]. Another study also found little association between maternal glucose during pregnancy and obesity in offspring at 2 years [10]. A systematic review of 12 studies reported that the crude

Table 4 Odds ratios of childhood obesity by maternal GDM status at all or at different BMI levels

Outcome	General obesity			Central obesity			High body fat		
	Non-GDM	GDM	p value	Non-GDM	GDM	p value	Non-GDM	GDM	p value
Total maternal sample									
No. of participants	4534	206		4534	206		5434	206	
No. of cases	546	38		437	33		359	25	
Model 1[a]	1.00	1.65 (1.13, 2.41)	0.009	1.00	1.83 (1.23, 2.72)	0.003	1.00	1.55 (0.99, 2.42)	0.06
Model 2[b]	1.00	1.62 (1.10, 2.40)	0.015	1.00	1.83 (1.21, 2.77)	0.004	1.00	1.51 (0.96, 2.40)	0.08
Model 3[c]	1.00	1.53 (1.03, 2.27)	0.034	1.00	1.73 (1.14, 2.62)	0.010	1.00	1.42 (0.90, 2.26)	0.14
Model 4[d]	1.00	1.37 (0.92, 2.04)	0.13	1.00	1.54 (1.01, 2.35)	0.046	1.00	1.30 (0.81, 2.06)	0.29
Maternal overweight									
No. of participants	2083	130		2083	130		2083	130	
No. of cases	338	34		284	28		251	23	
Model 1[a]	1.00	1.77 (1.16, 2.70)	0.009	1.00	1.71 (1.09, 2.68)	0.019	1.00	1.54 (0.95, 2.51)	0.08
Model 2[b]	1.00	1.75 (1.13, 2.73)	0.013	1.00	1.76 (1.10, 2.83)	0.019	1.00	1.53 (0.92, 2.55)	0.10
Model 3[c]	1.00	1.60 (1.02, 2.51)	0.04	1.00	1.62 (1.00, 2.61)	0.048	1.00	1.42 (0.85, 2.39)	0.18
Maternal normal weight									
No. of participants	2451	76		2451	76		2451	76	
No. of cases	208	4		153	5		108	2	
Model 1[a]	1.00	0.62 (0.22, 1.76)	0.37	1.00	1.22 (0.47, 3.15)	0.69	1.00	0.58 (0.14, 2.43)	0.46
Model 2[b]	1.00	0.63 (0.22, 1.81)	0.39	1.00	1.26 (0.48, 3.34)	0.64	1.00	0.59 (0.14, 2.50)	0.47
Model 3[c]	1.00	0.64 (0.22, 1.83)	0.40	1.00	1.27 (0.48, 3.35)	0.63	1.00	0.59 (0.14, 2.49)	0.47

[a] Model 1 adjusted for child age and sex

[b] Model 2 adjusted for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, age and sex

[c] Model 3 adjusted for variables in model 2 and birthweight

[d] Model 4 adjusted for variables in model 3 and current maternal BMI

Table 5 Odds ratios of childhood obesity by maternal GDM status of various subgroups

