Diabetologia
https://doi.org/10.1007/s00125-018-4758-0

ARTICLE

Association between maternal diabetes, being large for gestational age and breast-feeding on being overweight or obese in childhood

Padma Kaul [1,2] · Samantha L. Bowker [1] · Anamaria Savu [1] · Roseanne O. Yeung [2] · Lois E. Donovan [3] · Edmond A. Ryan [2]

Received: 15 April 2018 / Accepted: 24 September 2018

Abstract

Aims/hypothesis This study aimed to examine the association of maternal diabetes, being large for gestational age (LGA) and breast-feeding with being overweight or obese in pre-school-aged children.

Methods Data on height and weight at the time of their pre-school (age 4–6 years) immunisation visit between January 2009 and August 2017, as well as breast-feeding status in the first 5 months of life, for 81,226 children born between January 2005 and August 2013 were linked with maternal hospitalisation and outpatient records and birth registry data. Children were grouped into six categories based on maternal diabetes status during pregnancy (no diabetes, gestational diabetes or pre-existing diabetes) and birthweight (appropriate for gestational age [AGA] or LGA). WHO criteria were used to identify children who were overweight or obese.

Results There were 69,506 children in the no diabetes/AGA group (control), 5926 in the no diabetes/LGA group, 4563 in the gestational diabetes/AGA group, 573 in the gestational diabetes/LGA group, 480 in the pre-existing diabetes/AGA group and 178 in the pre-existing diabetes/LGA group. The rate of being overweight/obese at pre-school age ranged from 20.5% in the control group to 42.9% in the gestational diabetes/LGA group. The adjusted attributable risk per cent for LGA alone (39.4%) was significantly higher than that for maternal gestational diabetes (16.0%) or pre-existing diabetes alone (15.1%); the risk for the combinations of gestational diabetes/LGA and pre-existing diabetes/LGA were 50.1% and 39.1%, respectively. Further stratification of the pre-existing diabetes groups found the prevalence of being overweight/obese was 21.2% in the type 1/AGA group, 31.4% in the type 1/LGA group (similar to those in the no diabetes groups), 26.7% in the type 2/AGA group and 42.5% in the type 2/LGA group. Breast-feeding was associated with a lower likelihood of being overweight/obese in childhood in all groups except gestational diabetes/LGA and pre-existing diabetes/LGA (both type 1 and type 2).

Conclusion/interpretation LGA is a stronger marker for risk of being overweight/obese in early childhood, compared with maternal diabetes during pregnancy. Rates of being overweight/obese in childhood were highest in LGA children born to mothers with gestational diabetes or pre-existing type 2 diabetes. Breast-feeding was associated with a lower risk of being overweight/obese in childhood in the majority of children; however, this association was not maintained in LGA children of mothers with diabetes.

Keywords Childhood obesity · Gestational diabetes mellitus · Large for gestational age · Pre-existing diabetes

Abbreviations

AGA	Appropriate for gestational age
AHCIP	Alberta Health Care Insurance Population registry
aOR	Adjusted OR
C-section	Caesarean section
ICD	International Classification of Diseases

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-018-4758-0) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

✉ Padma Kaul
pkaul@ualberta.ca

1 Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada

2 Department of Medicine, University of Alberta, 2-132 Li Ka Shing Centre for Health Research Innovation, Edmonton, AB T6G 2E1, Canada

3 Department of Medicine, University of Calgary, Calgary, AB, Canada

Published online: 13 November 2018

Research in context

What is already known about this subject?

- Children who are large at birth are more likely to be obese in early childhood
- Maternal diabetes during pregnancy is associated with excess weight in the offspring during childhood
- Breast-feeding is associated with a lower risk of excess weight in childhood

What is the key question?

- What is a more important contributor to excess weight in childhood: maternal diabetes during pregnancy or being large for gestational age (LGA) at birth? How does breast-feeding in infancy reduce the risk of excess weight in childhood across these exposures?

What are the new findings?

- Both LGA and maternal diabetes during pregnancy are associated with an increased risk of the offspring being overweight/obese in early childhood
- LGA is a stronger marker for risk of being overweight/obese in early childhood than maternal diabetes
- Breast-feeding is associated with a lower risk of being overweight/obese in a majority of children; however, this association is not maintained in LGA children of mothers with diabetes

How might this impact on clinical practice in the foreseeable future?

- Women who are planning to become pregnant need to be advised about risk factors for LGA, such as maternal weight and dysglycaemia during pregnancy

LGA Large for gestational age
SES Socioeconomic status
SGA Small for gestational age

Introduction

The causes of being overweight or obese in childhood are multifactorial. Children who are born large are more likely to be larger in childhood [1]. Maternal weight, pre-pregnancy and gestational weight gain, and maternal diabetes status during pregnancy are established risk factors for having large for gestational age (LGA) infants [2–5]. However, little is known about the relative contribution of LGA and maternal diabetes during pregnancy on the risk of being overweight or obese in early childhood. In 13,037 full-term babies with normal birthweight, Hillier et al found that maternal gestational diabetes was associated with a 28.5% attributable risk of obesity in the first decade of life [6]. In a much smaller study of 84 LGA and 95 appropriate for gestational age (AGA) babies, Boney et al found that LGA children of women with gestational diabetes had the highest rates of childhood obesity at 6 years of age compared with AGA children of women with gestational diabetes and AGA or LGA children of mothers without gestational diabetes [7]. Neither study included women with pre-existing diabetes mellitus.

Breast-feeding has been shown to be inversely associated with the development of obesity [8–10] and women with diabetes are routinely advised to breast-feed [11, 12]. In the Growing Up Today Study (GUTS), survey data collected on 15,253 offspring (aged 9–14 years) of women included in the Nurses' Health Study II ($n = 116{,}000$), showed breast-feeding to be inversely associated with obesity in the children of mothers with diabetes ($n = 417$ gestational diabetes and 56 pre-existing diabetes), but the association did not reach statistical significance (adjusted [a]OR 0.62 [95% CI 0.24, 1.60]) [13]. There are currently no data on the extent to which breast-feeding modulates the risk of being overweight or obese in childhood in LGA and AGA babies overall, and after taking maternal diabetes status during pregnancy into account.

