Original Investigation

Association of Maternal Diabetes With Autism in Offspring

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IMPORTANCE Information about the association of maternal diabetes and autism spectrum disorders (ASDs) in offspring is limited, with no report on the importance of timing of exposure during gestation.

OBJECTIVE To assess ASD risk associated with intrauterine exposure to preexisting type 2 diabetes and gestational diabetes mellitus (GDM) by gestational age at GDM diagnosis.

DESIGN, SETTING, AND PATIENTS Retrospective longitudinal cohort study including 322 323 singleton children born in 1995-2009 at Kaiser Permanente Southern California (KPSC) hospitals. Children were tracked from birth until the first of the following: date of clinical diagnosis of ASD, last date of continuous KPSC health plan membership, death due to any cause, or December 31, 2012. Relative risks of ASD were estimated by hazard ratios (HRs) using Cox regression models adjusted for birth year.

EXPOSURES Maternal preexisting type 2 diabetes (n = 6496), GDM diagnosed at 26 weeks' gestation or earlier (n = 7456) or after 26 weeks' gestation (n = 17 579), or no diabetes (n = 290 792) during the index pregnancy.

MAIN OUTCOMES AND MEASURES Clinical diagnosis of ASD in offspring.

RESULTS During follow-up, 3388 children were diagnosed as having ASD (115 exposed to preexisting type 2 diabetes, 130 exposed to GDM at ≤26 weeks, 180 exposed to GDM at >26 weeks, and 2963 unexposed). Unadjusted annual ASD incidences were 3.26, 3.02, 1.77, and 1.77 per 1000 among children of mothers with preexisting type 2 diabetes, GDM diagnosed at 26 weeks or earlier, GDM diagnosed after 26 weeks, and no diabetes, respectively. The birth year–adjusted HRs were 1.59 (95% CI, 1.29-1.95) for preexisting type 2 diabetes, 1.63 (95% CI, 1.35-1.97) for GDM diagnosed at 26 weeks or earlier, and 0.98 (95% CI, 0.84-1.15) for GDM diagnosed after 26 weeks relative to no exposure. After adjustment for maternal age, parity, education, household income, race/ethnicity, history of comorbidity, and sex of the child, maternal preexisting type 2 diabetes was not significantly associated with risk of ASD in offspring (HR, 1.21; 95% CI, 0.97-1.52), but GDM diagnosed at 26 weeks or earlier remained so (HR, 1.42; 95% CI, 1.15-1.74). Antidiabetic medication exposure was not independently associated with ASD risk. Adjustment for a mother or older sibling with ASD in the full cohort and for maternal smoking, prepregnancy body mass index, and gestational weight gain in the subset with available data (n = 68 512) did not affect the results.

CONCLUSIONS AND RELEVANCE In this large, multiethnic clinical cohort of singleton children born at 28 to 44 weeks' gestation, exposure to maternal GDM diagnosed by 26 weeks' gestation was associated with risk of ASD in offspring.

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Exposure of fetuses to maternal hyperglycemia may have long-lasting effects on organ development and function.[1] Previous studies have revealed long-term risks of obesity[2-4] and related metabolic disorders[5] in offspring of women who had diabetes prior to pregnancy as well as women with hyperglycemia first detected during pregnancy (gestational diabetes mellitus [GDM][6]). Whether such exposure can disrupt fetal brain development and heighten risk of neurobehavioral developmental disorders in offspring is less clear.

ASD *autism spectrum disorders*

GDM *gestational diabetes mellitus*

PDD-NOS *pervasive developmental disorder not otherwise specified*

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairments in social interaction and communications and restricted and repetitive behaviors.[7] The diagnosis of ASD is increasing,[8] with an estimated prevalence of 1.47% among 8-year-old children in the United States.[9] Meta-analyses have shown some evidence of a significant association between exposure to maternal diabetes and risk of ASD in offspring.[10,11] Less information is available on the association of exposure to maternal GDM (defined as glucose intolerance with onset or first recognition during pregnancy[6]) with risk of ASD. The few cohort studies that included analysis of GDM lacked information on details of exposure to GDM and ASD risk.[12,13]

For the present study, we analyzed data from a single health care system to assess the association between maternal diabetes, both known prior to pregnancy and diagnosed during pregnancy, and the risk of ASD in children. Based on associations found between other exposures during early pregnancy and risk of ASD,[14,15] we also examined the importance of timing of GDM diagnosis as a surrogate of timing of exposure to hyperglycemia.

