

Maternal Gestational Diabetes and Type 2 Diabetes During Pregnancy and Risk of Childhood Asthma in Offspring

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Objective To examine maternal preexisting type 2 diabetes (T2D) and gestational diabetes mellitus (GDM) on risk of childhood asthma.

Study design This retrospective birth cohort study included 97 554 singletons born in 2007-2011 within hospitals from a single integrated healthcare system. Children were prospectively followed from age 5 until December 31, 2017, using electronic medical records. Relative risks of childhood asthma associated with maternal diabetes in utero were estimated by hazard ratios using Cox regression adjusting for potential confounders.

Results There were 3119 children (3.2%) who were exposed to preexisting T2D and 9836 (10.1%) to GDM. Among mothers with GDM, 3380 (34.4%) were dispensed antidiabetic medication during pregnancy. During a median of 7.6 years (IQR, 6.3-9.0 years) after birth, 15 125 children (15.5%) were diagnosed with asthma after age 5. Maternal diabetes interacted with maternal asthma history to affect child's asthma risk ($P = .05$). Among children without maternal asthma ($n = 89487$), the adjusted hazard ratios for childhood asthma were 1.21 (95% CI, 1.08-1.36; $P < .001$) for exposure to T2D, 1.12 (95% CI, 1.01-1.25; $P = .04$) for GDM requiring antidiabetic medications, and 1.01 (95% CI, 0.93-1.10; $P = .82$) for GDM not requiring medications compared with no diabetes during pregnancy. The corresponding hazard ratios were 1.53 (95% CI, 1.19-1.96; $P < .001$), 1.11 (95% CI, 0.65-1.46; $P = .44$), and 0.84 (95% CI, 0.66-1.08; $P = .17$) among children without maternal asthma ($n = 8067$). Gestational age at GDM diagnosis was not associated with childhood asthma ($P = .27$).

Conclusions The risk of childhood asthma was predominately observed for exposure to preexisting T2D, small for GDM requiring medication, and not increased for GDM not requiring medication during pregnancy, compared with no diabetes during pregnancy. (*J Pediatr* 2020; ■:1-7).

Exposure to maternal diabetes during pregnancy can cause perinatal complications and predispose offspring to chronic health complications. Substantial evidence shows an increased risk of metabolic disorders, and increased evidence shows neurobehavioral disorders in offspring who are exposed to diabetes in utero.¹⁻⁶ However, little is known about child's asthma risk in association with exposure to diabetes in utero.

Asthma is a chronic lung disease caused by continued airway inflammation that is marked by episodes or attacks of inflammation. Pediatric asthma is one of the most common chronic conditions in children. Among school-aged children in California (5-17 years), the lifetime asthma prevalence was 16.7% in 2014.⁷ Although morbidity from asthma in children compared with adults is relatively low, the burden of asthma is considerable.^{8,9} Depending on severity, asthma can limit physical activity, lead to missed school days, and significant healthcare spending to manage the condition.^{10,11} About 36% of intermittent asthma and 86% of severe asthma that develops in childhood persists into adulthood.¹²

Known risk factors for asthma include allergies, frequent respiratory infection, low birth weight, and second-hand smoke exposure.¹³ Fetal programming that occurs during pregnancy can impact fetal lung development, which may lead to an increased asthma risk in offspring. Yet, studies on exposure to diabetes in utero and risk of childhood asthma are limited. Azad et al identified 4 studies that have some results specific to childhood asthma.¹³⁻¹⁶ However, diabetes in pregnancy was not the primary focus in 3 of the 4 studies.¹⁷ Only the Canadian study primarily assessed exposure to maternal diabetes and risk of childhood asthma.¹³ The study included 3574 Canadian children where asthma and maternal diabetes exposure status were obtained through survey recalls. However, only 50 children were reported to be exposed to diabetes in utero and the type of diabetes in pregnancy were

BMI	Body mass index
EMR	Electronic medical record
GDM	Gestational diabetes mellitus
HR	Hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
KPSC	Kaiser Permanente Southern California
T2D	type 2 diabetes