Accordingly, we used data from a large contemporary population-based cohort residing within a defined geographic region with universal healthcare coverage to examine the association of maternal diabetes, LGA and breast-feeding with being overweight or obese, in pre-school-aged children.

Methods

Study population We included all mothers who delivered live infants between 1 January 2005 and 31 August 2013, and their offspring, who were residing in the Calgary Zone, AB, Canada. The Calgary Zone encompasses a 39,300 km^2 area and serves a population of approximately 1.5 million people, the majority of whom (>80%) reside in Calgary, the largest city in the province of AB, Canada [14].

Data sources and linkage The longitudinal pregnancy–birth cohort used for the study has been described in detail previously [15–17]. In brief, hospitalisation records and outpatient records, including emergency department visits, hospital outpatient clinic visits and visits to physician offices, of the mother and the offspring were linked, using unique scrambled identifiers, to the Vital Statistics Birth Registry. In addition to being the conduit for deterministic linkage between maternal and child records, the birth registry includes data on birthweight, gestational age, parity, birth order and singleton/multiple birth status. Maternal and child records were also linked to the Alberta Health Care Insurance Population (AHCIP) registry, which includes demographic data, residential postal code, treaty status (prior to 2009) and data on migration for all Alberta residents registered for provincial health insurance. Lastly, the 2011 census data from Statistics Canada were linked at the Forward Sortation Area (FSA) level, based on the first three values of the postal code.

For the current study, the longitudinal pregnancy–birth cohort data were linked with the public health immunisation database for the time period January 2009–August 2017, which includes data on immunisation status, breast-feeding status at each immunisation visit and the child's height and weight at their pre-school immunisation visit, which occurs between 4 and 6 years of age. The majority of children residing in the Calgary Zone are routinely immunised. Between 2009 and 2016, the percentage of children who had received the first dose of the DTaP-IPV-Hib vaccine by age 2 years ranged from 95% to 97% [18].

Maternal diabetes status during pregnancy Previously validated algorithms, based on International Classification of Diseases (ICD) versions 9 and 10 (www.icd9data.com/2007/Volume1, http://apps.who.int/classifications/icd10/browse/2016/en and https://www.cihi.ca/en/icd_10_ca_vol1_2009_en.pdf) were used to identify women with pre-existing diabetes and gestational diabetes during pregnancy [19–21]. The list of ICD codes for pre-existing diabetes, gestational diabetes and other comorbidities are provided in the electronic supplementary material (ESM) Table 1. Women with a hospitalisation or at least two outpatient records (either emergency department, outpatient clinics or physician office visits) with a code for diabetes in a non-gestational period prior to pregnancy or who had diabetes coded on their delivery hospitalisation record were categorised as having pre-existing diabetes. This algorithm for pre-existing diabetes has been found to have a sensitivity of 92% and a specificity of 100% [19]. Women with a hospitalisation or at least two outpatient records for gestational diabetes during pregnancy were categorised as having gestational diabetes. We have previously established the sensitivity and specificity for this gestational diabetes algorithm to be 92% and 97%, respectively, using laboratory values as the gold standard [20].

Breast-feeding status The immunisation database captures information on the child's nutrition source at all visits that occur prior to 24 months of age. The time of each visit (and the range it covers) is as follows: 2 months (5 weeks to 3 months); 4 months (4 to 5 months); 6 months (6 to 7 months); 12 months (12 to 17 months); and 18 months (18 to 23 months). The categories used to describe the feeding status of the child are provided in ESM Table 2. If a child was reported as having 'no breast milk' or 'no breast milk in the last 7 days' or 'solids and no breast milk in last 7 days' at the 2 month or 4 month visit, he/she was considered as not being breast-fed; otherwise a child was considered to have been breast-fed prior to 5 months.

Other maternal and child covariates Hypertensive disorders during pregnancy were identified if they were coded on the delivery hospitalisation records. Women with medical conditions prior to pregnancy, including pre-existing cardiovascular disease, pre-existing hypertension, lupus, epilepsy, chronic obstructive pulmonary disease, liver disease and renal disease, were identified based on the delivery hospitalisation and any previous hospitalisations as of 1 April 1997. The delivery hospitalisation record was used to identify children born via Caesarean section (C-section). The AHCIP data were used to identify women who had identified themselves as Status Aboriginal. This flag was available for all residents prior to 2009. Previously validated naming algorithms were used to identify mothers of South Asian and Chinese ethnicities [22, 23]. Women were categorised as living in rural or urban areas based on the first numerical digit of their postal code. The annual household income at the neighbourhood level from census data was used as a measure of socioeconomic status (SES). Previously developed criteria were used to categorise children as LGA or small for gestational age (SGA), based on their birthweight [24]. Children who were SGA at birth were excluded from the analysis so as not to confound overweight/obesity rates in the control group.

Pre-school overweight/obesity status The main outcome of interest was overweight/obesity status of the child at his/her pre-school immunisation visit, which occurred between ages 4 and 6 years. Using the height/weight data collected at this time point, we calculated the child's BMI as weight/(height × height) (kg/m^2). Pre-school children were categorised as being overweight/obese based on the age- and sex-specific measures from the WHO [25]. For children aged 5 to 19 years, the WHO defines overweight as a BMI-for-age greater than one

SD above the WHO Growth Reference median, and obesity as greater than two SDs above the WHO Growth Reference median [26]. Children who were 4 years of age at their pre-school immunisation visit were categorised as being overweight/obese using the same definition [27].

Statistical analysis We categorised children included in the study into six groups according to maternal diabetes status during pregnancy and birthweight as follows: (1) no diabetes/AGA (control group); (2) no diabetes/LGA; (3) gestational diabetes/AGA; (4) gestational diabetes/LGA; (5) pre-existing diabetes/AGA; and (6) pre-existing diabetes/LGA. We compared maternal characteristics and child characteristics at birth and pre-school across the six groups. Categorical variables were presented using counts and percentages and compared using the χ^2 test. Continuous variables were presented using means and SDs and compared using one-way ANOVA. Our unit of analysis was the child; therefore, maternal characteristics of women having multiple children were included multiple times in reported statistics.