Methods

Study Population

This retrospective longitudinal cohort study included singleton children born at 28 to 44 weeks' gestation in Kaiser Permanente Southern California (KPSC) hospitals between January 1, 1995, and December 31, 2009 (**Figure 1**). Children who were born to women with type 1 diabetes and those with congenital anomalies were not included. Kaiser Permanente Southern California is a large health care organization that provides comprehensive care and uses an integrated electronic medical record system. Demographic distribution of KPSC membership broadly represents southern California residents.[16]

Per KPSC guidelines, child behavior questionnaires are administered at preventive care and well child visits as early as age 4 months. A brief screening checklist (a modified version of the Checklist for Autism in Toddlers [CHAT][17]) is administered to all children at ages 18 and 24 months to screen for developmental delays including ASD. A clinical diagnosis of ASD is based on pediatric developmental specialist evaluations. For the present report, children not enrolled as KPSC plan members by age 1 year were not eligible. This decision minimizes ascertainment bias in identification of ASD and ensures relatively long-term follow-up. Follow-up ended on the first date that any of the following occurred: (1) clinical diagnosis of ASD; (2) last date of continuous KPSC plan membership; (3) death from any cause; or (4) December 31, 2012.

All maternal and child data were extracted from electronic medical records and birth certificate records and were linked by a unique membership identifier used for patient care. All data were checked for quality through data plots and frequency tables. Potential outliers and data errors were rectified by cross-checking against historical data in the electronic medical record. Validity of data was established in previous publications.[18-20] The institutional review board at KPSC approved this study and provided waiver of participant consent.

Exposures and Outcomes

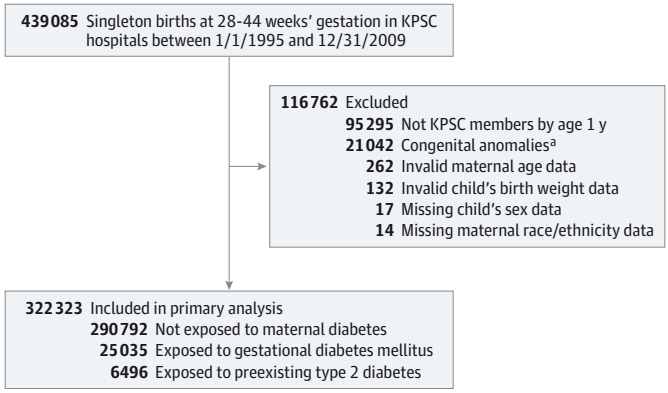
The primary exposure variable was maternal type 2 diabetes or maternal GDM during pregnancy. Exposures were divided into 3 categories based on *International Classification of Diseases, Ninth Revision* (*ICD*-9) codes, antidiabetic medication use, and glucose values from 1-hour 50-g glucose challenge tests and/or oral glucose tolerance tests administered during pregnancy: (1) no exposure to maternal diabetes; (2) exposure to maternal type 2 diabetes antedating pregnancy; and (3) exposure to maternal GDM. Women with polycystic ovary syndrome who took metformin outside of pregnancy (*ICD*-9 code 256.xx) were not considered to have type 2 diabetes unless type 2 diabetes was documented in the electronic medical record. Kaiser Permanente Southern California follows the American Congress of Obstetricians and Gynecologists guidelines for screening for GDM.[21] Diagnosis of GDM was based on laboratory values confirming a plasma glucose level of 200 mg/dL or higher on the glucose challenge test or at least 2 plasma glucose values meeting or exceeding the following values on the 100-g or 75-g oral glucose tolerance test: fasting, 95 mg/dL; 1 hour, 180 mg/dL; 2 hours, 155 mg/dL; and 3 hours, 140 mg/dL.[6,18] Gestational age at GDM diagnosis was calculated using the date of the first glucose test result that met the GDM diagnosis criteria, date of delivery, and gestational age at delivery available in the electronic medical record. (To convert glucose values to mmol/L, multiply by 0.0555.)

Main outcome measures were the presence or absence of ASD during the follow-up period and age at last follow-up. Cases of ASD were identified by *ICD*-9 codes 299.x or equivalent KPSC codes. These codes include autistic disorders, Asperger syndrome, or pervasive developmental disorder not otherwise specified (PDD-NOS) and excluded childhood disintegrative disorder and Rett syndrome. Codes from at least 2 separate visits were required for ASD diagnosis, and these codes were validated.[22]

Covariates

Covariates to control for potential confounding were maternal age at delivery, parity, education, self-reported maternal race/ethnicity, median family household income based on cen-

Figure 1. Kaiser Permanente Southern California (KPSC) Study Cohort Composition



[a] Congenital anomalies included central nervous system, digestive tract, genital or urinary tract, cardiovascular, lung, and musculoskeletal birth defects.

sus tract of residence, history of comorbidity (≥1 diagnosis of heart, lung, kidney, or liver disease; cancer), and sex of the child. For the GDM-exposed group, we also evaluated confounding due to differences in method used to diagnose GDM: (1) 1-hour glucose challenge test result alone; (2) impaired fasting glucose value and at least 1 impaired postchallenge glucose value from the diagnostic oral glucose tolerance test; or (3) impaired postchallenge glucose values from the diagnostic oral glucose tolerance test alone. Information about antidiabetic medication use (insulin, oral antihyperglycemia drugs) during pregnancy was extracted from the KPSC electronic pharmacy databases. Preeclampsia/eclampsia during the index pregnancy, gestational age at delivery, birth weight, and antidiabetic medication use during the index pregnancy were considered potential pathways for the association between diabetes exposure and risk of ASD. Potential confounding due to maternal prepregnancy body mass index, gestational weight gain, and smoking were assessed in a subset of the cohort in which these data had been collected electronically starting in late 2006.