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not specified. Additionally, they identified 3 studies that peripherally assessed exposure to diabetes in pregnancy and asthma risk in offspring.¹⁴⁻¹⁶ A major limitation of these studies was that types of diabetes during pregnancy were either not specified or pregestational diabetes and gestational diabetes mellitus (GDM) identified during pregnancy were not distinguished.¹³⁻¹⁶ It is important to characterize the risk associated with different types of diabetes because preexisting type 1 and type 2 diabetes (T2D) may carry different risk to the offspring than GDM owing to differences in exposure window, duration, and extent of dysglycemia during pregnancy as shown in previous studies.⁴⁻⁶

To address these knowledge gaps, the present study was developed to characterize the associations between maternal preexisting diabetes and GDM and risk of childhood asthma in offspring in a large sample study. The importance of the gestational age of GDM diagnosis was also assessed. GDM was further categorized as whether antidiabetic medications were dispensed to manage glucose during pregnancy.

Methods

This retrospective and longitudinal birth cohort study used data from a large population-based clinical cohort. Children included were singletons born at 28-44 weeks of gestation between January 1, 2007, and December 31, 2011, in Kaiser Permanente Southern California (KPSC) hospitals. The KPSC Institutional Review Board approved this study, with waiver of informed consent. KPSC is a large, integrated healthcare organization that provides comprehensive care to approximately 16% of the residents of Southern California. KPSC membership is generally representative of Southern California residents.¹⁸ In mid-1990, KPSC implemented electronic medical records (EMR) systems to capture diagnosis codes, laboratory testing date and values, and pharmacy records. In 2007, KPSC implemented a complete and comprehensive EMR system that additionally includes information on all care history, including inpatient and outpatient visits, vital signs, and all procedures.

To be eligible for this study, children had to be enrolled as a KPSC health plan member by age 5 and had follow-up from age 5. We applied these eligibility criteria because asthma diagnosis before age 5 is not reliable.^{19,20} Children were followed from age 5 through EMR until the first date of the following: (1) date of clinical diagnosis of asthma, (2) last date of continuous KPSC health plan membership, (3) death from any cause, or (4) December 31, 2017. The continuous KPSC health plan membership after age 5 will minimize potential asthma ascertainment bias. Children born at KPSC can be linked with maternal records through a unique patient identifier. Data on social demographics; prenatal care history including weight, height, diabetes diagnosis, laboratory glucose values, and medication use; and child's characteristics and asthma diagnosis and medications were extracted from the KPSC EMR. Data quality was assessed by means of data plots and frequency tables. Potential outliers and

data errors were rectified by cross-checking against historical data in EMR. Data from this cohort except information on child's asthma have been included in previous publications.⁴⁻⁶ **Figure 1** (available at www.jpeds.com) depicts the study sample size and cohort construction. Children with missing or invalid data on maternal race/ethnicity, prepregnancy body mass index (BMI), sex, birth weight, and maternal age outside of 15-55 years were excluded. A few children (n = 179) born to mothers with preexisting type 1 diabetes were also excluded owing to small sample size. A total of 97 554 children born to 85 422 unique women were eligible and included in the final data analysis.

Exposures and Outcomes

The primary exposure variables were maternal preexisting T2D and GDM identified during pregnancy. A detailed description of methods to identify T2D and GDM for this cohort has been reported previously.⁴⁻⁶ Briefly, a combination of the *International Classification of Diseases, Ninth Revision* (ICD-9) codes combined with glucose and glycated hemoglobin A1c values and use of antidiabetic medications before the index pregnancy were used to establish a diagnosis of maternal preexisting T2D. KPSC follows the standard American College of Obstetrics and Gynecology guideline for screening for GDM during pregnancy.²¹ The diagnosis of maternal GDM was based on laboratory glucose values from 1-hour, 50-g glucose challenge test of 200 mg/dL or greater or 3-hour 100-g or 2-hour 75-g oral glucose tolerance tests during pregnancy with at least 2 abnormal plasma glucose values using the Carpenter-Coustan thresholds.²² Gestational age at GDM diagnosis was calculated using date of the first glucose test that met the GDM diagnosis criteria, date of delivery, and gestational age at delivery available in the EMR. Data on antidiabetic medication (insulin or oral drugs such as glyburide and metformin) use during pregnancy was retrieved from the KPSC EMR pharmacy dispensing records.