	General obesity			Central obesity			High body fat		
	Non-GDM	GDM	p value	Non-GDM	GDM	p value	Non-GDM	GDM	p value
Sex of child[a]									
Boys									
No. of participants	2091	95		2091	95		2091	95	
No. of cases	323	19		236	13		126	7	
Model 1[b]	1.00	1.31 (0.74, 2.30)	0.35	1.00	1.26 (0.65, 2.43)	0.50	1.00	1.21 (0.52, 2.82)	0.67
Model 2[c]	1.00	1.26 (0.72–2.19)	0.42	1.00	1.17 (0.61, 2.24)	0.64	1.00	1.15 (0.49, 2.67)	0.75
Girls									
No. of participants	2443	111		2443	111		2443	111	
No. of cases	223	19		201	20		233	18	
Model 1[b]	1.00	1.72 (0.99, 2.99)	0.055	1.00	2.06 (1.19, 3.56)	0.01	1.00	1.50 (0.85, 2.63)	0.16
Model 2[c]	1.00	1.53 (0.88, 2.68)	0.13	1.00	1.81 (1.05, 3.13)	0.033	1.00	1.35 (0.77, 2.37)	0.30
GDM diagnostic criteria[a]									
ADA criteria									
No. of participants	2328	125		2328	125		2328	125	
No. of cases	258	23		199	21		190	14	
Model 1[b]	1.00	1.41 (0.85, 2.32)	0.18	1.00	1.77 (1.04, 2.99)	0.034	1.00	1.09 (0.59, 2.01)	0.79
Model 2[c]	1.00	1.50 (0.91, 2.48)	0.11	1.00	1.91 (1.12, 3.24)	0.017	1.00	1.23 (0.67, 2.27)	0.51
WHO criteria									
No. of participants	2206	81		2206	81		2206	81	
No. of cases	288	15		238	12		169	11	
Model 1[b]	1.00	1.76 (0.91, 3.38)	0.09	1.00	1.76 (0.88, 3.52)	0.11	1.00	2.24 (1.08, 4.64)	0.03
Model 2[c]	1.00	1.23 (0.64, 2.36)	0.53	1.00	1.11 (0.61, 2.40)	0.60	1.00	1.52 (0.73, 3.14)	0.26
Moderate-to-vigorous physical activity[a]									
High level									
No. of participants	2273	101		2273	101		2273	101	
No. of cases	179	13		124	10		85	6	
Model 1[b]	1.00	1.57 (0.82, 3.01)	0.18	1.00	1.91 (0.93, 3.92)	0.08	1.00	1.44 (0.58, 3.60)	0.44
Model 2[c]	1.00	1.29 (0.65, 2.53)	0.47	1.00	1.52 (0.72, 3.21)	0.019	1.00	1.06 (0.41, 2.78)	0.90
Low level									
No. of participants	2261	105		2261	105		2261	105	
No. of cases	367	25		313	23		274	19	
Model 1[b]	1.00	1.52 (0.93, 2.48)	0.10	1.00	1.68 (1.02, 2.77)	0.044	1.00	1.43 (0.84, 2.43)	0.19
Model 2[c]	1.00	1.40 (0.85, 2.31)	0.19	1.00	1.54 (0.92, 2.59)	0.10	1.00	1.34 (0.78, 2.29)	0.29
Unhealthy diet scores [a]									
High level									
No. of participants	2267	103		2267	103		2267	103	
No. of cases	270	21		210	17		179	11	
Model 1[b]	1.00	1.67 (0.97, 2.88)	0.07	1.00	1.84 (1.03, 3.29)	0.041	1.00	1.78 (0.59, 2.34)	0.65
Model 2[c]	1.00	1.51 (0.87, 2.62)	0.14	1.00	1.69 (0.93, 3.05)	0.08	1.00	1.03 (0.51, 2.07)	0.94
Low level									
No. of participants	2267	103		2267	103		2267	103	
No. of cases	276	17		227	16		180	14	
Model 1[b]	1.00	1.46 (0.82, 2.60)	0.19	1.00	1.65 (0.90, 3.01)	0.10	1.00	1.81 (0.95, 3.44)	0.07
Model 2[c]	1.00	1.29 (0.71, 2.32)	0.40	1.00	1.45 (0.78, 2.70)	0.24	1.00	1.67 (0.87, 3.21)	0.12
Sleep time[a]									
High level									
No. of participants	2282	90		2282	90		2282	90	
No. of cases	207	13		170	12		147	8	
Model 1[b]	1.00	1.72 (0.90, 3.29)	0.10	1.00	2.04 (1.04, 4.02)	0.039	1.00	1.41 (0.64, 3.14)	0.40
Model 2[c]	1.00	1.56 (0.80, 2.98)	0.20	1.00	1.83 (0.92, 3.63)	0.08	1.00	1.28 (0.58, 2.84)	0.54
Low level									
No. of participants	2252	116		2252	116		2252	116	
No. of cases	339	25		267	21		212	17	
Model 1[b]	1.00	1.55 (0.94, 2.54)	0.08	1.00	1.69 (0.99, 2.88)	0.054	1.00	1.59 (0.89, 2.82)	0.12
Model 2[c]	1.00	1.39 (0.84, 2.30)	0.21	1.00	1.52 (0.88, 2.63)	0.13	1.00	1.45 (0.81, 2.60)	0.22
Region[a]									
High income countries									
No. of participants	2320	130		2320	130		2320	130	
No. of cases	255	20		175	20		166	15	
Model 1[b]	1.00	1.23 (0.72, 2.08)	0.44	1.00	1.85 (1.08, 3.18)	0.023	1.00	1.37 (0.74, 2.53)	0.32
Model 2[c]	1.00	1.14 (0.67, 1.93)	0.64	1.00	1.70 (0.98, 2.95)	0.059	1.00	1.28 (0.69, 2.38)	0.43