Statistical Analysis

Maternal characteristics and obstetrical and neonatal outcomes were compared among the unexposed, GDM, and type 2 diabetes groups by χ^2 test for proportions and analysis of variance for means. Unadjusted average annual ASD incidence was calculated by number of children who were diagnosed as having ASD divided by total number of person-years of follow-up. Cumulative incidence of ASD in each exposure group was estimated by the Kaplan-Meier method. Relative risks of ASD were estimated by hazard ratios (HRs) using Cox regression models in which family was specified as a random effect to control for potential correlation due to multiple siblings born to the same mother. Birth year was included as a covariate to control for possible confounding due to changes in GDM testing and ASD screening over the study period.

Gestational weeks at diagnosis of GDM was considered a continuous variable and a categorical variable with 3 strata: 26 weeks or earlier (mean of 16 weeks), after 26 weeks but prior to 30 weeks (mean of 28 weeks), and 30 weeks or later (mean of 32 weeks). These cutoffs were the tertile cutoffs of gestational age of GDM diagnosis for the GDM group, rounded to the nearest week for clinical relevance. The tertile cutoffs also provided reasonable sample sizes in each stratum to have appropriate statistical power to assess ASD risk. Bivariable results indicated that the HRs were similar between the stratum of GDM diagnosed after 26 weeks but prior to 30 weeks and the stratum of 30 weeks or later. Therefore, only 2 strata were used in the multivariable-adjusted data analysis (≤26 weeks and >26 weeks).

The low percentage of children with missing covariate information on maternal parity, education, or household income were included in the multivariable-adjusted data analysis by including the category of "missing" in the data analysis. Potential pathways associated with preeclampsia/eclampsia at the index pregnancy, child birth weight, gestational age at delivery, and antidiabetic medication use for treatment of diabetes during pregnancy were assessed through covariate adjustment. Additional data analysis was performed by adjusting for whether mothers or older siblings had a diagnosis of ASD. Exploratory analysis was performed for ASD subtypes. Sensitivity analysis was conducted by including children who were excluded because of congenital anomalies. Confounding by maternal smoking and obesity was assessed through additional adjustment for these covariates in the subset with maternal body mass index data.

SAS Enterprise Guide, version 5.1 (SAS Institute Inc) and R, version 3.0.2 (64 bit) were used for data analysis. All statistical tests were 2-sided and statistical significance was defined as $P < .05$.

Results

The derivation of the study sample is shown in Figure 1. The primary data analysis included 322 323 children without congenital anomalies (born to 253 785 mothers). A subset of 68 512 children (21.3%) had data on maternal prepregnancy body mass index, gestational weight, and smoking during pregnancy.

Of the 322 323 children, 6496 (2.0%) were exposed to preexisting type 2 diabetes, 25 035 (7.8%) were exposed to GDM, and 290 792 (90.2%) were unexposed. Rates of preexisting type

Table 1. Characteristics of the Cohort by Exposure to Maternal Diabetes at the Index Pregnancy

Characteristics	No. (%) of Cohort[a]		
	Unexposed (n = 290 792)	Gestational Diabetes Mellitus (n = 25 035)	Preexisting Type 2 Diabetes (n = 6496)
Maternal characteristics			
Age, mean (SD), y	29.2 (5.8)	32.4 (5.4)	32.7 (5.4)
Parity			
0	115 603 (39.8)	8586 (34.3)	2108 (32.5)
1	94 858 (32.6)	7503 (30.0)	2145 (33.0)
≥2	77 002 (26.5)	8627 (34.5)	2153 (33.1)
Missing	3329 (1.1)	319 (1.3)	90 (1.4)
Education			
High school or lower	124 832 (42.9)	10 981 (43.9)	2619 (40.3)
Some college	79 150 (27.2)	6825 (27.3)	1986 (30.6)
College graduate or higher	80 470 (27.7)	6846 (27.3)	1781 (27.4)
Missing	4804 (1.7)	383 (1.5)	110 (1.7)
Household annual income, $			
<30 000	24 475 (8.4)	2013 (8.0)	615 (9.5)
30 000-49 999	99 360 (34.2)	8873 (35.4)	2400 (36.9)
50 000-69 999	90 669 (31.2)	7903 (31.6)	1966 (30.3)
70 000-89 999	45 380 (15.6)	3752 (15.0)	919 (14.1)
≥90 000	28 763 (9.9)	2336 (9.3)	564 (8.7)
Missing	2145 (0.7)	158 (0.6)	32 (0.5)
Race/ethnicity			
Non-Hispanic white	82 045 (28.2)	4942 (19.7)	1297 (20)
Non-Hispanic black	30 369 (10.4)	1849 (7.4)	711 (10.9)
Hispanic	142 458 (49.0)	13 288 (53.1)	3482 (53.6)
Asian/Pacific Islander	32 257 (11.1)	4688 (18.7)	890 (13.7)
Other	3663 (1.3)	268 (1.1)	116 (1.8)
History of comorbidity	19 996 (6.9)	2086 (8.3)	3188 (49.1)
Preeclampsia/eclampsia	10 282 (3.5)	1269 (5.1)	542 (8.3)
Prepregnancy body mass index, mean (SD)[b,c]	26.5 (6.0)	29.3 (6.7)	32.1 (7.7)
Gestational weight gain, mean (SD), kg[d]	13.1 (6.2)	9.5 (6.3)	10.7 (7.3)
Smoking during pregnancy[e]	556 (1.0)	63 (1.1)	20 (1.1)
Gestational diabetes mellitus diagnostic method			
1-h glucose challenge test alone		3200 (12.8)	
Impaired fasting glucose + impaired postchallenge glucose		9580 (38.2)	
Impaired postchallenge glucose alone		12 255 (49.0)	
Antidiabetic medication use		5888 (23.5)	3884 (59.8)
Child characteristics			
Birth weight, g	3309 (517)	3397 (568)	3433 (648)
Gestational age at birth, wk	39.3 (1.6)	38.8 (1.7)	38.5 (1.9)
Female sex	143 550 (49.4)	12 147 (48.5)	3204 (49.3)