We used multivariate generalised estimating equation (GEE) logistic regression models with exchangeable covariance matrices to examine the likelihood of the combined endpoint of the child being categorised as overweight/obese between 4 to 6 years of age across our groups of interest. We accounted for correlations between pregnancies of the same mother and included the following potential confounding variables as covariates in our final model: maternal age (per 5 years), maternal ethnicity, urban residence, parity, pre-existing medical conditions, hypertensive disorders of pregnancy, C-section delivery and annual median household income (per Canadian $10,000).

We calculated the attributable risk percentage, i.e., the proportion of cases of childhood overweight/obesity that can be attributed to being exposed to maternal diabetes during pregnancy or being LGA, or both, relative to the control group of no diabetes/AGA, as well as the population attributable fraction, i.e., the proportional reduction at a population-level, using adjusted relative risks calculated from a log-binomial regression model with the covariates mentioned above.

We examined the impact of breast-feeding status prior to 5 months on being overweight/obese in childhood, overall and within each group, after accounting for the variables mentioned above. We used inverse probability weighting to reduce selection bias [28] as a result of differential capture of breast-feeding data. Logistic regression was used to estimate the probability of having breast-feeding data for participants in each group. The inverse of each participant's probability of having breast-feeding data was included in the model examining the association between breast-feeding and being overweight/obese in childhood within each group.

Finally, in an exploratory analysis, we further categorised women with pre-existing diabetes as having type 1 or type 2 based on the presence of a code for type 1 diabetes in either an inpatient (including delivery hospitalisation) or ambulatory clinic setting between 2002 and the time of delivery. We examined rates of being overweight/obese in childhood in type 1/AGA, type 1/LGA, type 2/AGA and type 2/LGA groups, overall and by breast-feeding status.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Ethics approval for this study was obtained from the University of Alberta IRB (number Pro00020230). Given the de-identified nature of the data, informed consent was waived for this study.

Results

There were 150,901 live births of mothers residing in the Calgary Zone between 1 January 2005 and 31 August 2013. BMI data from their pre-school immunisation visit (scheduled between 4 and 6 years age) were available for 87,222 children born in the Calgary Zone and for 3660 children born elsewhere in Alberta (Fig. 1). The mothers of children for whom BMI data were available were slightly older, more likely nulliparous, of higher SES and had slightly higher rates of gestational diabetes and hypertension during pregnancy compared with mothers of children for whom BMI data were not available (ESM Table 3). After excluding 10,156 children who were born SGA, our final cohort consisted of 81,226 children of 65,079 mothers.

Overall, 69,506 (85.6%) children were in the no diabetes/AGA; 5926 (7.3%) in the no diabetes/LGA; 4563 (5.6%) in the gestational diabetes/AGA; 573 (0.7%) in the gestational diabetes/LGA; 480 (0.6%) in the pre-existing diabetes/AGA and 178 (0.2%) in the pre-existing diabetes/LGA groups (Table 1). The proportion of LGA increased across maternal diabetes categories: from 8% in women with no diabetes to 11% in women with gestational diabetes and 27% in women with pre-existing diabetes. Maternal characteristics differed significantly across the six groups. There were higher proportions of Chinese and South Asian mothers in the gestational diabetes and pre-existing diabetes groups. Mothers who gave birth to LGA infants or had diabetes during pregnancy were more likely multiparous than mothers in the control group. Hypertensive disorders during pregnancy ranged from 6.7% in the control group to 22.5% in the pre-existing diabetes/LGA group. More than two-thirds (68.5%) of children in the pre-existing diabetes/LGA group were born via C-section compared with 27.7% of children in the control group.

Overall, 17,811 (21.9%) children were either overweight or obese at the time of their pre-school immunisation visit (Table 1). In multivariate logistic regression, relative to the control group, the gestational diabetes/LGA group had the highest aOR for being overweight/obese (2.79 [95% CI 2.35, 3.30]; Table 2). The risk of being overweight/obese was similar

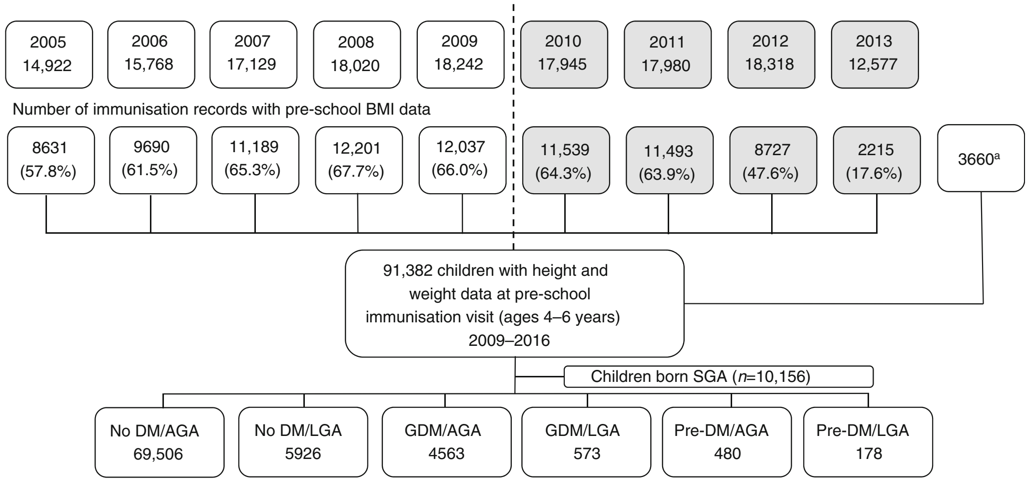

Fig. 1 Participant flow diagram. Grey boxes indicate time periods for which children may not have been old enough to receive their pre-school immunisation visit. [a]Children with pre-school height and weight data who were born to mothers residing outside the Calgary Zone, but within Alberta. DM, diabetes mellitus; GDM, gestational diabetes mellitus; pre-DM: pre-existing diabetes mellitus

in the no diabetes/LGA group (aOR 2.01 [95% CI 1.90, 2.13]) and the pre-existing diabetes/LGA group (aOR 2.05 [95% CI 1.50, 2.79]). Diabetes during pregnancy (either gestational or pre-existing) in the absence of LGA was associated with a 25% higher risk of being overweight/obese in childhood. Other factors positively associated with being overweight/obese in childhood were being Status Aboriginal, maternal hypertensive disorders during pregnancy and C-section delivery. Factors inversely associated with being overweight/obese in childhood were Chinese ethnicity, increasing maternal age, multiparity and higher socioeconomic status.