The main outcome measures were the presence or absence of asthma and age at initial diagnosis or last follow-up. Asthma cases were identified if the children had one of following conditions: (1) one or more inpatient or emergency encounter owing to asthma (ICD-9 code 493 and ICD-10 code J45), (2) one or more outpatient encounter owing to asthma and at least one asthma-specific medication dispensed within 1 year of the diagnosis, or (3) 3 or more outpatient encounters owing to asthma if no asthma-specific medications were dispensed. This algorithm has been used previously at KPSC to identify childhood asthma.²³

Covariates

Covariates to control for potential confounding were maternal age at delivery, parity, education, self-reported race/ethnicity, median family household income based on census tract of residence, maternal history of asthma, history of medical comorbidity (diagnosis of heart, lung, kidney, liver disease or cancer) other than diabetes or asthma, birth

year, and sex of the child. In addition, potential confounding by smoking during pregnancy and maternal obesity measured by prepregnancy BMI and gestational weight gain were assessed. Maternal preeclampsia/eclampsia during pregnancy, gestational age at delivery, and child's birth weight might confound or mediate the associations between diabetes exposure and child's asthma risk, and thus were assessed separately by additionally including these variables as covariates in the models.

Statistical Analyses

Maternal and child characteristics were compared among unexposed, GDM, and T2D groups by χ^2 test for proportions and ANOVA F-test for means. Cumulative incidences of asthma by exposure groups were estimated by the Kaplan-Meier method. Relative risks were estimated by hazard ratios (HRs) from Cox regression models in which family was specified as a random effect to control for potential correlation owing to multiple siblings born to the same mother. The outcome is age to asthma diagnosis or last follow-up age if no asthma diagnosis. The exposure variable of interest is maternal T2D or GDM status and gestational age of GDM diagnosis as well as antidiabetic medication use status within GDM exposed group. Proportional hazard assumptions were evaluated by checking for parallel lines among the exposure groups in the log (-log (survival)) plot against age. Potential confounding owing to birth year, maternal age, race/ethnicity, parity, education, household income, maternal history of asthma, history of comorbidity, and sex of the child were assessed through covariate adjustment. Birth year, maternal age, prepregnancy BMI, and gestational weight gain were analyzed as continuous variables in the multivariate adjusted analyses. Potential confounding or pathways associated with maternal preeclampsia/eclampsia, birth weight, and gestational age at delivery were assessed through additional adjustment of them as covariates in the models. Potential interaction with maternal history of asthma, smoking during pregnancy, and child's sex was explored by adding an interaction term between diabetes status and each of the variables in the model.

SAS Enterprise Guide 5.1 (SAS Institute Inc, Cary, North Carolina) and R 3.4.0 (64 bit; The R Foundation, Vienna, Austria) were used for data analysis. All statistical tests were 2-sided.

Results

Among the study sample of 97 554 children, 3119 (3.2%) were exposed to T2D and 9836 (10.1%) to GDM in utero. The 2 diabetes-exposed groups and the unexposed group differed in maternal age, parity, household income, race/ethnicity, history of asthma, history of comorbidity, preeclampsia/eclampsia, prepregnancy BMI, and gestational weight gain, as well as child's birth weight and gestational weeks at delivery. No differences were observed for maternal education, smoking during pregnancy, and child's sex (Table I).

