Original Article
PEDIATRIC OBESITY

Obesity

Associations of Maternal Diabetes During Pregnancy with Overweight in Offspring: Results from the Prospective TEDDY Study

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Objective: This study aimed to determine the relationship between different forms of, and potential pathways between, maternal diabetes and childhood obesity at different ages.
Methods: Prospective cohort data from The Environmental Determinants of Diabetes in the Young (TEDDY) study, which was composed of 5,324 children examined from 0.25 to 6 years of age, were analyzed. Cross-sectional and longitudinal analyses taking into account potential confounders and effect modifiers such as maternal prepregnancy BMI and birth weight *z* scores were performed.
Results: Offspring of mothers with gestational diabetes mellitus (GDM) or type 1 diabetes mellitus (T1DM) showed a higher BMI standard deviation score and increased risk for overweight and obesity at 5.5 years of age than offspring of mothers without diabetes. While these associations could be substantially explained by maternal prepregnancy BMI in offspring of mothers with GDM, significant associations disappeared after adjustment for birth weight *z* scores in offspring of T1DM mothers. Furthermore, overweight risk became stronger with increasing age in offspring of mothers with diabetes compared with offspring of mothers without diabetes.
Conclusions: Maternal diabetes is associated with increased risk of offspring overweight, and the association appears to get stronger as children grow older. Indeed, intrauterine exposure to maternal T1DM may predispose children to later obesity through increased birth weight, while maternal BMI is more important in children exposed to GDM.

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Introduction

The worldwide increase in the prevalence of childhood obesity in recent decades is alarming because it is also associated with other health consequences such as metabolic syndrome, diabetes, and cardiovascular disease in adulthood (1,2). Previous research has indicated that overweight at age 5 to 6 years is a strong predictor of overweight later in life (3), emphasizing the need to identify determinants of

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obesity in early life and even before birth (4). In particular, there is a growing body of literature that recognizes the role of maternal diabetes during pregnancy in the risk of offspring obesity (5–7). While several studies have shown that offspring of women with gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), or type 2 diabetes mellitus (T2DM) have a higher risk for obesity during late childhood and adolescence (8–13), there is only weak and inconsistent evidence for an association between maternal diabetes and obesity during early childhood (14–18). Therefore, it is still not clear whether maternal diabetes has a delayed effect on offspring obesity.

In addition, most studies associating GDM with offspring obesity have shown that maternal obesity largely confounds this association (5,9,19,20). Only in one study did a positive association between GDM and overweight in 6-year-old offspring remain significant after adjustment for maternal BMI (21); therefore, it remains unclear whether this association is causal. Furthermore, high birth weight has been reported to be associated with maternal hyperglycemia in pregnancy regardless of the type of diabetes (22,23), potentially via exposure to excess fetal glucose and insulin and thus overgrowth of the fetus (4). However, the influence of birth weight on the pathway from maternal diabetes to childhood obesity has not been well investigated.

Therefore, this study aims to investigate (1) whether exposure to maternal diabetes during pregnancy (GDM, T1DM, or T2DM) is associated with subsequent offspring growth during early childhood, (2) whether this association varies by offspring age or maternal diabetes status, and (3) whether birth weight or maternal prepregnancy BMI is in the potential pathway.

Methods

The Environmental Determinants of Diabetes in the Young (TEDDY) study is an ongoing international, multicenter, prospective cohort study that seeks to identify the environmental factors triggering islet autoimmunity and T1DM. This large longitudinal cohort also offers the opportunity to investigate the factors influencing childhood overweight and obesity. The TEDDY study screened 424,788 newborns for T1DM-associated human leukocyte antigen genotypes between 2004 and 2010, and of these children, 8,676 were enrolled and followed up in six clinical research centers located in the United States, Finland, Germany, and Sweden. Children's study visits were scheduled every 3 months from birth until age 4 years and every 6 months thereafter. Further details on study design, eligibility, and data collection have been described elsewhere (24–26). Written informed consent for all participants was obtained separately from a parent or primary caretaker. The study is funded by the National Institutes of Health, was approved by local institutional review boards, and has been monitored by an external evaluation committee formed by the National Institutes of Health.

Maternal characteristics and offspring measurements

During each visit, children's height and weight were measured by trained TEDDY personnel at TEDDY clinics. Using a wall-mounted stadiometer, each child's height was measured as length before age 2 and as standing height to the nearest 0.1 cm after age 2 (27). Body weight was measured in kilograms using regularly calibrated electronic scales. For subjects who missed their study visit, anthropometric data were taken from their pediatricians' records collected near the TEDDY clinic visit date.

Information on maternal factors such as diabetes status during pregnancy, age, prepregnancy BMI, gestational weight gain, gestational age at delivery, education, and smoking or alcohol intake during pregnancy, as well as the child's birth weight, was obtained by self-administered questionnaires or structured interviews conducted during one of the follow-up visits in the first year of the study. Duration of both any and exclusive breastfeeding was assessed by giving a specific booklet to the parents at study entry, in which they recorded the age at weaning and age at introduction of all new foods.

Assessment of diet and physical activity

Dietary intake was assessed using a 3-day food record every 3 months until 12 months of age and every 6 months thereafter. Participating families were instructed to keep a consecutive 3-day record of their child's consumption of food and beverages, ideally for two weekdays and one weekend day, as described in detail elsewhere (27). To assess energy and nutrient intake, the food consumption data were entered and analyzed using country-specific food record databases that were harmonized for the TEDDY study (28). Average duration (in minutes) of moderate to vigorous physical activity per day was assessed using the ActiGraph GT3X accelerometer (ActiGraph, Pensacola, Florida) (29) on an annual basis, beginning at age 5. TEDDY staff provided demonstrations on how to wear and use the accelerometer for seven consecutive days, including two weekend days, during the study visit prior to the specific TEDDY visit targeted for activity data collection.

