The Association of Maternal Obesity and Diabetes With Autism and Other Developmental Disabilities

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abstract

BACKGROUND: Obesity and diabetes are highly prevalent among pregnant women in the United States. No study has examined the independent and combined effects of maternal prepregnancy obesity and maternal diabetes on the risk of autism spectrum disorder (ASD) in parallel with other developmental disorders (DDs).

METHODS: This study is based on 2734 children (including 102 ASD cases), a subset of the Boston Birth Cohort who completed at least 1 postnatal study visit at Boston Medical Center between 1998 and 2014. Child ASD and other DDs were based on physician diagnoses as documented in electronic medical records. Risks of ASD and other DDs were compared among 6 groups defined by maternal prepregnancy obesity and diabetes status by using Cox proportional hazard regression controlling for potential confounders.

RESULTS: When examined individually, maternal prepregnancy obesity and pregestational diabetes (PGDM) were each associated with risk of ASD. When examined in combination, only mothers with obesity and PGDM (hazard ratio 3.91, 95% confidence interval 1.76–8.68) and those with obesity and gestational diabetes (hazard ratio 3.04, 95% confidence interval 1.21–7.63) had a significantly increased risk of offspring ASD. Intellectual disabilities (IDs), but not other DDs, showed a similar pattern of increased risk associated with combined obesity and PGDM. This pattern of risk was mostly accounted for by cases with co-occurring ASD and ID.

CONCLUSIONS: Maternal prepregnancy obesity and maternal diabetes in combination were associated with increased risk for ASD and ID. ASD with ID may be etiologically distinct from ASD without ID.

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WHAT'S KNOWN ON THIS SUBJECT: Maternal diabetes has been associated with increased risk of autism spectrum disorder (ASD) in children; the association between maternal prepregnancy obesity and ASD has been inconsistent. No study has examined the combined effects of the 2 conditions.

WHAT THIS STUDY ADDS: The combination of maternal obesity and diabetes was associated with greater risk of ASD than either obesity or diabetes alone, in particular when ASD co-occurred with intellectual disability. ASD with and without intellectual disability may be etiologically distinct.

To cite: Li M, Fallin MD, Riley A, et al. The Association of Maternal Obesity and Diabetes With Autism and Other Developmental Disabilities. *Pediatrics.* 2016;137(2): e20152206

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by severe deficits in socialization, communication, and repetitive or unusual behaviors, affecting 1 in 68 US children.[1,2] Since the 1960s, prevalence rates of ASD have increased dramatically, which cannot be entirely explained by changes in diagnostic practices.[3] During a similar time frame, obesity and diabetes rose to epidemic levels in the United States. Currently among women of reproductive age, more than a third are obese,[4] ~9% have prepregnancy diabetes, and an additional 2% to 10% will develop gestational diabetes (GDM) during pregnancy.[5] Emerging evidence links maternal prenatal diabetes with the risk of ASD in children.[6] Research on the connection between maternal obesity and the risk of ASD has produced inconsistent results.[7–10] Although obesity and diabetes are highly comorbid,[11] rarely have studies attempted to disentangle their independent and combined effects on ASD. In addition, although ASD frequently co-occurs with other developmental disorders (DDs) and may have shared etiology with some DDs,[12] few of the aforementioned studies included other DDs as alternative outcomes.

In this study, we used a prospective birth cohort to (1) examine the independent and combined associations of maternal obesity and diabetes with ASD in children controlling for potential confounders; and (2) contrast them with the effects on intellectual disability (ID), attention-deficit/hyperactivity disorder (ADHD), and other DDs in children. In addition, we also explored potential etiologic heterogeneity of ASD relative to ID by distinguishing ASD with and without ID, as well as ID without ASD. The cohort is a low-income US urban minority population, where burdens of maternal obesity and diabetes are especially high.

METHODS

Participants and Data Collection Procedures

This study included 2734 mother-child pairs, a subset of the Boston Birth Cohort (BBC) recruited at birth at the Boston Medical Center (BMC) from 1998 to 2014 who had at least 1 postnatal follow-up. Initially designed as a molecular epidemiologic study on determinants of low birth weight and preterm birth,[13] mothers who delivered a singleton live birth were eligible, and for every preterm (<37 weeks) and/or low birth weight (<2500 g) birth, 2 term (≥37 weeks) and normal birth weight (>2500 g) infants and mothers were enrolled. The exclusion criteria included multiple-gestation pregnancies, pregnancies resulting from in vitro fertilization, deliveries resulting from maternal trauma, and newborns with major birth defects.

We approached the mothers 24 to 72 hours postpartum. After gaining informed consent, we conducted a face-to-face interview with the mother by using a standardized questionnaire. We reviewed maternal and infant medical records by using a standardized abstraction form.

Children who continued to seek postnatal care at BMC were followed. We obtained all child electronic medical records (EMRs), which contained physician primary and secondary diagnoses in the *International Classification of Diseases, Ninth Revision* for each postnatal visit since 2003. The median length of postnatal follow-up is 6.0 years (interquartile range 3.6–9.0). The study was approved by the institutional review board of Johns Hopkins Bloomberg School of Public Health and Boston University Medical Center.