Compared with the control group, the adjusted attributable risk per cent of LGA alone (39.4% [95% CI 37.0%, 41.7%]) was more than twice that of gestational diabetes alone (16.0% [95% CI 11.3%, 20.5%]) or pre-existing diabetes alone (15.1% [95% CI −0.2%, 28%]; Fig. 2). The adjusted attributable risk percentage of gestational diabetes/LGA and pre-existing diabetes/LGA on childhood overweight/obesity status was 50.1% (95% CI 44.9%, 54.7%) and 39.1% (95% CI 26%, 49.9%), respectively. Adjusted population attributable fractions for LGA alone, gestational diabetes alone, pre-existing diabetes alone, gestational diabetes/LGA and pre-existing diabetes/LGA were 5.00%, 1.14%, 0.13%, 0.85% and 0.18%, respectively.

Breast-feeding data were available for 56,164 (69%) children. Mothers of children for whom breast-feeding data were available were slightly older, more likely to live in urban areas, more likely to be of Chinese or South Asian ethnicity and had higher rates of gestational diabetes compared with mothers of children for whom breast-feeding data were not available (ESM Table 4). Breast-feeding rates differed significantly across the six groups: from 80% in the no diabetes/AGA and no diabetes/LGA groups to 70% in the gestational diabetes/LGA and pre-existing diabetes/LGA groups at 2 months; and from 73% in the no diabetes/AGA and no diabetes/LGA groups to 60% in the gestational diabetes/LGA and pre-existing diabetes/LGA groups at 4 months (ESM Fig. 1). Compared with mothers of infants who were not breast-fed, mothers of infants who were breast-fed were older, more likely to be of Chinese ethnicity, more likely to reside in areas with higher annual household income, more likely to be multiparous and had lower rates of gestational diabetes, pre-existing diabetes, hypertension during pregnancy, pre-existing medical conditions and C-section (ESM Table 5). Overall, rates of being overweight/obese were significantly higher in children who were not breast-fed (25.7%) than in children who were breast-fed (19.8%; Table 3). Breast-feeding, after adjusting for other maternal and birth characteristics, was associated with a lower likelihood of being overweight/obese in childhood, overall, and in the following groups: no diabetes/AGA; no diabetes/LGA; gestational diabetes/AGA; pre-existing diabetes/AGA. However, there was no association between breast-feeding and being overweight/obese in childhood in the gestational diabetes/LGA and pre-existing diabetes/LGA groups.

In the exploratory analysis stratifying the pre-existing diabetes groups according to type 1 or type 2 diabetes, we found that a higher proportion (41.0%) of women with type 1 diabetes had LGA babies than women with type 2 (18.2%; Table 4). Rates of being overweight/obese were highest in the type 2/LGA group (42.5%), followed by those in the type 1/LGA group (31.4%). In type 1/AGA and type 2/AGA groups, rates of being overweight/obese in childhood were lower in breast-fed infants than in non-breast-fed infants. However, this was not the case in type 1/LGA and type 2/LGA groups.

Discussion

This is the first population-based study to examine the relative contribution of maternal diabetes, excess birthweight and

Table 1 Maternal characteristics, child characteristics at birth and at pre-school age (4 to 6 years), stratified by maternal diabetes status during pregnancy and weight for gestational age at birth