Data transformations

Children were classified into different groups according to maternal diabetic status during pregnancy: (1) offspring of mothers with GDM (O-GDM), (2) offspring of mothers with T1DM (O-T1DM), (3) offspring of mothers with T2DM (O-T2DM), and (4) offspring of mothers without diabetes (O-nonDM). BMI was calculated as weight in kilograms divided by height in meters squared. Prior to analysis, height, weight, and BMI were transformed to standard deviation scores (SDSs) using World Health Organization (WHO) reference values (30,31). SDS values less than −5 or greater than 5 were deemed implausible and excluded. BMI SDS values were also used to define overweight (including obesity; BMI SDS > 1) and obesity (BMI SDS > 2) according to WHO recommendations. Anthropometric outcomes at the age of 5.5 years were defined as those assessed at the 66-month visit if available (as in 86% of the children) or at the next closest visit between the ages of 54 and 72 months. Similarly, diet and physical activity at age 5 were defined as those outcomes assessed at the 60-month visit if available or at the next closest visit between the ages of 66 and 72 months. Gestational weight gain was classified as inadequate, adequate, or excessive according to Institute of Medicine guidelines (32). Birth weight was transformed to a *z* score adjusting for country, sex, gestational age, maternal height, and birth type (singleton or multiplet), similar to previous analyses of the TEDDY data (27,33).

Statistical analysis

To assess our main hypothesis that maternal diabetes was associated with offspring anthropometric measures, we performed several analyses. First, mean BMI, weight, and height were visually compared in yearly time intervals between O-GDM, O-T1DM, and O-nonDM. Second, cross-sectional associations between maternal diabetes and anthropometric outcomes (BMI, height, weight, overweight, and obesity) measured in the children at 5.5 years of age were investigated through linear and logistic regression models.

Third, longitudinal analyses between maternal diabetes and anthropometric outcomes measured between 0.25 and 6 years of age were performed through mixed-effects regression models with random intercepts for each subject in order to account for the correlation between repeated observations within subjects. Associations in both the cross-sectional and the longitudinal setting were analyzed based on stepwise adjustment. In the first model, we adjusted for age (only longitudinal analysis), sex, and country for all outcomes; in the second model, we additionally adjusted for maternal prepregnancy BMI. Furthermore, we included maternal age, gestational weight gain, maternal smoking during pregnancy (yes or no), maternal alcohol intake during pregnancy (any or none), maternal education (high school, less than high school, or more than high school), and duration of any breastfeeding (less than 6 months or more than 6 months) as potential confounders in the third model and, additionally, birth weight *z* scores in the fourth model to explore potential pathways. Furthermore, we explored interaction terms between maternal diabetes and child's age (in years) in the fully adjusted longitudinal model to explore whether the association changed with an increase in age.

Sensitivity analyses

We performed several sensitivity analyses. We added interaction terms between country and maternal diabetes in the cross-sectional and longitudinal models to explore whether association between maternal diabetes and anthropometric outcomes differed by country. Because the human leukocyte antigen DQ2/2 (HLA-DQ2/2) genotype was reported to be associated with increased risk for obesity at age 2 to 4 in a previous TEDDY study (33), we additionally adjusted for HLA-DQ2/2 genotype in the cross-sectional and longitudinal models. We further recalculated the cross-sectional analyses after the exclusion of children who had developed persistent islet autoantibodies or T1DM by 5.5 years of age. Furthermore, based on the subset of children with available energy intake and physical activity data at age 5 (54% of all children with available BMI measurements), we additionally adjusted for these two variables as potential confounders in cross-sectional models 3 and 4. We also assessed whether treatment with insulin compared with any other or no treatment during pregnancy was associated with anthropometric outcomes at 5.5 years of age in offspring of women with GDM and T2DM. All calculations were carried out with SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Of 8,676 children, 3,352 children with missing data on height and weight measurements after age 5 ($n=3,181$) or maternal diabetes status during pregnancy ($n=171$) were excluded (Figure 1). Our final study sample consisted of 5,324 children; of these, 2,746 (51.58%) were male, 326 (6.12%) and 225 (4.23%) were O-GDM and O-T1DM, respectively, and only 14 (0.26%) were O-T2DM (Table 1). Children who were excluded because of missing height and weight measurements were less likely to have a mother with diabetes (GDM: 4.94%; T1DM: 3.11%; χ^2 test: $P=0.02$). However, children who were excluded because of missing maternal diabetes status did not differ significantly from those included with respect to BMI SDS at 5.5 years of age (Mann–Whitney U test: $P=0.70$). Children had a mean BMI SDS of 0.35, with 1,154 (21.87%) and 303 (5.74%) children classified as having overweight and obesity, respectively, at 5.5 years of age. O-nonDM had a mean birth weight *z* score of −0.05, which was significantly lower than that in O-T1DM (0.87; $P<0.0001$) or O-GDM (0.13; $P=0.004$).