The 97 554 children were followed from age 5 for a median of 7.6 years (IQR, 6.3-9.0 years) from birth. During this time, 15 125 children (15.5%) were diagnosed with asthma. Frequencies of children with asthma after exposure to T2D, GDM, or no diabetes were, 19.5%, 15.9%, and 15.3%, respectively ($P < .001$ for differences among groups). Among GDM cases, gestational age at GDM diagnosis, when analyzed as a continuous variable, was not associated with child's asthma risk (bivariate $P = .27$). There were 3380 women (34.4%) with GDM who were dispensed antidiabetic medication during pregnancy; among them, 78.8% were dispensed insulin. Frequencies of children with asthma were 17.7% and 15.0% for the GDM with and without medication use groups, respectively ($P < .001$). The risk of child's asthma was significantly greater for the GDM dispensed medication than for GDM not dispensed medication (bivariate HR, 1.35; 95% CI, 1.15-1.58; $P < .001$). Figure 2 depicts the crude cumulative incidences of asthma by maternal diabetic exposure and GDM medication treatment. Asthma risk was greatest in T2D-exposed, followed by GDM with medication treatment. The GDM who did not use medications had no greater risk than the unexposed group ($P = .75$).

Table II presents the unadjusted and adjusted relative risks of child's asthma associated with diabetic exposure. In the unadjusted analysis, the HR associated with preexisting T2D compared with no diabetes was 1.43 (95% CI, 1.29-1.59; $P < .001$). The HR associated with GDM requiring medication treatment to control glucose during pregnancy was 1.24 (95% CI, 1.12-1.37; $P < .001$). Interestingly, GDM not requiring medication treatment during pregnancy was not associated with the child's asthma risk (HR, 0.99; 95% CI, 0.91-1.17; $P = .75$). Adjustment for potential confounding owing to social demographics and maternal history decreased the HR estimates associated with T2D (to an HR of 1.31; $P < .001$) and GDM with medications (to an HR of 1.17; $P = .002$), but did not eliminate the significance (Table II, multivariate adjusted 1). Further adjusting for maternal prepregnancy BMI and gestational weight gain additionally reduced the HR estimates for both T2D (to an HR of 1.23; $P < .001$) and GDM with medication (to an HR of 1.09; $P = .08$), such that the association with GDM requiring medications was borderline significant (Table II, multivariate adjusted 2). Additional adjusting for preeclampsia/eclampsia had little impact on the results (adjusted HR, 1.23; 95% CI, 1.11-1.36; $P < .001$ for T2D; adjusted HR, 1.09; 95% CI, 0.99-1.21; $P = .08$ for GDM with medication). Of note, gestational age at GDM diagnosis remained not associated with child's asthma risk after adjusting for potential confounders ($P = .62$). Including birthweight and gestational age at delivery as covariates did not decrease the HR estimates (T2D: HR, 1.26; 95% CI, 1.13-1.39; $P < .001$; GDM with medication: HR, 1.12; 95% CI, 1.01-1.24; $P = .03$). There were no significant interactions between maternal diabetes and smoking or sex on child's asthma risk ($P = .38$ and $.45$, respectively, after including these