[a] Data are expressed as No. (%) of cohort unless otherwise indicated.

[b] Body mass index was calculated as weight in kilograms divided by height in meters squared.

[c] Sample size was 60 857 for unexposed, 6008 for gestational diabetes mellitus, and 1972 for preexisting type 2 diabetes.

[d] Sample size was 60 577 for unexposed, 5982 for gestational diabetes mellitus, and 1958 for preexisting type 2 diabetes.

[e] Sample size was 57 468 for unexposed, 5609 for gestational diabetes mellitus, and 1847 for preexisting type 2 diabetes.

2 diabetes and GDM increased from 1.0% and 5.2% in 1995 to 2.8% and 8.6% in 2009, respectively. Maternal age, parity, education, household income, race/ethnicity, history of comorbidity, preeclampsia/eclampsia, prepregnancy body mass index, gestational weight gain, and smoking during pregnancy as well as child birth weight, gestational age at delivery, and sex were all significantly different among the 3 groups (P<.001 for all except P=.04 for sex of child) (**Table 1**). Within the GDM group, 12.8% had diagnoses by 1-hour glucose challenge test alone, 38.2% by impaired fasting glucose plus impaired postchallenge glucose, and 49.0% by impaired postchallenge glucose alone. Approximately 60% of mothers in the type 2 diabetes group and 23.5% of mothers in the GDM group used antidiabetic medication during the index pregnancy (Table 1).

The 322 323 children were followed up for a median of 5.5 years (interquartile range, 2.2-8.7 years) after birth. During this

time, 3388 children (2963 unexposed, 115 type 2 diabetes exposed, and 310 GDM exposed) were diagnosed as having ASD. Unadjusted average annual incidences of ASD were 1.77, 3.26, and 2.14 per 1000, respectively ($P < .001$). **Table 2** presents the bivariable associations between maternal and child characteristics during the index pregnancy and the risk of ASD in offspring with adjustment for birth year. Compared with no exposure, exposure to preexisting type 2 diabetes was associated with ASD with an HR of 1.59 (95% CI, 1.29-1.95), while exposure to GDM at any time during pregnancy had an HR of 1.18 (95% CI, 1.04-1.33). Stratified analysis revealed an HR of 1.63 (95% CI, 1.35-1.97) for ASD for exposure to GDM diagnosed at 26 weeks' gestation or earlier. In contrast, the HR was 0.94 (95% CI, 0.76-1.15) for exposure to GDM diagnosed after 26 weeks but prior to 30 weeks and 1.04 (95% CI, 0.81-1.32) with GDM diagnosed at 30 weeks or later (for combined exposure to GDM >26 weeks, HR, 0.98; 95% CI, 0.84-1.15).

Among the covariates assessed, older maternal age, being first born, high maternal education, low household income, history of comorbidity, preeclampsia/eclampsia, early delivery, and being male were significantly associated with ASD risk. Risk of ASD was slightly lower among Hispanics than non-Hispanic whites. Maternal prepregnancy body mass index and gestational weight gain were modestly and positively associated with ASD risk, but smoking during pregnancy was not. Birth weight was not significantly associated with ASD risk. Among GDM and preexisting type 2 diabetes, antidiabetic medication use was associated with higher ASD risk (HR, 1.44; 95% CI, 1.16-1.79) compared with nonuse. Among GDM-exposed children, ASD risk did not vary significantly by GDM diagnostic method ($P = .10$). When gestational age at GDM diagnosis was treated as a continuous variable, there was a significant negative association with ASD risk ($P = .002$).