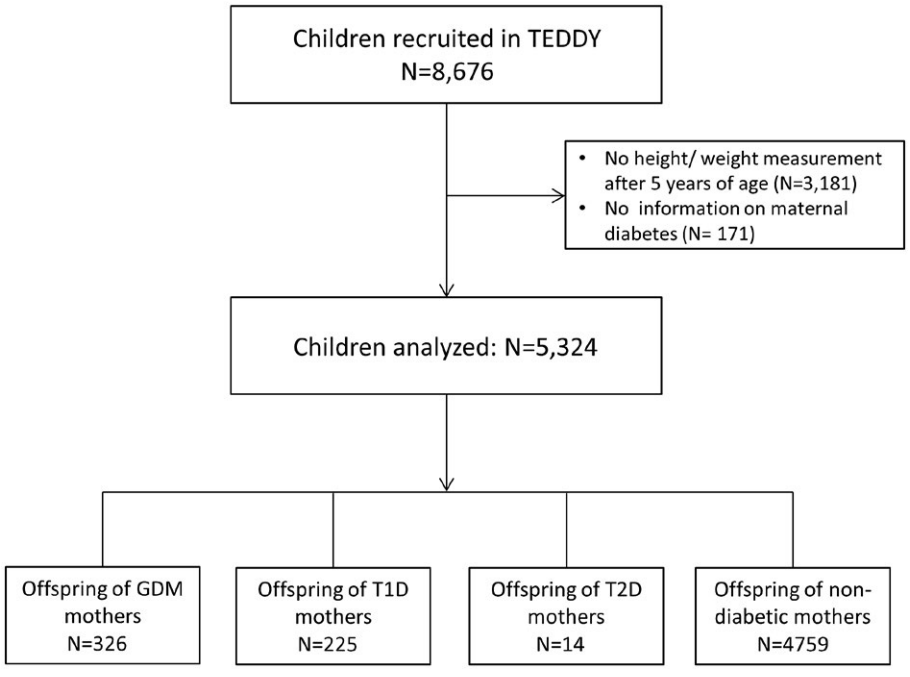

Figure 1 Flowchart of children analyzed. GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

TABLE 1 Characteristics of the study population stratified according to maternal diabetes

Variable	Available n	Category	*n* (%) in each category	O-nonDM (*n* = 4,759) *n* (%)	O-GDM (*n* = 326) *n* (%)	O-T1DM (*n* = 225) *n* (%)	O-T2DM (*n* = 14) *n* (%)
Sex	5,324	Males	2,746 (51.6)	2,457 (51.6)	174 (53.4)	109 (48.4)	6 (42.9)
Country		US	2,013 (37.8)	1,807 (38.0)	117 (35.9)	78 (34.7)	11 (78.6)
	5,324	Finland	1,237 (23.2)	1,052 (22.1)	138 (42.3)	47 (20.9)	0
		Germany	274 (5.2)	192 (4.0)	17 (5.2)	65 (28.9)	0
		Sweden	1,800 (33.8)	1,708 (35.9)	54 (16.6)	35 (15.6)	3 (21.4)
Maternal smoking during pregnancy	5,320	Yes	497 (9.3)	426 (9.0)	40 (12.3)	30 (13.3)	1 (7.1)
Maternal alcohol drinking during pregnancy	5,322	Yes	1,831 (34.4)	1,623 (34.1)	109 (33.4)	95 (42.2)	4 (28.6)
Maternal education	5,251	High school	4,371 (83.2)	3,877 (82.6)	288 (89.2)	194 (87.4)	12 (85.7)
Gestational weight gain (according to Institute of Medicine guidelines)	5,241	Inadequate	909 (17.3)	754 (16.1)	117 (36.7)	34 (15.2)	4 (28.6)
		Adequate	1,899 (36.2)	1,725 (36.8)	92 (28.8)	78 (34.9)	4 (28.6)
		Excessive	2,433 (46.4)	2,205 (47.1)	110 (34.5)	112 (50.0)	6 (42.9)
Breastfed ≥ 6 months	5,324	Yes	3,469 (65.2)	3,150 (66.2)	193 (59.2)	121 (53.8)	5 (35.7)
Overweight at age 5.5	5,277	Yes	1,154 (21.9)	998 (21.2)	89 (27.6)	58 (25.9)	9 (64.3)
Obesity at age 5.5	5,277	Yes	303 (5.7)	252 (5.3)	32 (9.9)	17 (7.6)	2 (14.3)
			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Maternal prepregnancy BMI (kg/m^2)	5,276		24.8 ± 5.2	24.5 ± 5.0	28.3 ± 6.4	25.3 ± 4.7	35.0 ± 7.5
Maternal age at delivery (y)	5,324		31.0 ± 4.9	30.9 ± 4.9	32.2 ± 5.3	30.8 ± 4.9	34.0 ± 5.6
Gestational age (wk)	5,318		39.5 ± 1.6	39.6 ± 1.6	39.2 ± 1.7	37.7 ± 1.8	38.1 ± 2.1
Birth weight *z* score	5,186		0.0 ± 1.0	−0.1 ± 1.0	0.1 ± 1.1	0.9 ± 1.3	0.2 ± 1.0
BMI SDS at age 5.5	5,277		0.4 ± 1.0	0.3 ± 1.0	0.5 ± 1.1	0.4 ± 1.1	1.1 ± 1.3
Height SDS at age 5.5	5,291		0.4 ± 1.0	0.4 ± 1.0	0.3 ± 1.0	0.3 ± 0.9	0.2 ± 0.7
Weight SDS at age 5.5	5,304		0.5 ± 1.0	0.5 ± 1.0	0.5 ± 1.0	0.5 ± 0.9	0.9 ± 1.2
Mean energy intake (kcal/d) at age 5	4,263		1,442.7 ± 362.2	1,443.6 ± 359.7	1,461.7 ± 428.5	1,402.1 ± 316.4	1,353.2 ± 317.3
MVPA (min/d) at age 5	3,276		68.0 ± 34.4	68.3 ± 34.4	63.0 ± 33.8	69.4 ± 36.8	54.4 ± 29.8

MVPA, moderate to vigorous physical activity; O-GDM, offspring of mothers with gestational diabetes mellitus; O-nonDM, offspring of mothers without diabetes mellitus; O-T1DM, offspring of mothers with type 1 diabetes mellitus; O-T2DM, offspring of mothers with type 2 diabetes mellitus; SDS, standard deviation score.