Table I. Characteristics of the cohort at the time of the index pregnancy

Characteristics	Diabetes status			P value*
	Unexposed (n = 84 599)	GDM (n = 9836)	Preexisting T2D (n = 3119)	
Maternal				
Age (years)	30.0 ± 5.68	32.9 ± 5.16	33.0 ± 5.27	<.001
Parity				<.001
0	31 072 (36.7)	3310 (33.7)	1031 (33.1)	
1	26 243 (31)	2947 (30)	962 (30.8)	
≥2	21 196 (25.1)	3004 (30.5)	927 (29.7)	
Missing	6088 (7.2)	575 (5.8)	199 (6.4)	
Education				.46
≤High school	27 919 (33)	3234 (32.9)	1032 (33.1)	
Some college	25 528 (30.2)	2909 (29.6)	961 (30.8)	
≥College graduate	30 276 (35.8)	3601 (36.6)	1089 (34.9)	
Missing	876 (1)	92 (0.9)	37 (1.2)	
Household income				.04
<\$30 000	4836 (5.7)	549 (5.6)	187 (6)	
\$30 000-\$49 999	24 777 (29.3)	2934 (29.8)	986 (31.6)	
\$50 000-\$69 999	27 578 (32.6)	3257 (33.1)	1013 (32.5)	
\$70 000-\$89 999	16 627 (19.7)	1867 (19)	594 (19)	
≥\$90 000	10 761 (12.7)	1226 (12.5)	338 (10.8)	
Missing	20 (0)	3 (0)	1 (0)	
Race/ethnicity				<.001
Non-Hispanic white	20 554 (24.3)	1659 (16.9)	659 (21.1)	
Non-Hispanic black	7754 (9.2)	586 (6)	274 (8.8)	
Hispanic	43 953 (52)	5273 (53.6)	1646 (52.8)	
Asian/Pacific islanders	10 812 (12.8)	2121 (21.6)	483 (15.5)	
Others	1526 (1.8)	197 (2)	57 (1.8)	
History of asthma	6902 (8.2)	781 (7.9)	384 (12.3)	<.001
History of comorbidity other than diabetes or asthma	5343 (6.4)	840 (8.5)	452 (14.5)	<.001
Smoking during pregnancy	704 (0.8)	91 (0.9)	27 (0.9)	.12
Preeclampsia/eclampsia	2820 (3.3)	493 (5)	238 (7.6)	<.001
Prepregnancy BMI (kg/m ²)	26.4 (5.92)	29.4 (6.88)	31.8 (7.75)	<.001
Gestational weight gain (lbs)	28.8 ± 13.45	20.4 ± 14.10	23.7 ± 16.02	<.001
Child				
Birth weight (g)	3358.3 ± 517.73	3330.9 ± 573.33	3398.2 ± 674.11	<.001
Gestational weeks at birth	38.8 ± 1.63	38.4 ± 1.78	38.1 ± 2.03	<.001
Female sex	41 256 (48.8)	4792 (48.7)	1494 (47.9)	.64

Values are mean ± SD or number (%).

*P values are calculated from χ^2 test for categorical variables and from ANOVA F-test for continuous variables.

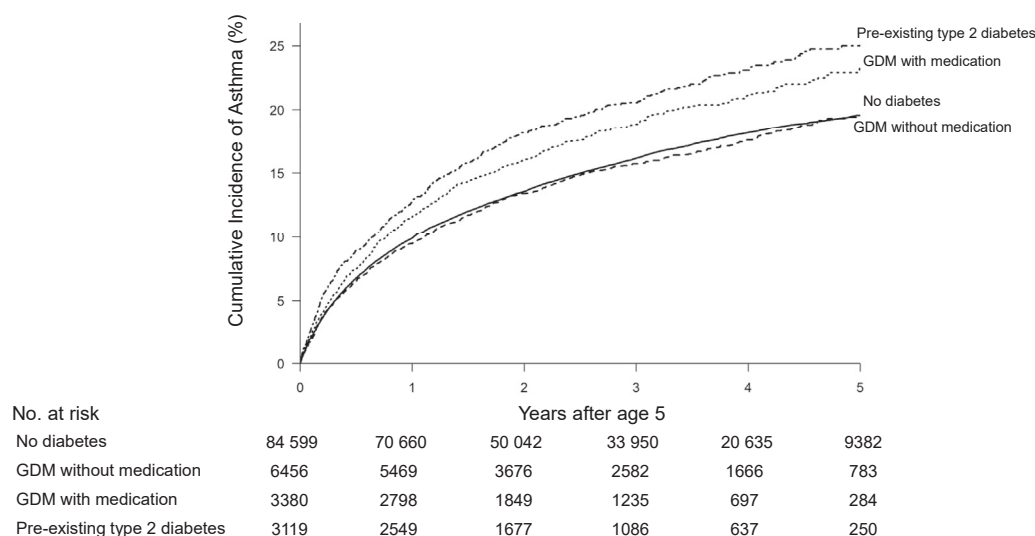


Figure 2. Crude cumulative incidence of asthma by diabetic exposure in utero: preexisting T2D, GDM dispensed antidiabetic medications during pregnancy (GDM with medication), GDM not dispensed antidiabetic medications during pregnancy (GDM without medication), and no diabetes.