	No diabetes/ AGA	No diabetes/ LGA	Gestational diabetes/ AGA	Gestational diabetes/ LGA	Pre-existing diabetes/ AGA	Pre-existing diabetes/ LGA	*p* value
Children, *n*	69,506	5926	4563	573	480	178	
Mothers, *n*	54,495	5420	4041	546	418	159	
Maternal characteristics							
Maternal age at delivery, years, mean (SD)	30.9 (5.0)	31.3 (4.9)	33.3 (4.9)	33.0 (4.9)	33.0 (5.0)	32.5 (5.6)	<0.01
Ethnicity, *n*, %							<0.01*
General population	61,694 (88.8)	5486 (92.6)	3539 (77.6)	504 (88.0)	405 (84.4)	165 (92.7)	
Status Aboriginal	706 (1.0)	145 (2.4)	29 (0.6)	12 (2.1)	10 (2.1)	4 (2.2)	
South Asian	3047 (4.4)	126 (2.1)	431 (9.4)	25 (4.4)	30 (6.3)	6 (3.4)	
Chinese	4059 (5.8)	169 (2.9)	564 (12.4)	32 (5.6)	35 (7.3)	3 (1.7)	
Multiparous, *n* (%)	36,581 (52.6)	3820 (64.5)	2712 (59.4)	406 (70.9)	287 (59.8)	112 (62.9)	<0.01
Urban residence, *n* (%)	66,290 (95.4)	5613 (94.7)	4451 (97.5)	543 (94.8)	451 (94.0)	166 (93.3)	<0.01
2010 annual household income, $, mean (SD)[a]	87,037 (20,781)	87,913 (20,663)	85,113 (19,780)	84,652 (20,080)	85,315 (20,160)	84,571 (17,147)	<0.01
Hypertensive disorders in pregnancy, *n* (%)	4632 (6.7)	374 (6.3)	478 (10.5)	78 (13.6)	94 (19.6)	40 (22.5)	<0.01
Pre-existing medical conditions, *n* (%)	885 (1.3)	84 (1.4)	77 (1.7)	9 (1.6)	24 (5.0)	13 (7.3)	<0.001
C-section, *n* (%)	19,250 (27.7)	2293 (38.7)	1722 (37.7)	308 (53.8)	199 (41.5)	122 (68.5)	<0.01
Child characteristics at birth							
Female, *n* (%)	33,942 (48.8)	2896 (48.9)	2183 (47.8)	279 (48.7)	234 (48.8)	90 (50.6)	0.86
Weight, g, mean (SD)	3310.5 (461.4)	4160.6 (415.2)	3214.0 (467.0)	4067.6 (427.4)	3148.5 (546.0)	3943.6 (471.1)	<0.01
Child characteristics at age 4 to 6 years							
Age, *n* (%)							<0.01*
4 years	46,510 (66.9)	3787 (63.9)	3179 (69.7)	380 (66.3)	331 (69.0)	107 (60.1)	
5 years	20,186 (29.0)	1900 (32.1)	1228 (26.9)	175 (30.5)	134 (27.9)	61 (34.3)	
6 years	2810 (4.0)	239 (4.0)	156 (3.4)	18 (3.1)	15 (3.1)	10 (5.6)	
Height, cm, mean (SD)	108.9 (5.7)	111.5 (5.8)	108.4 (5.7)	110.7 (5.9)	108.4 (5.6)	110.3 (6.7)	<0.01
Weight, kg, mean (SD)	18.8 (3.1)	20.5 (3.4)	18.9 (3.4)	20.7 (3.9)	18.9 (3.8)	20.5 (4.3)	<0.01
BMI, kg/m^2, mean (SD)	15.8 (1.6)	16.4 (1.7)	16.0 (1.9)	16.8 (2.1)	16.0 (2.1)	16.7 (2.1)	<0.01
Childhood overweight/obesity, *n* (%)	14,226 (20.5)	2063 (34.8)	1092 (23.9)	246 (42.9)	120 (25.0)	64 (36.0)	<0.01
Overweight, *n* (%)	10,738 (15.4)	1539 (26.0)	691 (15.1)	158 (27.6)	81 (16.9)	36 (20.2)	<0.01
Obese, *n* (%)	3488 (5.0)	524 (8.8)	401 (8.8)	88 (15.4)	39 (8.1)	28 (15.7)	<0.01

*p<0.01 by χ^2 test of independence comparing characteristic across 6 groups

[a] Annual household income available at the neighbourhood level, in Canadian $

Table 2 Factors associated with being overweight/obese in pre-school-aged children (4–6 years)

Variable	OR (95% CI) for being overweight/obese	*p* value
Group		
No diabetes/AGA	Ref.	
No diabetes/LGA	2.01 (1.90, 2.13)	<0.01
Gestational diabetes/AGA	1.25 (1.16, 1.34)	<0.01
Gestational diabetes/LGA	2.79 (2.35, 3.30)	<0.01
Pre-existing diabetes/AGA	1.25 (1.00, 1.56)	0.05
Pre-existing diabetes/LGA	2.05 (1.50, 2.79)	<0.01
Maternal age per 5 years	0.92 (0.91, 0.94)	<0.01
Ethnicity		
General population	Ref.	
Chinese	0.7 (0.64, 0.76)	<0.01
South Asian	1.05 (0.97, 1.14)	0.24
Status Aboriginal	1.54 (1.33, 1.79)	<0.01
Urban	0.98 (0.90, 1.07)	0.67
Multiparous	0.95 (0.92, 0.99)	<0.01
Pre-existing medical conditions	1.12 (0.97, 1.29)	0.12
Hypertensive disorders in pregnancy	1.24 (1.17, 1.32)	<0.01
C-section delivery	1.15 (1.11, 1.20)	<0.01
2010 annual household income per $10,000[a]	0.95 (0.94, 0.96)	<0.01

Ref., reference

[a] Annual household income available at the neighbourhood level, in Canadian $

breast-feeding on the risk of being overweight and obese in childhood. In a large contemporary cohort of 81,226 children, the proportion who were overweight/obese at their pre-school immunisation visit (between ages 4 and 6 years) differed significantly by maternal diabetes status during pregnancy and LGA vs AGA status at birth: ranging from a low of 20.5% in the control group of no diabetes/AGA to a high of 42.9% in the gestational diabetes/LGA group. The attributable risk of LGA alone on being overweight/obese in childhood was significantly higher than that of maternal gestational diabetes or pre-existing diabetes alone. When the pre-existing diabetes group was further stratified into type 1 and type 2, rates of being categorised as overweight/obese in the type 1/AGA and type 1/LGA groups were similar to those in the no diabetes/AGA and no diabetes/LGA, respectively. In fact, LGA children of mothers with gestational diabetes or pre-existing type 2 diabetes had the highest rates of being overweight/obese in childhood. In the subset of children (70%) for whom breast-feeding data were available, we found that breast-feeding in the first 5 months was associated with a significantly lower risk of being overweight/obese in childhood in all groups except gestational diabetes/LGA and pre-existing diabetes/LGA (either type 1 or type 2).