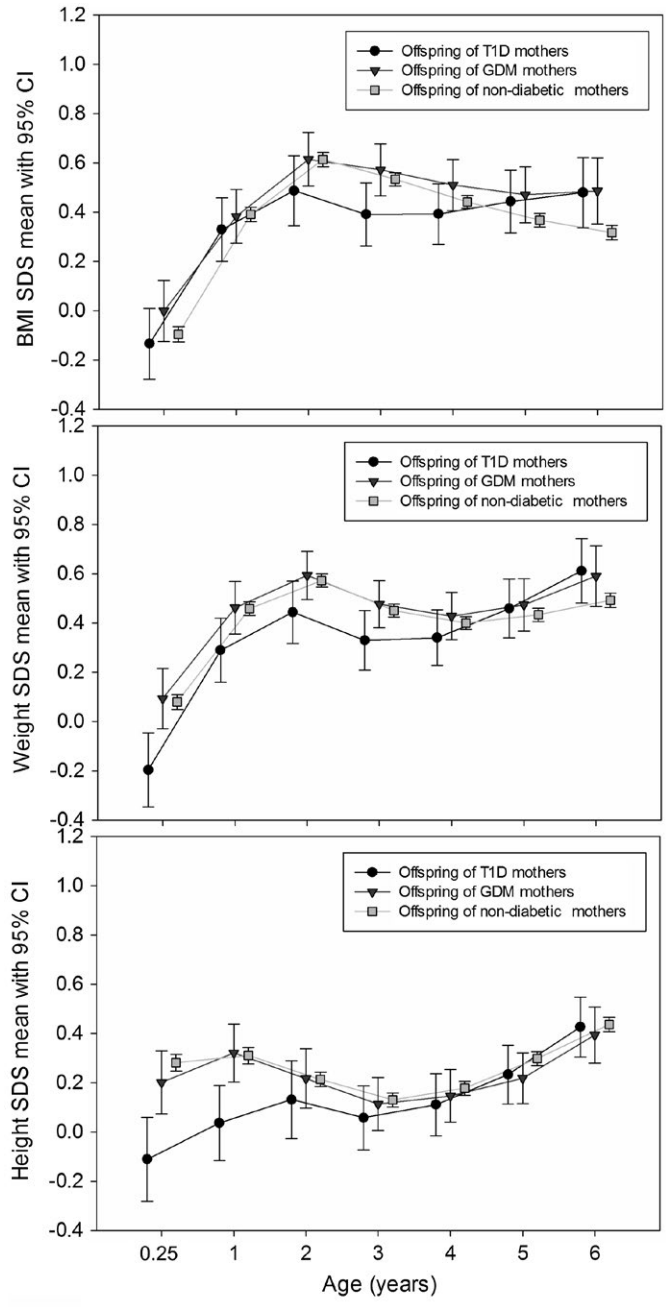

Figure 2 Comparison of mean BMI, weight, and height standard deviation scores (SDSs) with 95% CIs between offspring of mothers with gestational diabetes (GDM), offspring of mothers with type 1 diabetes mellitus (O-T1DM), and offspring of mothers without diabetes mellitus at different ages in the TEDDY study. This figure does not include trends for offspring of mothers with type 2 diabetes mellitus because of low numbers ($n = 14$) and wide CIs.

O-GDM had a similar SDS of both height and weight compared with O-nonDM from 3 months to 2 to 3 years of age; however, O-T1DM showed clearly lower values at this age but caught up with O-GDM until age 5 to 6 years of age (Figure 2). O-nonDM had similar mean BMI SDSs as O-GDM at age 2 but gradually declined afterward and had considerably lower values than O-GDM and O-T1DM at age 6. Accordingly, maternal diabetes was associated with higher BMI SDS (O-GDM: +0.19 [95% CI: 0.07-0.29]; O-T1DM: +0.22 [95% CI: 0.08-0.35]) and increased risk for overweight (O-GDM odds ratio [OR]: 1.48 [95% CI: 1.14-1.92]; O-T1DM OR: 1.60 [95% CI: 1.16-2.20]) and obesity (O-GDM OR: 1.98 [95% CI: 1.34-2.93]; O-T1DM OR: 1.84 [95% CI: 1.09-3.10]) at 5.5 years of age compared with O-nonDM when adjusted for sex and country (Table 2). After additional adjustment for maternal prepregnancy BMI, the respective associations for O-GDM were attenuated and became nonsignificant (e.g., OR for overweight: 1.05 [95% CI: 0.80-1.38]). In contrast, the O-T1DM estimates remained largely unaffected by adjustment for maternal BMI and also for further confounders such as breastfeeding, but they were attenuated considerably after adjustment for birth weight z scores (OR for overweight: 1.15 [95% CI: 0.81-1.62]). O-T2DM had a largely increased risk for overweight despite the small sample size (9 of the 14 O-T2DM children had overweight) and independently of birth weight z scores (OR in the full model: 4.92 [95% CI: 1.40-17.30]). No significant differences between offspring of mothers with diabetes and O-nonDM were observed for height SDS and weight SDS, with the exception of lower height and weight SDSs in O-T1DM after adjustment for birth weight z scores. The observed associations between maternal diabetes and offspring anthropometric outcomes remained similar even after adjusting for the HLA-DQ2/2 genotype or excluding children with islet autoantibodies or T1DM (data not shown). Sensitivity analyses on the reduced subset where physical activity and energy intake were available did not indicate a major confounding role for these two variables (Supporting Information Table S1).