Table 5 (continued)

	General obesity			Central obesity			High body fat		
	Non-GDM	GDM	p value	Non-GDM	GDM	p value	Non-GDM	GDM	p value
Low–middle income countries									
No. of participants	2214	76		2214	76		2214	76	
No. of cases	291	18		262	13		193	10	
Model 1[b]	1.00	1.93 (1.03, 3.62)	0.041	1.00	1.38 (0.70, 2.71)	0.36	1.00	1.43 (0.69, 3.00)	0.34
Model 2[c]	1.00	1.66 (0.87, 3.16)	0.13	1.00	1.19 (0.60, 2.38)	0.62	1.00	1.23 (0.58, 2.59)	0.60
Infant feeding mode[a]									
Exclusive breast feeding									
No. of participants	1722	63		1722	63		1722	63	
No. of cases	190	14		161	12		110	10	
Model 1[b]	1.00	2.12 (1.09, 4.14)	0.028	1.00	2.20 (1.09, 4.45)	0.028	1.00	2.34 (1.10, 4.98)	0.03
Model 2[c]	1.00	1.57 (0.78, 3.14)	0.21	1.00	1.64 (0.79, 3.40)	0.19	1.00	1.69 (0.77, 3.72)	0.19
Not exclusive breast feeding									
No. of participants	2812	143		2812	143		2812	143	
No. of cases	356	24		276	21		249	15	
Model 1[b]	1.00	1.44 (0.89, 2.34)	0.14	1.00	1.66 (0.99, 2.78)	0.054	1.00	1.20 (0.67, 2.15)	0.55
Model 2[c]	1.00	1.37 (0.84, 2.25)	0.21	1.00	1.24 (0.95, 2.71)	0.08	1.00	1.16 (0.65, 2.10)	0.62

[a] All p values for interactions are >0.05.

[b] Model 1 adjusted for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex and birthweight, other than the variable for stratification

[c] Model 2 adjusted for variables in model 1 and current maternal BMI

odds ratios for the relationship between maternal GDM and childhood overweight and obesity ranged from 0.7 to 6.3 and the association was not statistically significant in eight of the studies [28]. Most of these studies were conducted in high income countries, with only one from a middle income country [29]. Therefore, large studies using uniform methods to assess maternal GDM and childhood obesity across various populations are needed to evaluate this question. Our study is the first to evaluate the association between maternal GDM and childhood obesity using such widespread, multinational data. We found that maternal GDM was associated with an increased risk of childhood obesity among children aged 9–11 years from 12 countries. Moreover, our results indicate that the positive associations between maternal GDM and the risk of childhood obesity were significant among children from low to middle income countries and between maternal GDM and an increased risk of central obesity among children from high income countries; however, these associations were no longer significant after additional adjustment for current maternal BMI (Table 5).