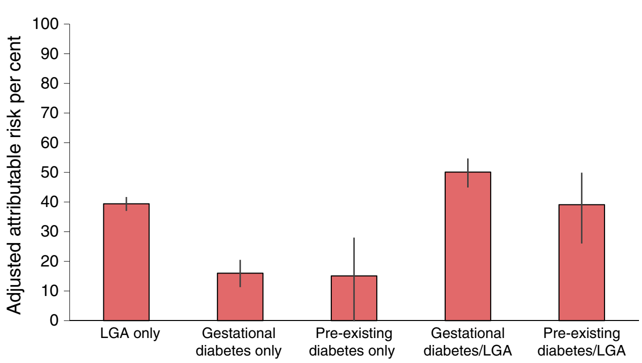

Fig. 2 Adjusted attributable risk per cent of maternal diabetes during pregnancy and LGA on being overweight/obese at age 4–6 years. Error bars represent 95% CI

Being LGA at birth is a potentially modifiable factor and our study highlights the need to better understand the factors associated with its incidence in order to develop strategies to reduce the number of children who are overweight/obese. We believe that LGA may be a surrogate marker for two unmeasured variables in our study: maternal weight (either excess pre-pregnancy or gestational weight gain) or glycaemic control during pregnancy. Maternal weight is an established predictor of LGA [29]. Previous studies have found women with gestational diabetes or type 2 diabetes to have higher BMI compared with women with type 1 [30–32]. Our finding that the rates of being overweight/obese in childhood were higher in the gestational diabetes/LGA (42.9%) and type 2/LGA (42.5%) than in the type 1/LGA (31.4%) and also in the gestational diabetes/AGA (23.9%) and type 2/AGA (26.7%) than in the type 1/AGA (21.2%) supports the increasing emphasis on maternal weight as a major contributor to excessive weight in children [33–35].

Table 3 Association between breast-feeding prior to 5 months and being overweight/obese in childhood

Population	*n*	Breast-fed *n* (%)	Overweight/obesity in breast-fed infants, *n* (%)	Overweight/obesity in non-breast-fed infants, *n* (%)	aOR and 95% CI[a]	*p* value
Overall	56,164	40,274 (71.7)	7976 (19.8)	4086 (25.7)	0.75 (0.72, 0.78)	<0.01
No diabetes/AGA	47,876	34,532 (72.1)	6344 (18.4)	3212 (24.1)	0.74 (0.71, 0.78)	<0.01
No diabetes/LGA	3981	2887 (72.5)	946 (32.8)	432 (39.5)	0.79 (0.68, 0.91)	<0.01
Gestational diabetes/AGA	3431	2315 (67.5)	507 (21.9)	319 (28.6)	0.75 (0.64, 0.89)	<0.01
Gestational diabetes/LGA	414	253 (61.1)	106 (41.9)	67 (41.6)	1.04 (0.68, 1.58)	0.84
Pre-existing diabetes/AGA	339	213 (62.8)	44 (20.7)	41 (32.5)	0.61 (0.36, 1.03)	0.02
Pre-existing diabetes/LGA	123	74 (60.2)	29 (39.2)	15 (30.6)	1.61 (0.72, 3.61)	0.14

[a] Adjusted for maternal age at delivery, ethnicity, urban residence, parity, hypertensive disorders in pregnancy, pre-existing medical conditions, 2010 annual household income at the neighbourhood level, C-section delivery and expected likelihood of having data on breast-feeding

The clear relationship between the type of diabetes and LGA rate in our study—8% in women with no diabetes, 11% in women with gestational diabetes and 27% in women with pre-existing diabetes—suggests that LGA may also be a marker for worse dysglycaemia. When the pre-existing diabetes group was further stratified, the proportion of type 2 participants with LGA was 18% compared with 41% in participants with type 1, a group that struggles the most with achieving glycaemic control [36]. The higher rate of LGA in the group with pre-existing type 2 diabetes compared with the group with gestational diabetes—two groups with likely comparable BMI—probably results from worse dysglycaemia in the former group.

Relative to the control group of no diabetes/AGA, the gestational diabetes/AGA and pre-existing diabetes/AGA groups had a 25% higher risk of being overweight/obese in early childhood. However, the risk of being overweight/obese was double (in the no diabetes/LGA and pre-existing diabetes/LGA groups) and almost triple (in the gestational diabetes/LGA group) that of the control group in children who were born LGA. Therefore, regardless of the reason, our study establishes that a larger proportion of excess weight in childhood can be attributed to LGA than maternal diabetes during pregnancy. We hope that these findings will reinforce public health campaigns advising women who are planning to get pregnant that, just like smoking, alcohol consumption and other lifestyle choices, their weight prior to, and weight gain and glycaemic control during, pregnancy may have a significant impact on the future health of their children.

In the control group (no diabetes/AGA), the rate of pre-school-aged children being overweight/obese was 20.5%, suggesting that factors beyond maternal diabetes and birthweight are at play. Breast-feeding has been found to be an effective strategy to reduce the incidence of being overweight/obese in childhood [8–10]. In our study, we found breast-feeding rates in the first 5 months of life to be significantly lower in women with gestational diabetes and pre-existing diabetes, particularly in those with LGA infants, compared with the control group. Breast-feeding was associated with a reduction in the risk of being overweight/obese in the no diabetes/AGA, no diabetes/LGA, gestational diabetes/AGA and pre-existing diabetes/AGA groups. This was even true in the type 1/AGA and type 2/AGA subsets of the pre-existing diabetes groups. However, its protective effect did not extend to the gestational diabetes/LGA and pre-existing diabetes/LGA groups (overall, or in the

Table 4 Childhood overweight/obesity outcomes in pre-existing diabetes groups further stratified into type 1 and type 2 diabetes subgroups

Maternal characteristics	Type 1/AGA	Type 1/LGA	Type 2/AGA	Type 2/LGA
Children, *n*	151	105	329	73
Mothers, *n*	126	90	295	69
Childhood overweight/obesity, *n* (%)	32 (21.2)	33 (31.4)	88 (26.7)	31 (42.5)
Overweight, *n* (%)	22 (14.6)	22 (21.0)	59 (17.9)	14 (19.2)
Obese, *n* (%)	10 (6.6)	11 (10.5)	29 (8.8)	17 (23.3)
Breast-feeding data available	107	71	232	52
Children breast-fed (*n*)	67	44	146	30
Overweight/obesity, *n* (%)	10 (14.9)	14 (31.8)	34 (23.3)	15 (50.0)
Children not breast-fed (*n*)	40	27	86	22
Overweight/obesity, *n* (%)	12 (30.0)	7 (25.9)	29 (33.7)	8 (36.4)

type 1/LGA and type 2/LGA subgroups). If, as hypothesised above, LGA is a marker for poor glycaemic control during pregnancy, further research is needed to examine whether, as suggested previously, glucose and insulin levels in the breast milk of mothers with diabetes may increase, rather than protect against, the risk of childhood obesity [37, 38]. It must be noted that the numbers of children in the gestational diabetes/LGA and pre-existing diabetes/LGA groups were relatively small compared with the other groups and our findings need to be confirmed in larger observational cohorts. More information is also needed to determine whether postnatal care practices, such as supplementation by formula, may account for the observed lack of association between breast-feeding and being overweight/obese in childhood in LGA children of mothers with diabetes.