In the longitudinal analysis, O-GDM was again not significantly associated with any outcome when adjusted for maternal prepregnancy BMI (Table 3). Similarly, O-T1DM showed no significant differences in any outcome except height SDS compared with O-nonDM in longitudinal models without birth weight z scores. After inclusion of birth weight z scores, maternal T1DM was associated with lower BMI, overweight, and obesity risk as well as lower height and weight SDS in the offspring.

After including an interaction term between child's age and maternal diabetes in the fully adjusted model, we observed that O-GDM, O-T1DM, and O-T2DM showed comparatively higher increases in BMI SDS per year compared with O-nonDM (Figure 3), indicating that the potential impact of maternal diabetes on childhood BMI becomes stronger with increasing age. For example, the average increase in BMI SDS per year increase in age was 0.06 (95% CI: 0.05 to 0.07) in O-T1DM compared with 0.02 (95% CI: 0.01 to 0.02) in O-nonDM. Therefore, a child with a BMI SDS of 0.00 at age 2 would be expected to have a BMI SDS of 0.08 at age 6 if O-nonDM compared with 0.24 at age 6 if O-T1DM. Similarly, a 1-year increase in age was associated with a higher risk for overweight or obesity in O-GDM, O-T1DM, and O-T2DM, while null or negative effects were found in O-nonDM. For example, the OR for overweight risk per year increase in age was 1.08 (95% CI: 1.02 to 1.14) in O-T1DM compared with 0.95 (95% CI: 0.94 to 0.96) in O-nonDM, implying a relative increase in risk of +13% per year in O-T1DM compared with O-nonDM. Furthermore, we observed no significant interaction terms between country and maternal diabetes in any of the cross-sectional and longitudinal models (data not shown). In addition, treatment with insulin ($n = 72$) compared with diet ($n = 243$), pills only ($n = 1$), or no treatment ($n = 24$) during pregnancy in women with GDM and T2DM was not associated with any of the anthropometric outcomes in offspring at 5.5 years of age (e.g., difference in BMI

TABLE 2 Cross-sectional analysis of anthropometric outcomes between 5.5-year-old offspring of mothers with and without diabetes of different types during pregnancy

Outcome	Exposure (maternal diabetes)	Model 1 (n = 5,277)		Model 2 (n = 5,232)		Model 3 (n = 5,119)		Model 4 (n = 4,994)	
		Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Absolute change in SD scores									
BMI SDS	O-GDM	**0.19 (0.07 to 0.29)**	**0.002**	−0.02 (−0.13 to 0.10)	0.78	0.03 (−0.08 to 0.14)	0.61	0.001 (−0.11 to 0.11)	0.99
	O-T1DM	**0.22 (0.08 to 0.35)**	**0.002**	**0.18 (0.04 to 0.31)**	**0.009**	**0.17 (0.04 to 0.30)**	**0.01**	−0.007 (−0.14 to 0.13)	0.91
	O-T2DM	**0.75 (0.23 to 1.27)**	**0.005**	0.24 (−0.27 to 0.74)	0.36	0.28 (−0.22 to 0.78)	0.27	0.32 (−0.18 to 0.83)	0.21
Height SDS	O-GDM	−0.02 (−0.13 to 0.09)	0.67	−0.07 (−0.18 to 0.04)	0.24	−0.04 (−0.16 to 0.07)	0.44	−0.08 (−0.19 to 0.04)	0.20
	O-T1DM	−0.07 (−0.20 to 0.07)	0.34	−0.08 (−0.21 to 0.06)	0.26	−0.08 (−0.22 to 0.05)	0.24	**−0.27 (−0.40 to −0.13)**	**0.0001**
	O-T2DM	−0.06 (−0.57 to 0.45)	0.82	−0.20 (−0.71 to 0.32)	0.45	−0.20 (−0.71 to 0.31)	0.44	−0.21 (−0.73 to 0.31)	0.44
Weight SDS	O-GDM	0.10 (−0.01 to 0.21)	0.08	−0.06 (−0.17 to 0.05)	0.32	−0.01 (−0.12 to 0.10)	0.84	−0.05 (−0.16 to 0.06)	0.36
	O-T1DM	0.12 (−0.02 to 0.25)	0.08	0.08 (−0.05 to 0.21)	0.23	0.07 (−0.06 to 0.20)	0.27	**−0.16 (−0.29 to −0.03)**	**0.02**
	O-T2DM	0.51 (−0.01 to 1.02)	0.05	0.08 (−0.42 to 0.58)	0.31	0.11 (−0.39 to 0.61)	0.67	0.13 (−0.37 to 0.63)	0.60
Odds ratios									
Overweight	O-GDM	**1.48 (1.14 to 1.92)**	**0.003**	1.05 (0.80 to 1.38)	0.75	1.14 (0.86 to 1.51)	0.38	1.10 (0.82 to 1.46)	0.52
	O-T1DM	**1.60 (1.16 to 2.20)**	**0.004**	**1.52 (1.10 to 2.11)**	**0.01**	**1.50 (1.08 to 2.09)**	**0.02**	1.15 (0.81 to 1.62)	0.44
	O-T2DM	**7.39 (2.46 to 22.23)**	**0.0004**	**3.36 (1.06 to 10.70)**	**0.04**	**3.68 (1.14 to 11.81)**	**0.03**	**4.92 (1.40 to 17.30)**	**0.01**
Obesity	O-GDM	**1.98 (1.34 to 2.93)**	**0.0007**	1.23 (0.81 to 1.86)	0.34	1.33 (0.87 to 2.04)	0.19	1.31 (0.85 to 2.01)	0.23
	O-T1DM	**1.84 (1.09 to 3.10)**	**0.02**	**1.79 (1.05 to 3.06)**	**0.03**	**1.75 (1.02 to 3.00)**	**0.04**	1.48 (0.85 to 2.59)	0.17
	O-T2DM	2.93 (0.65 to 13.22)	0.16	0.95 (0.20 to 4.57)	0.95	0.94 (0.19 to 4.60)	0.94	1.02 (0.20 to 5.09)	0.98