Several prenatal and perinatal factors including maternal prepregnancy BMI, gestational weight gain, maternal GDM and child birthweight have been found to be associated with an increased risk of obesity in offspring [2, 30, 31]. Previous studies have demonstrated the significant association between maternal GDM and an increased risk of childhood obesity to be both independent of [32] and dependent on [33] maternal prepregnancy BMI. Since maternal prepregnancy obesity is a risk factor for maternal GDM [34], adjustment for maternal prepregnancy BMI as a confounding factor or as a proxy for

genetic predisposition in the analysis of maternal GDM and childhood obesity may be over-adjusted. The present study found that the positive association between maternal GDM and childhood obesity risk was only slightly attenuated by birthweight and was not fully independent of current maternal BMI. We used current maternal BMI (postpartum BMI at about 10 years) but not maternal prepregnancy BMI in the multivariable-model for three reasons: first, data on maternal prepregnancy BMI and gestational weight gain were not available in the present study; second, a strong correlation (0.827) has been shown between maternal prepregnancy BMI and current BMI [35]; third, although current maternal BMI represents shared postnatal environmental factors, we still included current maternal BMI in the final multivariable-adjusted model (Model 4) which can partially control for the maternal prepregnancy BMI effect.

Inconsistent associations have been found in studies that assessed children at different ages. The Northwestern University Diabetes in Pregnancy Study reported that the relative weight in children of GDM mothers increased dramatically after 5 years of age, and that half of the children of GDM mothers had a weight >90th percentile by age 8 years [6]. One study in China found that maternal GDM increased the cardiometabolic risk in early childhood at 8 years of age, but not at 15 years of age [36]. Our study found that the children of GDM mothers had 1.42–1.73 times higher odds of developing obesity than children of non-GDM mothers at 9–11 years old. A prospective pregnancy cohort from the UK reported that the odds ratio of obesity among children of GDM mothers at 9–

11 years old was 1.51 (0.76, 2.98), which is similar to our study [37].

Waist circumference, BMI and body fat are the three main indicators used to evaluate obesity. In the USA, the National Institutes of Health clinical guidelines for the identification and treatment of overweight and obesity among adults recognise the importance of including measurements of both obesity and central obesity, which are assessed by BMI and waist circumference, respectively [38]. Some studies have established that central obesity predicts obesity-related health risk [39]. However, the majority of the available studies used BMI, and few studies have included concurrent measurements of waist circumference and body fat [11, 37, 40]. Our study demonstrated a positive association between maternal GDM and the odds of childhood obesity and central obesity; however, after additional adjustment for current maternal BMI, this association was only significant for central obesity and not for general obesity. Therefore, more studies are needed to confirm the effect of maternal GDM on the risks of childhood obesity and central obesity.

The mechanisms by which exposure to diabetes in utero increases the risk of offspring obesity are not fully understood. Exposure to maternal diabetes is associated with excess fetal growth in utero, possibly mainly due to an increase in fetal fat mass and alterations in fetal hormone levels [2]. In addition, exposure to maternal diabetes results in elevated hyperglycaemia hyperinsulinaemia and elevated leptin synthesis in offspring [2]. Maternal prenatal GDM may also influence the fetal epigenome; thereby influencing the expression of genes that direct the accumulation of body fat or related metabolism [2].

There were several strengths of our study including the recruitment of a large multinational sample of children from low to high income countries across several regions of the world, the highly standardised measurement protocol, the use of direct measurements whenever possible and the rigorous quality control programme. In addition, body weight, waist circumference and body fat were directly measured by standardised methods. One limitation of the study is that it is a cross-sectional study. Thus, we could not make cause-and-effect inferences. Second, since data on maternal prepregnancy BMI and gestational weight gain were not available, we were not able to assess the effect of these variables on the association of GDM with the risk of childhood obesity. Third, the information on maternal GDM status, current maternal body weight and height, infant feeding mode, gestational age and child's birthweight was recalled by parents in a self-reported questionnaire, which may have introduced recall bias. Although no specific assessment of validity of self-reporting of these variables was carried out in the present study, similar questionnaires have been used in a large number of epidemiological studies. Finally, maternal GDM was diagnosed by different criteria across the different sites, which may bias the results.

In conclusion, GDM was associated with an increased risk of obesity among children aged 9–11 years; however, this association was not fully independent of maternal BMI. Furthermore, this study provided evidence for a long-term effect of the different diagnostic criteria for maternal GDM on the risk of childhood obesity.

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