Table II. Associations between maternal diabetes during pregnancy and risk of asthma in offspring

Maternal diabetes	No. with asthma/total	Unadjusted		Multivariate adjusted 1*		Multivariate adjusted 2†	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
None	12 949/84 599	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Preexisting T2D	609/3119	1.43 (1.29-1.59)	<.001	1.32 (1.19-1.46)	<.001	1.23 (1.11-1.36)	<.001
GDM with medications	598/3380	1.23 (1.12-1.37)	<.001	1.17 (1.06-1.30)	.002	1.10 (0.99-1.21)	.07
GDM without medications	967/6456	0.99 (0.91-1.07)	.75	1.00 (0.92-1.08)	.93	0.98 (0.90-1.06)	.55

*Adjusted 1: variables included birth year (continuous), maternal age at delivery (continuous), parity, education, household income, maternal race/ethnicity, history of comorbidity other than diabetes or asthma, history of maternal asthma, smoking during pregnancy, and sex of the child.

†Adjusted 2: adjusted for potential confounders in adjusted 1 plus prepregnancy BMI and gestational weight gain.

covariates in the multivariate adjusted 2 model). However, maternal history of asthma significantly interacted with maternal diabetes during pregnancy to affect child's asthma risk ($P = .05$ testing for interaction).

Table III presents the fully adjusted HRs of child's asthma associated with maternal diabetes stratified by maternal history of asthma status. The significant interaction was mainly owing to the greater risk associated with maternal preexisting T2D relative to no diabetes for mothers with a history of asthma (HR, 1.53; 95% CI, 1.19-1.96; $P < .001$) than mothers without a history of asthma (HR, 1.21; 95% CI, 1.08-1.36; $P < .001$). The child's asthma risk associated with GDM requiring medications was generally similar between mothers with a history of asthma (HR, 1.12; 95% CI, 1.01-1.25; $P = .04$) and mothers without a history of asthma (HR, 1.11; 95% CI, 0.85-1.46; $P = .44$). GDM not requiring medications was not associated with childhood asthma for mothers without or with a history of asthma.

Discussion

Compared with no diabetes during pregnancy, maternal preexisting T2D was associated with a statistically significant effect on child's asthma risk (approximately 20% increased risk) among mothers without a history of asthma, but the risk increased to approximately 50% among mothers with a history of asthma. GDM requiring antidiabetic medication treatment during pregnancy was associated with a small effect on child's asthma risk (approximately 10% increased risk) and the risk was similar for mothers with or without a history

of asthma. GDM not requiring antidiabetic medication treatment during pregnancy was not associated with childhood asthma compared with no diabetes for mothers with or without a history of asthma. Last, the timing (early and late in gestation) of GDM diagnoses during pregnancy was not associated with childhood asthma. Our results show that the associations between maternal diabetes and childhood asthma vary by types of diabetes and may depend on the severity of maternal diabetes (T2D vs GDM requiring antidiabetic medication vs GDM without requiring medications) and family history of asthma.

Results from this large cohort provide insight into the relationship between diabetic pregnancy and risk of asthma in offspring. The comprehensive data with detailed information on pregestational and gestational diabetes diagnosis and medication use allowed us to evaluate GDM and preexisting T2D separately, and to assess antidiabetic medication treatment and subsequently identify high-risk subgroups. The rich covariate information including prepregnancy BMI and gestational weight gain during pregnancy allowed us to control for important confounding owing to maternal obesity. Maternal obesity is a well-established risk factor for both T2D and GDM.²⁴ Maternal obesity is also a risk factor for childhood asthma.²⁵ We demonstrated the importance of controlling for potential confounding owing to social demographics as well as maternal obesity. Without adjusting for these factors, the risk associated with childhood asthma was higher and significantly increased for both T2D and GDM requiring medications. However, adjusting for maternal prepregnancy BMI and gestational weight gain greatly decreased the associations such that the association

Table III. Associations between maternal diabetes during pregnancy and risk of asthma in offspring stratified by maternal history of asthma status*