Significant associations ($P < 0.05$) shown in bold font.
Model 1: adjusted for sex and country; model 2: model 1 + maternal prepregnancy BMI; model 3: model 2 + breastfeeding, maternal smoking and drinking during pregnancy, gestational weight gain, maternal age, and education; model 4: model 3 + birth weight.
Reference: no diabetes.
O-GDM, offspring of mothers with gestational diabetes mellitus; O-T1DM, offspring of mothers with type 1 diabetes mellitus; O-T2DM, offspring of mothers with type 2 diabetes mellitus; SDS, standard deviation score.

TABLE 3 Longitudinal analysis of anthropometric outcomes assessed during study visits from 0.25 to 6 years of age in offspring of mothers with or without diabetes during pregnancy

Outcome	Exposure (maternal diabetes)	Model 1 (n = 95,162)		Model 2 (n = 94,330)		Model 3 (n = 92,782)		Model 4 (n = 90,569)	
		Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Absolute change in SD scores									
BMI SDS	O-GDM	**0.10 (0.01 to 0.19)**	**0.03**	−0.02 (−0.11 to 0.07)	0.70	0.03 (−0.06 to 0.12)	0.52	−0.003 (−0.09 to 0.09)	0.94
	O-T1DM	0.09 (−0.02 to 0.20)	0.12	0.06 (−0.05 to 0.17)	0.27	0.04 (−0.06 to 0.15)	0.42	**−0.15 (−0.26 to −04)**	**0.006**
	O-T2DM	**0.46 (0.04 to 0.87)**	**0.03**	0.15 (−0.26 to 0.56)	0.48	0.19 (−0.22 to 0.60)	0.36	0.19 (−0.22 to 0.60)	0.37
Height SDS	O-GDM	−0.002 (−0.10 to 0.10)	0.97	−0.03 (−0.14 to 0.07)	0.53	−0.001 (−0.11 to 0.11)	0.98	−0.04 (−0.15 to 0.06)	0.40
	O-T1DM	**−0.14 (−0.26 to −0.01)**	**0.03**	**−0.15 (−0.27 to −0.02)**	**0.02**	**−0.16 (−0.28 to −0.03)**	**0.01**	**−0.41 (−0.54 to −0.29)**	**<0.001**
	O-T2DM	−0.18 (−0.65 to 0.29)	0.46	−0.28 (−0.75 to 0.20)	0.25	−0.27 (−0.75 to 0.20)	0.26	−0.30 (−0.78 to 0.17)	0.21
Weight SDS	O-GDM	0.07 (−0.03 to 0.17)	0.15	−0.03 (−0.12 to 0.07)	0.56	0.02 (−0.07 to 0.12)	0.64	−0.02 (−0.12 to 0.07)	0.60
	O-T1DM	−0.02 (−0.14 to 0.09)	0.72	−0.05 (−0.16 to 0.07)	0.44	−0.06 (−0.18 to 0.05)	0.28	**−0.35 (−0.46 to −0.24)**	**<0.001**
	O-T2DM	0.23 (−0.21 to 0.67)	0.31	−0.05 (−0.48 to 0.39)	0.85	−0.01 (−0.44 to 0.42)	0.96	−0.03 (0.45 to 0.39)	0.88
Odds ratios									
Overweight	O-GDM	1.29 (0.99 to 1.68)	0.06	0.94 (0.72 to 1.23)	0.66	1.06 (0.76 to 1.30)	0.69	0.98 (0.75 to 1.28)	0.89
	O-T1DM	1.27 (0.92 to 1.75)	0.14	1.18 (0.86 to 1.62)	0.30	1.14 (0.83 to 1.57)	0.41	**0.69 (0.50 to 0.96)**	**0.03**
	O-T2DM	**3.84 (1.19 to 12.83)**	**0.03**	1.72 (0.54 to 5.48)	0.36	1.93 (0.61 to 6.11)	0.27	1.95 (0.60 to 6.34)	0.27
Obesity	O-GDM	**1.47 (1.11 to 1.95)**	**0.01**	1.08 (0.81 to 1.45)	0.60	1.19 (0.89 to 1.61)	0.24	1.14 (0.85 to 1.54)	0.38
	O-T1DM	0.99 (0.69 to 1.44)	0.97	0.94 (0.65 to 1.35)	0.72	0.91 (0.63 to 1.31)	0.61	**0.62 (0.42 to 0.91)**	**0.01**
	O-T2DM	2.53 (0.79 to 8.11)	0.12	1.14 (0.35 to 3.65)	0.83	1.19 (0.37 to 3.85)	0.77	1.39 (0.42 to 4.59)	0.59