Figure 2 depicts the Kaplan-Meier plot of crude cumulative incidence. Because the HRs for GDM diagnosed after 26 weeks but prior to 30 weeks and GDM diagnosed at 30 weeks or later were similar, these 2 groups were combined in Figure 2 and for subsequent data analyses. Unadjusted average annual ASD incidences were 1.77 and 3.02 per 1000 for exposure to GDM diagnosed after 26 weeks and GDM diagnosed at 26 weeks or earlier, respectively. Multivariable-adjusted analysis (**Table 3**) revealed that adjustment for potential confounding due to differences in maternal age, parity, education, household income, race/ethnicity, history of comorbidity, and sex of the child reduced the HR estimates associated with type 2 diabetes and GDM exposure. After adjustment, the association with preexisting type 2 diabetes was not statistically significant (HR, 1.21; 95% CI, 0.97-1.52; $P = .09$). Gestational diabetes mellitus as a whole was no longer associated with ASD (HR, 1.04; 95% CI, 0.91-1.19). However, this adjustment did not explain the risk associated with GDM diagnosed at 26 weeks or earlier (adjusted HR, 1.42; 95% CI, 1.15-1.74).

The reduction in the HR for preexisting type 2 diabetes was primarily due to adjustment for maternal age and history of comorbidity, while the reductions in the HRs for GDM overall and GDM diagnosed at 26 weeks or earlier were primarily due to adjustment for maternal age. Including the covariates of preeclampsia/eclampsia at index pregnancy, birth weight, and gestational age at delivery did not change the HRs appreciably (Table 3). Similar results were obtained when children with congenital anomalies were included in data analysis (eTable 1 in the Supplement).

When data analysis was restricted to children exposed to preexisting type 2 diabetes or GDM, risks of ASD in children exposed to preexisting type 2 diabetes (HR, 1.43; 95% CI, 1.06-1.92) or GDM diagnosed at 26 weeks or earlier (HR, 1.64; 95% CI, 1.27-2.11) were higher than in children exposed to GDM diagnosed after 26 weeks after adjustment for potential confounders. Including information on use of antidiabetic medication had minimal statistical effect on the results (HR, 1.35 [95% CI, 0.99-1.83] for exposure to preexisting type 2 diabetes; HR, 1.60 [95% CI, 1.23-2.06] for exposure to GDM diagnosed ≤26 weeks). Antidiabetic medication use was no longer significantly associated with ASD risk after controlling for types of diabetic exposure and potential confounders (HR, 1.18; 95% CI, 0.93-1.50; $P = .17$). The greater risk of ASD in GDM diagnosed at 26 weeks or earlier than after 26 weeks was not explained by differences in the method used to diagnose GDM.

A total of 26 mothers had a documented *ICD-9* code for ASD. Among the children with ASD, 121 had older siblings with ASD. Further adjustment for mothers or older siblings with ASD slightly reduced the HR of ASD associated with maternal diabetes, but the risk associated with GDM diagnosed at 26 weeks or earlier remained significant (adjusted HR, 1.38 [95% CI, 1.15-1.66; $P<.001$] for GDM diagnosed ≤26 weeks; adjusted HR, 1.20 [95% CI, 0.99-1.47; $P = .07$] for preexisting type 2 diabetes). Among the 3388 children with ASD, 79% had autistic disorders, 18% had Asperger syndrome, and 3% had PDD-NOS. The ASD risk associated with GDM diagnosed at 26 weeks or earlier was observed for both autistic disorders and Asperger syndrome although the HR was not statistically significant for Asperger syndrome because of the low number of cases (eTable 2 in the Supplement). The sample size was too small to estimate HRs for PDD-NOS.

The subcohort with maternal obesity and smoking data was generally comparable with the group without these data (eTable 3 in the Supplement). Because these variables were routinely recorded in the electronic medical record after 2006, the follow-up (median of 4 years) was shorter than that for the full cohort. Even with reduced sample size and shorter follow-up, children exposed to GDM diagnosed at 26 weeks or earlier (35 ASD cases in 1976 pregnancies) had a significantly greater ASD risk than unexposed children (608 ASD cases in 60 573 pregnancies) after adjustment for potential confounders (HR, 1.55; 95% CI, 1.03-2.32). The risks associated with exposure to preexisting type 2 diabetes (28 ASD cases in 1958 pregnancies) (HR, 1.11; 95% CI, 0.71-1.75) and GDM diagnosed after 26 weeks (37 ASD cases in 4005 pregnancies) (HR, 0.79; 95% CI, 0.55-1.15) were not significant after adjustment for potential confounders in this subcohort. The risk associated with exposure to GDM diagnosed at 26 weeks or earlier was not explained by maternal smoking (adjusted HR, 1.52; 95% CI, 1.01-2.28), prepregnancy body mass index (adjusted HR, 1.50; 95% CI, 0.99-2.26), or gestational weight gain (adjusted HR, 1.67; 95% CI, 1.10-2.53).