Our study is large, contemporary and population-based, and its findings are therefore highly generalisable. However, it has several limitations. In addition to the lack of data on maternal weight and glycaemic control during pregnancy addressed previously, we acknowledge that we did not have child BMI data and breast-feeding data for all children. While we found some differences in demographic characteristics between mothers of children with and without these data, we do not believe that these missing data impact the internal validity of our study findings. As with maternal weight, we were limited by our inability to assess the impact of paternal weight, which may be correlated with LGA. Our study did not take into account any treatments that women with gestational diabetes and pre-existing diabetes may have received and their impact on the outcomes of interest. The breast-feeding data were not collected on a daily basis and were instead available at specific time points. Therefore, although we considered children who were not exclusively breast-fed prior to 5 months as not being breast-fed, there may be some variability in the actual duration of breast-feeding in these children. Our dichotomised definition of breast-feeding prior to 5 months does not take into account supplemental formula feeding and its impact on being overweight/obese in childhood. Although BMI is the most common metric used to identify children who are overweight or obese, it may not be highly correlated with total fat mass or percentage body fat, particularly in young children. Finally, our study used ICD codes to identify women with gestational diabetes and pre-existing diabetes. However, the algorithms used to identify these women were based on data linked across healthcare settings (hospitals, outpatient clinics and physician offices) and have been previously validated [20]. Although there may be some misclassification, it is likely to be non-differential and thus bias our results towards the null. Further stratification of the pre-existing diabetes group was based on the presence of type 1 diabetes mellitus codes being present in the inpatient or ambulatory records only, and future validation using laboratory, treatment and outpatient (physician office) diagnoses are needed to ascertain the accuracy of this categorisation.

Conclusions In a large contemporary population-based cohort, we found LGA to be a stronger marker for risk of being overweight/obese in early childhood than maternal diabetes during pregnancy alone. There is a need to better understand pregnancy factors associated with the incidence of LGA, such as maternal weight and dysglycaemia, to develop strategies to reduce the number of children who are overweight/obese. Breast-feeding was associated with a lower risk of being overweight/obese in childhood in a majority of children; however, this association was not maintained in LGA babies of mothers with diabetes. Further research into the components of breast milk and infant feeding practices of mothers with diabetes is required to identify reasons for this lack of association.

Acknowledgements This study is based on data provided by Alberta Health. We thank Kenneth Morrison at Alberta Health for assistance in creating the linked database. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. The immunisation data were made available by R. Andersen and J. Coldham from the Calgary Zone Public Health System, Alberta Health Services, AB, Canada. The authors acknowledge L. Luoma for her critical review and editing of the manuscript.

Data availability Data are proprietary and not publicly available. Aggregate data are available upon request.

Funding This study was funded by the Canadian Institutes of Health Research (CIHR) through a peer-reviewed operating grant (number RN125845–251412). The funding agencies did not have input into study design, data collection, interpretation of results, manuscript preparation or approval for submission.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement PK, SLB, LED, ROY and EAR conceived the study. PK, LED, and EAR obtained funding. PK and SLB drafted the manuscript. AS conducted all analyses. All authors edited subsequent versions of the manuscript and approved the final manuscript for submission. PK is the guarantor of this manuscript.

References

1. Baird J, Fisher D, Lucas P et al (2005) Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 331(7522):929. https://doi.org/10.1136/bmj.38586.411273.E0
2. Kc K, Shakya S, Zhang H (2015) Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 66(Suppl 2):14–20. https://doi.org/10.1159/000371628
3. He X-J, Qin F-Y, Hu C-L et al (2015) Is gestational diabetes mellitus an independent risk factor for macrosomia: a meta-analysis? Arch Gynecol Obstet 291(4):729–735. https://doi.org/10.1007/s00404-014-3545-5
4. Mitanchez D, Burguet A, Simeoni U (2014) Infants born to mothers with gestational diabetes mellitus: mild neonatal effects, a long-term threat to global health. J Pediatr 164(3):445–450. https://doi.org/10.1016/j.jpeds.2013.10.076