Significant associations ($P < 0.05$) shown in bold font.
Model 1: adjusted for age, sex and country; model 2: model 1 + maternal prepregnancy BMI; model 3: model 2 + breastfeeding, maternal smoking and drinking during pregnancy, gestational weight gain, maternal age, and education; model 4: model 3 + birth weight.
Reference: no diabetes.
O-GDM, offspring of mothers with gestational diabetes mellitus; O-T1DM, offspring of mothers with type 1 diabetes mellitus; O-T2DM, offspring of mothers with type 2 diabetes mellitus; SDS: standard deviation score.

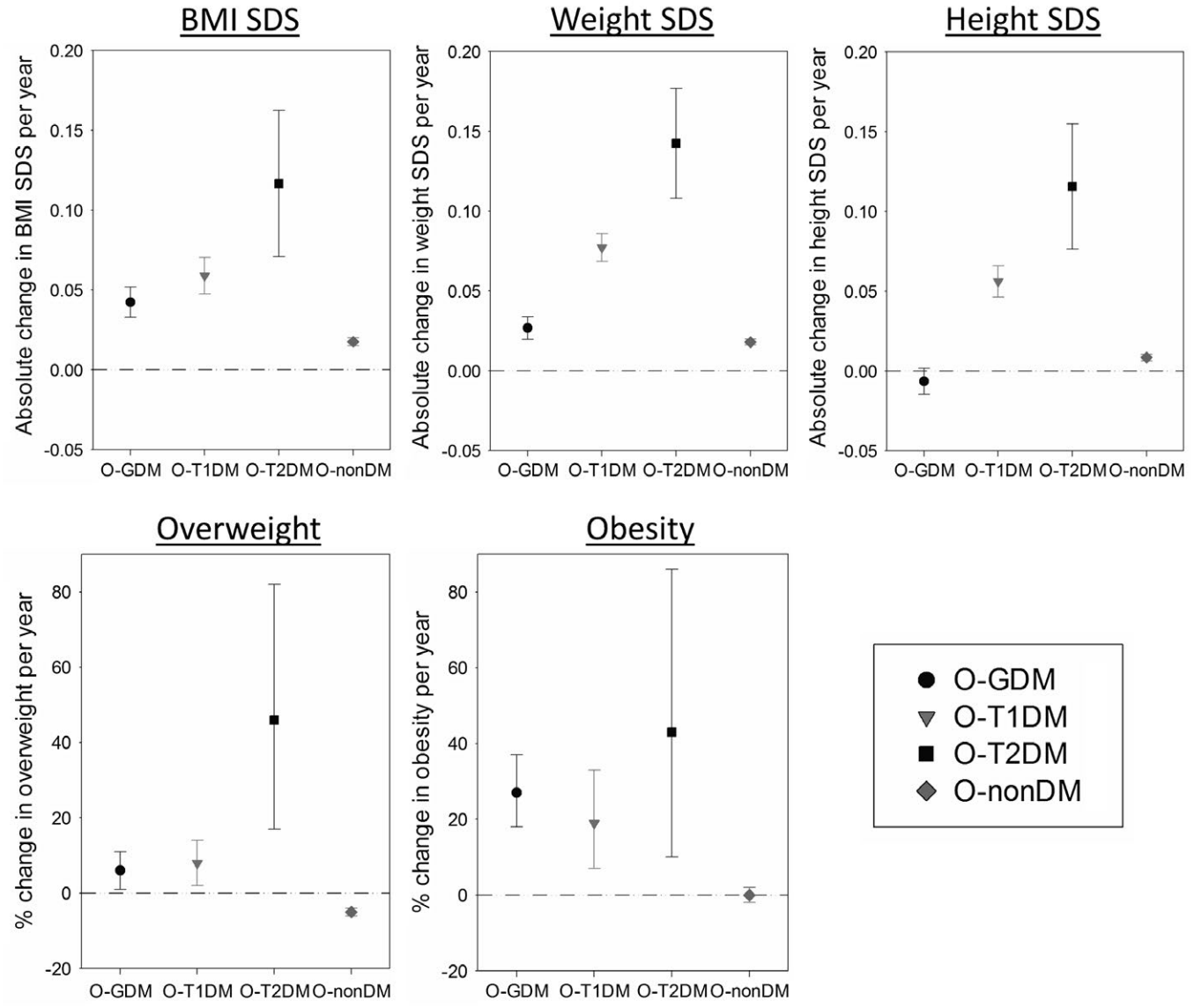

Figure 3 Modifications of association between child's age (per year) and anthropometric outcomes by maternal diabetes status presented as estimates (symbols) with 95% CIs (lines). O-GDM, offspring of mothers with gestational diabetes mellitus; O-nonDM, offspring of mothers without diabetes mellitus; O-T1DM, offspring of mothers with type 1 diabetes mellitus; O-T2DM, offspring of mothers with type 2 diabetes mellitus; SDS, standard deviation score.

SDS of insulin compared with no-insulin treatment: −0.05 [95% CI: −0.34 to 0.25]).