Table 2. Bivariable Associations Between Maternal and Child Characteristics at the Index Pregnancy and Risk of ASD in Offspring

Characteristics	No. With ASD/Total	Hazard Ratio (95% CI)[a]	*P* Value
Maternal characteristics			
All children			
Maternal diabetes			
None	2963/290 792	1 [Reference]	
Preexisting type 2 diabetes	115/6496	1.59 (1.29-1.95)	<.001
GDM	310/25 035	1.18 (1.04-1.33)	.01
Gestational wk at GDM diagnosis			
≤26	130/7456	1.63 (1.35-1.97)	<.001
>26 to <30	101/10 049	0.94 (0.76-1.15)	.55
≥30	79/7530	1.04 (0.81-1.32)	.77
Age (per year)		1.04 (1.03-1.04)	<.001
Parity[b]			
0	1524/126 297	1 [Reference]	<.001
1	1122/104 506	0.85 (0.78-0.92)	
≥2	719/87 782	0.64 (0.58-0.70)	
Education[b]			
High school or lower	1127/138 432	1 [Reference]	<.001
Some college	1016/89 281	1.33 (1.21-1.45)	
College graduate or higher	1208/89 313	1.45 (1.33-1.59)	
Household annual income, $[b]			
<30 000	299/27 103	1.41 (1.23-1.63)	<.001
30 000-49 999	1138/110 633	1 [Reference]	
50 000-69 999	1116/100 538	0.94 (0.86-1.03)	
70 000-89 999	490/50 051	0.74 (0.66-0.84)	
≥90 000	329/31 663	0.76 (0.66-0.87)	
Race/ethnicity			
Non-Hispanic white	963/88 284	1 [Reference]	.002
Non-Hispanic black	367/32 929	0.96 (0.84-1.10)	
Hispanic	1545/159 228	0.87 (0.80-0.95)	
Asian/Pacific Islander	472/37 835	1.07 (0.95-1.22)	
Other	41/4047	0.92 (0.65-1.30)	
History of comorbidity			
No	3015/297 053	1 [Reference]	<.001
Yes	373/25 270	1.34 (1.18-1.51)	
Preeclampsia/eclampsia			
No	3209/310 230	1 [Reference]	<.001
Yes	179/12 093	1.44 (1.22-1.70)	
Prepregnancy body mass index			
Per 5 units[c]		1.07 (1.00-1.14)	.04
Categorical[c]			
Underweight (<18.5)	17/1722	1.07 (0.62-1.84)	.29
Normal (≥18.5 to <25)	289/30 002	1 [Reference]	
Overweight (≥25 to <30)	206/19 579	1.11 (0.91-1.35)	
Obese (≥30)	200/17 534	1.22 (1.00-1.49)	
Gestational weight gain, per 4 kg[d]		1.07 (0.62 1.84)	.04
Pregnancy smoking[e]			
No	638/64 285	1 [Reference]	.69
Yes	5/639	0.83 (0.33-2.09)	

(continued)

Table 2. Bivariable Associations Between Maternal and Child Characteristics at the Index Pregnancy and Risk of ASD in Offspring (continued)

Characteristics	No. With ASD/Total	Hazard Ratio (95% CI)[a]	*P* Value
Children exposed to GDM or preexisting type 2 diabetes			
Antidiabetic medication use			
No	259/21 759	1 [Reference]	.001
Yes	166/9772	1.44 (1.16-1.79)	
Children exposed to GDM			
GDM diagnostic method			
Impaired postchallenge glucose alone	149/12 255	1 [Reference]	.34
1-h glucose challenge test alone	32/3200	0.83 (0.55-1.25)	
Impaired fasting glucose + impaired postchallenge glucose	129/9580	1.12 (0.87-1.45)	
Gestational age at GDM diagnosis, per wk		0.98 (0.96-0.99)	.002
Child characteristics			
Birth weight, per kg		1.05 (0.98-1.13)	.15
Gestational age at delivery, per wk		0.97 (0.96-0.99)	<.001
Sex			
Female	583/158 901	1 [Reference]	<.001
Male	2805/163 422	5.10 (4.62-5.62)	

Abbreviations: ASD, autism spectrum disorders; GDM, gestational diabetes mellitus.

[a] From Cox regression models in which family was specified as a random effect and birth year was included as a covariate.

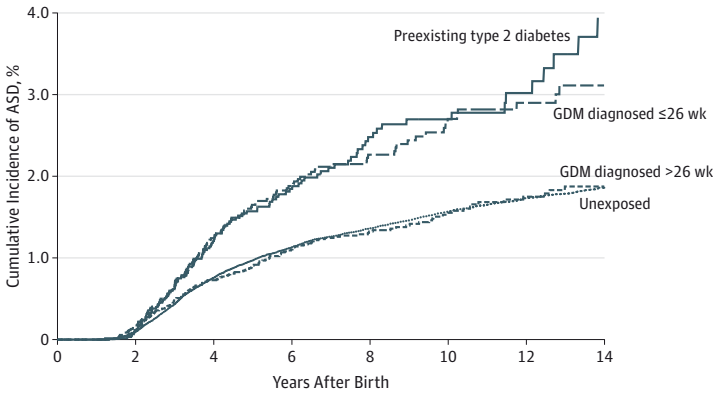
[b] Bivariable hazard ratios were not reported for children with missing data in these variables.