5. Tyrrell J, Richmond RC, Palmer TM et al (2016) Genetic evidence for causal relationships between maternal obesity-related traits and birth weight. JAMA 315(11):1129–1140. https://doi.org/10.1001/jama.2016.1975
6. Hillier TA, Pedula KL, Vesco KK et al (2016) Impact of maternal glucose and gestational weight gain on child obesity over the first decade of life in normal birth weight infants. Matern Child Health J 20(8):1559–1568. https://doi.org/10.1007/s10995-016-1955-7
7. Boney CM, Verma A, Tucker R, Vohr BR (2005) Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 115(3):e290–e296. https://doi.org/10.1542/peds.2004-1808
8. Owen CG, Martin RM, Whincup PH et al (2005) Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics 115(5):1367–1377. https://doi.org/10.1542/peds.2004-1176
9. Arenz S, Rückerl R, Koletzko B, Kries von R (2004) Breast-feeding and childhood obesity–a systematic review. Int J Obes Relat Metab Disord 28(10):1247–1256. https://doi.org/10.1038/sj.ijo.0802758
10. Yan J, Liu L, Zhu Y et al (2014) The association between breastfeeding and childhood obesity: a meta-analysis. BMC Public Health 14(1):1267. https://doi.org/10.1186/1471-2458-14-1267
11. Dugas C, Perron J, Kearney M et al (2017) Postnatal prevention of childhood obesity in offspring prenatally exposed to gestational diabetes mellitus: where are we now? Obes Facts 10(4):396–406. https://doi.org/10.1159/000477407
12. Gunderson EP (2008) Breast-feeding and diabetes: long-term impact on mothers and their infants. Curr Diab Rep 8(4):279–286. https://doi.org/10.1007/s11892-008-0050-x
13. Mayer-Davis EJ, Rifas-Shiman SL, Zhou L et al (2006) Breast-feeding and risk for childhood obesity: does maternal diabetes or obesity status matter? Diabetes Care 29(10):2231–2237. https://doi.org/10.2337/dc06-0974
14. Alberta Health Services Calgary Zone. Available from www.albertahealthservices.ca/about/calgaryzone.aspx. Accessed 5 Feb 2018
15. Kaul P, Savu A, Nerenberg KA et al (2015) Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabet Med 32(2):164–173. https://doi.org/10.1111/dme.12635
16. Bowker SL, Savu A, Yeung RO et al (2017) Patterns of glucose-lowering therapies and neonatal outcomes in the treatment of gestational diabetes in Canada, 2009-2014. Diabet Med 34(9):1296–1302. https://doi.org/10.1111/dme.13394
17. Beka Q, Bowker S, Savu A et al (2017) Development of perinatal mental illness in women with gestational diabetes mellitus: a population-based cohort study. Can J Diabetes. https://doi.org/10.1016/j.jcjd.2017.08.005
18. Alberta Health. Interactive health data application. Available from www.ahw.gov.ab.ca/IHDA_Retrieval/selectSubCategoryParameters.do. Accessed 5 Feb 2018
19. Allen VM, Dodds L, Spencer A et al (2012) Application of a national administrative case definition for the identification of pre-existing diabetes mellitus in pregnancy. Chronic Dis Inj Can 32(3):113–120
20. Bowker SL, Savu A, Donovan LE et al (2017) Validation of administrative and clinical case definitions for gestational diabetes mellitus against laboratory results. Diabet Med 34(6):781–785. https://doi.org/10.1111/dme.13271
21. Bowker SL, Savu A, Lam NK et al (2015) Validation of administrative data case definitions for gestational diabetes mellitus. Diabet Med 34(1):51–55. https://doi.org/10.1111/dme.13030
22. Shah BR, Chiu M, Amin S et al (2010) Surname lists to identify south Asian and Chinese ethnicity from secondary data in Ontario, Canada: a validation study. BMC Med Res Methodol 10(1):42. https://doi.org/10.1186/1471-2288-10-42
23. Quan H, Wang F, Schopflocher D et al (2006) Development and validation of a surname list to define Chinese ethnicity. Med Care 44(4):328–333. https://doi.org/10.1097/01.mlr.0000204010.81331.a9
24. Kramer MS, Platt RW, Wen SW et al (2001) A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 108(2):e35–e35. https://doi.org/10.1542/peds.108.2.e35
25. WHO Media Centre: Obesity and overweight. Available from www.who.int/mediacentre/factsheets/fs311/en/. Accessed 8 Jan 2018
26. WHO Growth reference 5–19 years: BMI-for-age (5–19 years). Available from www.who.int/growthref/who2007_bmi_for_age/en/. Accessed 6 Dec 2017
27. WHO Child growth standards: BMI-for-age (2–5 years). Available from www.who.int/childgrowth/standards/b_f_a_tables_z_boys/en/. Accessed 6 Dec 2017
28. Hernan MA, Hernandez-Diaz S, Robins JM (2004) A structural approach to selection bias. Epidemiology 15(5):615–625. https://doi.org/10.1097/01.ede.0000135174.63482.43
29. Yu Z, Han S, Zhu J et al (2013) Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS One 8(4):e61627. https://doi.org/10.1371/journal.pone.0061627
30. Owens LA, Sedar J, Carmody L, Dunne F (2015) Comparing type 1 and type 2 diabetes in pregnancy- similar conditions or is a separate approach required? BMC Pregnancy Childbirth 15(1):69. https://doi.org/10.1186/s12884-015-0499-y
31. Hillman N, Herranz L, Vaquero PM et al (2006) Is pregnancy outcome worse in type 2 than in type 1 diabetic women? Diabetes Care 29(11):2557–2558. https://doi.org/10.2337/dc06-0680
32. Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB (2001) Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. Diabetes Endocrine Pregnancy Outcome Study in Toronto. QJM 94(7):347–356. https://doi.org/10.1093/qjmed/94.7.347
33. Bider-Canfield Z, Martinez MP, Wang X et al (2017) Maternal obesity, gestational diabetes, breastfeeding and childhood overweight at age 2 years. Pediatr Obes 12(2):171–178. https://doi.org/10.1111/ijpo.12125
34. Kim SY, Sharma AJ, Callaghan WM (2012) Gestational diabetes and childhood obesity: what is the link? Curr Opin Obstet Gynecol 24(6):376–381. https://doi.org/10.1097/GCO.0b013e328359f0f4
35. Donovan LE, Cundy T (2015) Does exposure to hyperglycaemia in utero increase the risk of obesity and diabetes in the offspring? A critical reappraisal. Diabet Med 32(3):295–304. https://doi.org/10.1111/dme.12625
36. Murphy HR, Steel SA, Roland JM et al (2011) Obstetric and perinatal outcomes in pregnancies complicated by Type 1 and Type 2 diabetes: influences of glycaemic control, obesity and social disadvantage. Diabet Med 28(9):1060–1067. https://doi.org/10.1111/j.1464-5491.2011.03333.x
37. Rodekamp E, Harder T, Kohlhoff R et al (2005) Long-term impact of breast-feeding on body weight and glucose tolerance in children of diabetic mothers: role of the late neonatal period and early infancy. Diabetes Care 28(6):1457–1462. https://doi.org/10.2337/diacare.28.6.1457
38. Plagemann A, Harder T, Franke K, Kohlhoff R (2002) Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. Diabetes Care 25(1):16–22. https://doi.org/10.2337/diacare.25.1.16