Discussion

In this large, prospective, multicenter cohort study, we observed that children with intrauterine exposure to diabetes had an increased risk for overweight and obesity at 5.5 years of age. This association was not clearly evident when the whole time span of 0.25 to 6 years of age was investigated in a longitudinal analysis. However, we observed that as children grew older, their overweight or obesity risk tended to increase when born to mothers with diabetes compared with when born to mothers without diabetes, implying that the association may not be evident in the first years of life. Furthermore, the observed associations were attenuated significantly after adjustment for prepregnancy BMI in O-GDM and for birth weight *z* scores in O-T1DM, indicating possible mediating effects of these two factors.

Our findings for exposure to maternal T1DM or GDM were generally in line with other studies indicating a positive association with offspring overweight or obesity. These positive associations have been predominantly seen in studies examining offspring older than 5 years (8–12,21,34). However, studies on early childhood offspring have shown inconsistent results. Silverman et al. (35) observed an increased weight in offspring of mothers with diabetes at birth and progressively after age 4 but not between ages 1 and 3. Similarly, Baptiste-Roberts et al. (36) reported a significantly increased BMI in O-GDM at age 7 but not at age 3 and 4. A recent meta-analysis that pooled studies according

to different age subgroups reported a higher risk for overweight and obesity in O-GDM or O-T1DM only during late childhood and adolescence (7). Accordingly, our study showed stronger effects as children grew older. Therefore, it may be possible that maternal diabetes has a delayed influence on offspring obesity that increases with age (37,38). However, two other studies, one of which examined 3-year-old children (15) and the other predominantly 3- to 6-year-old children (16), showed positive associations of GDM with offspring adiposity measured by the sum of skinfolds or fat mass but not by BMI SDS. Therefore, it could be speculated that the differences may be subtle in early ages and become evident with respect to BMI only after a certain age. Moreover, evidence has suggested that early catch-up growth may lead to obesity in later life (39). Accordingly, the associations between maternal diabetes and offspring obesity at 5.5 years of age may be partly attributable to early catch-up growth; Figure 2 indicates that O-T1DM seemed to have accelerated growth during early childhood compared with O-nonDM. These findings may further indicate that environmental factors may contribute to the association between maternal diabetes and offspring overweight. However, the associations in our data remained stable after adjustment for several of those variables, such as breastfeeding, parental education, or maternal age.

In addition, we found that the positive association of maternal GDM with offspring overweight or obesity was attenuated significantly after adjustment for maternal prepregnancy BMI. Several GDM studies have shown similar findings of maternal BMI playing a major confounding role in their analyses (5,9,37,40,41). Indeed, maternal obesity is clearly a risk factor for and often precedes GDM; therefore, it may be difficult to clearly separate the effects of GDM and maternal BMI on offspring obesity. Furthermore, birth weight seemed to substantially explain the positive association between maternal T1DM and offspring overweight or obesity in our data. Moreover, we found no considerable mediating effect of birth weight on the association between GDM and offspring obesity, in accordance with other studies (8,16,19,37). Rates of macrosomia as well as of other adverse outcomes have been reported to be higher in offspring of mothers with pre-GDM than with GDM (42,43). High birth weight may therefore be a proxy of poor glycemic control, which is possibly of greater importance in O-T1DM than O-GDM because the former are exposed to hyperglycemia during the whole pregnancy period. In that case, adding birth weight to the model might even lead to an overadjustment of the O-T1DM association, which might help to explain why we observed protective associations with respect to overweight in O-T1DM compared with O-nonDM in longitudinal analyses.

The main strengths of our study include the large sample size, the prospective study design with standardized protocols, multiple follow-up visits, and availability of many important covariates such as maternal prepregnancy BMI, gestational weight gain, birth weight, breastfeeding, and other postnatal influences such as children's diet and physical activity at age 5. These data allowed us to investigate the effects of different types of diabetes during pregnancy on offspring BMI and overweight at different ages from shortly after birth until age 6. It should be mentioned, however, that the number of children exposed to maternal T2DM during pregnancy was quite limited ($n = 14$), and therefore all associations for this subgroup showed large variability and should be interpreted with great caution. Furthermore, we were not able to assess such associations beyond age 6 because most subjects did not have sufficient follow-up after 6 years at the time these analyses were performed. GDM was defined based on maternal reports only and therefore could be neither confirmed by medical records, lab values, or similar nor harmonized between countries, unfortunately. This issue might have somewhat contributed to different prevalences of GDM between countries, but we do not expect that it has substantially biased our main results. A note of caution is due here with regard to generalizability of our results because these TEDDY cohort participants are all at increased genetic or familial risk to develop T1DM. We therefore cannot exclude that the associations were slightly overestimated, as all the children may generally have a higher background prevalence of overweight regardless of maternal diabetes status. We investigated several outcomes using different statistical models without formal adjustment for multiple testing. Although we cannot exclude that this approach yielded some false-positive results, we would not expect this to be a major limitation because the main findings were relatively consistent between the different models. Furthermore, exclusion because of missing height and weight measurements after age 5 was significantly associated with maternal diabetes status, indicating that families with mothers with diabetes were slightly less likely to drop out of the TEDDY follow-up. However, these differences were small, and we do not expect that they have biased our findings considerably.

In summary, maternal hyperglycemia seems to be associated with increased risk for childhood overweight and obesity. The strength of this association appears to increase as children grow older. Moreover, the association of maternal GDM with offspring obesity can be largely explained by confounding through maternal BMI, whereas the association of maternal T1DM with offspring overweight is substantially mediated by birth weight, possibly suggesting different pathways. Nevertheless, our study indicates that children exposed to maternal diabetes during pregnancy may need closer attention with respect to obesity and its consequences beyond early childhood.**O**

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