[c] A total of 68 837 children (712 ASD cases) had maternal prepregnancy body mass index data, calculated as weight in kilograms divided by height in meters squared.

[d] A total of 68 517 children (708 ASD cases) had maternal gestational weight gain data.

[e] A total of 64 924 children (643 ASD cases) had maternal smoking data.

Figure 2. Unadjusted Cumulative Incidence of ASD by In Utero Exposure to Maternal Diabetes



No. at risk

Preexisting type 2 diabetes	6496	5847	4363	2927	1935	1238	709	389
GDM diagnosed ≤26 wk	7456	6669	4991	3521	2519	1747	1135	594
GDM diagnosed >26 wk	17 579	15 552	11 616	8249	5878	4121	2799	1668
Unexposed	290 792	254 504	187 707	134 782	97 865	69 348	47 357	28 568

ASD indicates autism spectrum disorder; GDM, gestational diabetes mellitus.

Discussion

We found that maternal preexisting type 2 diabetes was not significantly associated with risk of ASD in offspring but that GDM diagnosed by 26 weeks' gestation was significantly associated with risk of ASD in offspring after adjustment for covariates. The ASD risk associated with GDM diagnosed by 26 weeks was independent of maternal smoking, prepregnancy body mass index, and gestational weight gain in a subcohort. Antidiabetic medication use was not independently associated with ASD risk in offspring.

Our results help to clarify the relationship between exposure to maternal diabetes in utero and risk of ASD in offspring. We found that maternal preexisting type 2 diabetes was not independently associated with risk of ASD in offspring. The high ASD risk observed in the preexisting type 2 diabetes group in the crude cumulative incidence plot and bivariable HR was primarily due to confounding by maternal covariates. Exposure to preexisting type 2 diabetes was associated with an HR of approximately 1.60 for ASD in the bivariable analysis. However, in mothers with preexisting type 2 diabetes, after controlling for potential confounders, especially maternal age and the presence of comorbidities, the HR was reduced to approximately 1.20 and was not statistically significant ($P = .09$).

The 2 large cohort studies in Canada that separated preexisting type 2 diabetes from GDM reported relative risks of

Table 3. Multivariable-Adjusted Risk of ASD in Offspring Associated With In Utero Exposure to Maternal Diabetes and Gestational Age at GDM Diagnosis During the Index Pregnancy

	No. With ASD/Total	Hazard Ratio (95% CI)[a]	*P* Value
Adjusted for potential confounders[b]			
Unexposed	2963/290 792	1 [Reference]	
Preexisting type 2 diabetes	115/6496	1.21 (0.97-1.52)	.09
GDM	310/25 035	1.04 (0.91-1.19)	.57
Gestational wk at GDM diagnosis			
≤26	130/7456	1.42 (1.15-1.74)	.001
>26	180/17 579	0.87 (0.74-1.03)	.11
Adjusted for potential confounders plus preeclampsia/eclampsia[b]			
Unexposed	2963/290 792	1 [Reference]	
Preexisting type 2 diabetes	115/6496	1.20 (0.96-1.50)	.11
GDM	310/25 035	1.04 (0.91-1.18)	.61
Gestational wk at GDM diagnosis			
≤26	130/7456	1.41 (1.15-1.72)	.001
>26	180/17 579	0.87 (0.74-1.03)	.11
Adjusted for potential confounders plus child birth weight and gestational age at delivery[b]			
Unexposed	2963/290 792	1 [Reference]	
Preexisting type 2 diabetes	115/6496	1.19 (0.95-1.49)	.13
GDM	310/25 035	1.03 (0.90-1.17)	.70
Gestational wk at GDM diagnosis			
≤26	130/7456	1.39 (1.13-1.71)	.002
>26	180/17 579	0.87 (0.73-1.02)	.09

Abbreviations: ASD, autism spectrum disorders; GDM, gestational diabetes mellitus.

[a] From Cox regression models in which family was specified as a random effect and birth year was included as a covariate.

[b] Potential confounders included maternal age, parity, education, household income, race/ethnicity, history of comorbidity, and sex of the child.

1.87[12] and 1.98[13] with exposure to preexisting type 2 diabetes in the unadjusted analysis. Adjustment for potential confounders in the first study reduced the relative risk to 1.65, but maternal history of comorbidity and race/ethnicity were not assessed. Together, these studies demonstrate the importance of controlling for potential confounders in assessing the independent association between maternal preexisting type 2 diabetes and the risk of ASD in offspring.