Maternal diabetes statuses	Maternal history of asthma					
	No			Yes		
	No. of kids with asthma/total	HR [†] (95% CI)	P value	No. of kids with asthma/total	HR [†] (95% CI)	P value
None	11 052/77 697	1.00 (reference)		1897/6902	1.00 (reference)	
Preexisting T2D	479/2735	1.21 (1.08-1.36)	<.001	130/384	1.53 (1.19-1.96)	<.001
GDM with medications	503/3066	1.12 (1.01-1.25)	.04	95/314	1.11 (0.85-1.46)	.44
GDM without medications	860/5989	1.01 (0.93-1.10)	.82	107/467	0.84 (0.66-1.08)	.17

*Maternal history of asthma significantly interacted with maternal diabetes during pregnancy to affect child's asthma risk ($P = .05$ testing for interaction).

†Adjusted for birth year (continuous), maternal age at delivery (continuous), parity, education, household income, maternal race/ethnicity, history of comorbidity other than diabetes or asthma, smoking during pregnancy, prepregnancy BMI, gestational weight gain and sex of the child.

with GDM requiring medications became small and borderline significant.

Compared with prior studies, only 1 study from Canada formally assessed the association between diabetes in pregnancy and risk of asthma in children.¹³ The study found that maternal diabetes was associated with an OR of 1.95 (95% CI, 0.98-3.86) for children to have asthma. Paternal diabetes was not associated with child's asthma (OR, 0.82; 95% CI, 0.33-2.05), which supports the premise that the intrauterine glycemic environment plays a role in child's asthma risk. They also found that, in the absence of maternal asthma or exposure to tobacco smoking, maternal diabetes was not associated with child's asthma risk (OR, 0.65; 95% CI, 0.16-2.56). We also found significant interaction between maternal diabetes and maternal history of asthma. The significant interaction was mainly owing to preexisting T2D, where the risk was approximately 20% compared with no diabetes for mothers without a history of asthma, and approximately 50% for mothers with a history of asthma. The small sample size from the Canadian study (50 mothers were reported to have diabetes during pregnancy) and lack of information on types of diabetes and treatment information as well as no adjustment for social demographics and maternal obesity precludes detailed comparisons between the 2 studies. Among the 3 studies that have reported an association between maternal diabetes and childhood asthma, although maternal diabetes was not the major focus of these studies, the small US study showed maternal diabetes (unknown types) was associated with a 3-fold increased risk of physician-diagnosed asthma.¹⁶ However, this estimate was not adjusted for any confounders. The large-sample Swedish and Finnish studies both found a modest association between maternal diabetes and childhood asthma.^{14,15} However, pregestational diabetes and GDM were combined and there was no information on GDM treatment and no adjustment for maternal obesity. Additional large-sample studies are needed to confirm our findings.

Potential biological mechanisms linking asthma risk in offspring and diabetes during pregnancy may involve multiple pathways. Women with preexisting T2D may have relatively higher glucose levels during pregnancy than women with GDM diagnosed during pregnancy. In addition, women with GDM requiring medication treatment during pregnancy may have higher glucose levels than women with GDM not requiring medication treatment. Clinical guidelines for GDM management indicate that management should start with nonpharmacologic approaches, such as dietary changes, physical activity, and glucose monitoring.²¹ When this approach is ineffective at consistently achieving target glucose levels, then pharmacologic treatment such as insulin or oral antidiabetic medications may be prescribed.²¹ The suboptimal glycemic environment may predispose fetuses to stress, chronic inflammation, hypoxia, and fetal hyperinsulinemia, which in turn may lead to immune suppression and interfere with lung growth and maturation; alveolar sac formation, proliferation, and expansion; and impaired surfactant production which then predispose

offspring to newborn respiratory conditions and chronic lung disease such as wheezing and asthma.^{26,27} Future work is needed to assess whether the risk of asthma observed in our clinical observational cohort was owing to suboptimal glycemic control throughout pregnancy.