Regarding GDM, we showed that not including gestational age at diagnosis of GDM reduced the risk associated with early exposure. We found an overall unadjusted HR of 1.18 (P = .01) that became nonsignificant (HR, 1.04; P = .57) after adjustment for potential confounders. This blended risk was composed of the high risk associated with GDM diagnosed by 26 weeks' gestation and no risk associated with GDM diagnosed after that. This pattern may explain inconsistent findings in previous studies.[10,11] Using gestational age at diagnosis of GDM as a surrogate measure of timing of exposure to hyperglycemia, we found a significant negative association with ASD risk when gestational age at diagnosis of GDM was treated as a continuous variable. By stratification we found that children exposed to GDM diagnosed at 26 weeks or earlier had an HR of 1.42 for ASD compared with unexposed children. Because the association was stronger for GDM diagnosed at 26 weeks or earlier than for recognized preexisting type 2 diabetes, we speculate that some children in the group with GDM diagnosed at 26 weeks or earlier may have been exposed to untreated hyperglycemia during early critical brain developmental windows, which led to ASD risk after birth. Preexisting (that is, known) type 2 diabetes may have been treated aggressively during pregnancy, which may have reduced the effect on fetal brain development.

Our observation is consistent with other exposures examined during pregnancy. For example, folic acid supplementation during early pregnancy was associated with a lower risk,[14] but antidepressant treatment during the first trimester was associated with a higher risk of ASD.[15] Also, excessive maternal weight gain in the first half of pregnancy was shown to have a greater association with offspring adiposity at birth than excessive maternal weight gain in the second half of pregnancy.[23] Taken together, these results suggest that early exposure to abnormal intrauterine environments can have important effects on long-term offspring health.

Potential biological mechanisms linking intrauterine hyperglycemia and ASD risk in offspring may include multiple pathways,[11] such as hypoxia in the fetus,[24,25] oxidative stress in cord blood and placental tissue,[26,27] chronic inflammation,[28] and epigenetics.[29] Gestational diabetes mellitus is often accompanied by maternal obesity, as demonstrated in our subcohort in whom prepregnancy body mass index was higher for the GDM groups than for the unexposed group. Both maternal prepregnancy body mass index and gestational weight gain were associated with modest ASD risk in our study in the unadjusted analysis. Maternal obesity was associated with positive screening results for autism in very preterm children in a recent study.[30] However, adjustment for maternal obesity and gestational weight gain did not affect the ASD risk associated with early GDM diagnosis in our study.

Our results came from the largest, most diverse longitudinal cohort reported to date. All data were from a unified clinical patient care system. Children had to have been enrolled in the KPSC health plan by age 1 year and continuously followed up through electronic medical records to avoid screening and ascertainment bias. The prevalence of ASD in the entire cohort was 1.09%, slightly lower than the 1.47% reported by the Centers for Disease Control and Prevention among 8-year-old children.[9] The difference may be due to the fact that children diagnosed as having ASD after leaving KPSC were not included and that we required 2 separate encounters with relevant *ICD*-9 codes to identify ASD cases. Using 1 encounter in our cohort yielded a prevalence of 1.40%, close to that of the Centers for Disease Control and Prevention report.

The availability of actual GDM diagnostic glucose values and dates of glucose testing in the clinical laboratory database and medication data in the clinical pharmacy database allowed us to separate influences of timing of GDM exposure and effect of antidiabetic medication on ASD risk. Additional strengths of this study included adjustment for potential confounding due to sociodemographics, smoking, and maternal obesity in the subcohort.

We acknowledge some important limitations. Confounding due to paternal risk factors such as paternal obesity could not be evaluated because of lack of data.[31] We could not rule out confounding bias due to exposure to other intrauterine factors,[14,32] postnatal exposures, or genetic susceptibility, although adjustment for ASD among mothers and older siblings did not explain the associations. We could not assess ascertainment bias due to differential screening for GDM and ASD. Follow-up for the subcohort with maternal body mass index data was relatively short to assess the long-term effect of maternal obesity. Caution is needed to interpret the ASD subtype results because of low reliability of subtype diagnosis and the small number with Asperger syndrome and PDD-NOS. Whether the ASD risk associated with GDM diagnosed earlier than 26 weeks was due to abnormal glucose levels prior to GDM diagnosis and/or suboptimal glucose control after GDM diagnosis requires further investigation. Because this is an observational study, no causal inferences can be drawn. However, our results suggest that early screening for ASD in offspring of women with GDM diagnosed by 26 weeks' gestation may be warranted. Our results also suggest that screening for GDM and control of glucose levels early in pregnancy may be important in reducing ASD risk for offspring. Whether early diagnosis and treatment of GDM can reduce the risk of ASD remains to be determined.

Conclusions

In this large, multiethnic clinical cohort of singleton children born at 28 to 44 weeks' gestation, exposure to GDM diagnosed by 26 weeks' gestation was associated with risk of ASD in offspring.

ARTICLE INFORMATION

Author Contributions: Dr Xiang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Xiang, Curry.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Xiang.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Xiang, Wang, Coleman.
Obtained funding: Xiang.
Administrative, technical, or material support: Xiang, Martinez, Curry.
Study supervision: Xiang, Curry, Buchanan, Getahun.

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