This study has several important strengths. This study evaluated asthma risk associated with diabetes exposure by diabetes type (T2D vs GDM), assessed the timing of exposure by using gestational age of GDM diagnosis, and the severity of GDM by using antidiabetic medication treatment during pregnancy to identify subgroup with high risk. This study controlled for multiple confounding factors including sociodemographics, maternal history of asthma, comorbidity, smoking during pregnancy, preeclampsia/eclampsia, maternal prepregnancy BMI, and gestational weight gain. The rates of diabetes in pregnancy observed in this cohort (3.2% for T2D and 10.1% for GDM) as well as the rate of asthma in children aged 5 years and older (15.5%) are comparable with rates reported for the US population.^{7,8,28} All data came from a single, integrated clinical care system in which the demographics of the members are representative of Southern California residents.¹⁸ Children had to be born at KPSC and enrolled in the KPSC health plan by age 5 years and continued KPSC membership to minimize screening and outcome ascertainment bias. All data were collected prospectively as part of routine clinical care, eliminating recall bias.

Some important limitations are acknowledged. The degree of glycemia control during pregnancy was not assessed because data were not available. Potential confounding bias owing to unmeasured factors such as air pollution, allergies, respiratory infections, second hand smoke exposure, or genetic susceptibility could not be ruled out and we do not have paternal data, although maternal history of asthma was adjusted in the data analysis. Exposure to maternal preexisting type 1 diabetes was not assessed owing to the limited number of mothers who had type 1 diabetes. The severity of asthma was not assessed because the classification of asthma severity is not readily available. Future studies on the association with severity of asthma are needed. Although our study population is representative of Southern California residents, these results may not be generalizable to other populations with different population characteristics. Finally, this is an observational study and causal inferences cannot be made.

Data from this multiethnic, longitudinal birth cohort study indicated that, compared with no diabetes during pregnancy, maternal preexisting T2D was associated with approximately 20% increased risk for childhood asthma among mothers without a history of asthma but approximately 50% increased risk among mothers with a history of asthma; GDM requiring medication treatment during pregnancy was associated with approximately 10% increased risk of childhood asthma among mothers without or with a history of asthma; and GDM not requiring medication treatment during pregnancy was not associated with the risk of childhood asthma. ■

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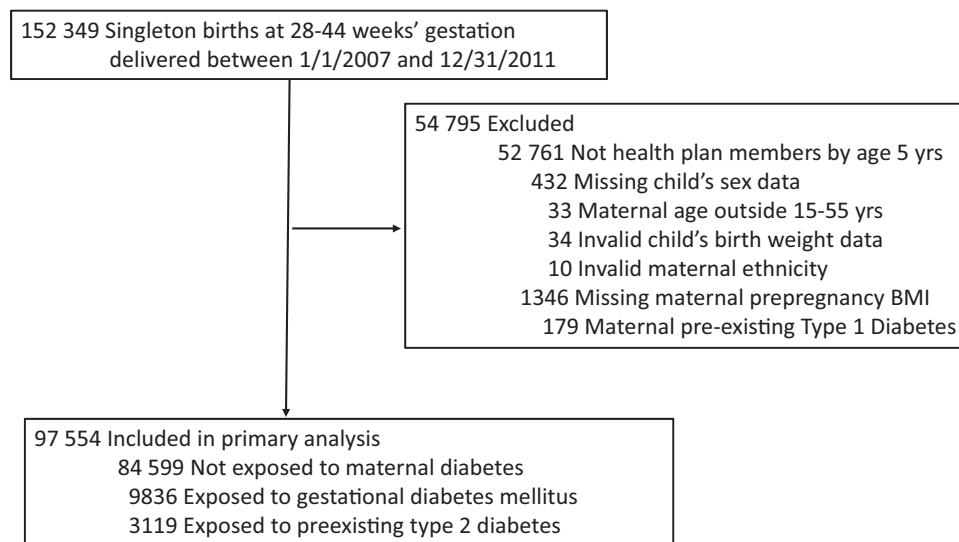


Figure 1. Study cohort derivation.