Definition of Maternal Obesity, Maternal Diabetes, and Other Covariates

Maternal prepregnancy weight and height were reported in maternal postpartum interview, and were used to calculate BMI. Overweight and obesity status were defined separately for mothers older than and younger than 20 years.[14] Underweight mothers constituted a very small proportion of our sample, and did not demonstrate differences in offspring ASD risk compared with those of normal weight, thus were combined with those of normal BMI. For a subset of mothers (n = 738), height and weight during preconception or within 6 weeks of gestation were also available in their prenatal EMR. There was a high correlation between maternal self-report and EMR recorded BMI (Pearson r = 0.91).

Pregestational diabetes (PGDM) and GDM were identified based on maternal medical records. Mothers ever diagnosed with diabetes mellitus (250.00–250.93) constituted the PGDM cases; those ever diagnosed with diabetes mellitus complicating pregnancy (648.00 and 648.03) but never diagnosed with diabetes mellitus constituted the GDM cases. The joint status of maternal obesity status (obese versus nonobese) and diabetes status (no diabetes, GDM, and PGDM) defined 6 nonoverlapping groups: no diabetes or obesity, GDM without obesity, PGDM without obesity, obesity without diabetes, obesity with GDM, and obesity with PGDM.

Maternal demographics and health behaviors were based on maternal postpartum interview. Preeclampsia, chronic hypertension, and mode

of delivery were defined by using maternal medical review. Birth outcomes were defined by using infant medical record review: gestational age was classified as full term (≥37 weeks), late preterm (≥34 weeks and <37 weeks), and early preterm (<34 weeks); birth weight was classified as non-low birth weight (≥2500 g), low birth weight (1500–2499 g), and very low birth weight (≤1499 g); gestational age–specific birth weight percentile defined small for gestational age (<10th percentile for the gestational age), appropriate for gestational age (between 10th and 90th percentile for the gestational age), and large for gestational age (>90th percentile for the gestational age).

Identification of Children With ASD, ID, ADHD, and Other DD

Based on EMRs, children ever diagnosed with autism (299.00), Asperger syndrome (299.80), and/or pervasive developmental disorder not otherwise specified (299.90) constituted the ASD cases. More than 80% (84 of 102) of ASD cases were diagnosed by relevant specialists (developmental behavioral pediatrics, pediatric psychology assessment clinic, developmental assessment clinic, pediatric neurology, and child psychology), the rest were diagnosed by pediatric clinical (10 children), pediatric comprehensive care (3 children), and other departments (eg, pediatric gastroenterologist, family medicine, 5 children). The median age when they were most recently diagnosed was 67 months (maximum 166 months, minimum 12 months). Children ever diagnosed with developmental delay not elsewhere classified (315.8), tuberous sclerosis with developmental delay (316 and 759.5), intellectual disability (317, 318.0–318.2, and 319), and/or Down syndrome (758.0) constituted the ID cases. Children ever diagnosed with ADHD (314.0–314.9) constituted the ADHD cases. Children ever diagnosed with language delay, coordination disorders, or learning disorders (315.0–315.5) constituted the other DD cases. The classification of DDs is similar to Levy et al.[12] Children who did not belong to any of the DD groups constituted the typically developing (TD) group. As there is no evidence that 1 type of DD is secondary to another type, we allowed subjects to be classified into multiple DD groups; as a result, the sum of all DD groups and TD group exceeded 100%.

Statistical Analysis

Rates of DDs were compared among exposure groups by using Cox proportional hazard regressions to account for the variability in length of postnatal follow-up. We defined time origin as the birth of the child, and time of entry as the child's first postnatal visit recorded in the EMR. Time of event is when a case is diagnosed, and time of censoring for those never diagnosed with any DD is the last visit recorded on EMR. We first regressed each covariate on ASD status adjusting for demographic variables (year of birth, maternal age, gender of the child, and maternal parity) to identify covariates meaningfully associated with ASD (defined as $P \leq .1$). Then, we examined the association between risk of ASD and (1) maternal BMI, (2) maternal diabetes, and (3) the joint status of maternal BMI and diabetes, adjusting for the demographic variables and the covariates identified previously. The same regression models were repeated by using ID, ADHD, and other DD as outcomes, respectively.

To explore potential etiologic heterogeneity, we cross-classified ASD and ID cases into ASD without ID, co-occurring ASD and ID, and ID without ASD, and repeated the aforementioned model in (3) on these outcomes.

To evaluate the sensitivity of our results relative to the definition of ASD, we repeated our analyses restricting ASD cases to those with at least 2 instances of diagnosis, and ever diagnosed by the specialists.

RESULTS

Of the 2734 children, we identified 102 (3.7%) ASD cases, 137 (5.0%) ID cases, 301 (11.0%) ADHD cases, and 864 (31.6%) other DD cases (groups are not mutually exclusive); 1748 (63.9%) children did not receive any of the DD diagnoses, thus were identified as TD. Most ASD cases (92.2%) received another DD diagnosis, of which the most common is other DD; substantial proportions of ID cases (88.3%), ADHD cases (69.1%), and other DD cases (35.8%) also received another DD diagnosis. The characteristics of each developmental condition group are shown in Table 1. Compared with TD children, children with ASD were more likely to be boys, to be born early preterm, and of very low birth weight; their mothers were more likely to be older, to be obese prepregnancy, and to have PGDM or GDM. Children with ID had similar maternal and child characteristics as children with ASD, in addition to being more likely to be of the mothers' third or higher-order birth, to be small for gestational age, and to be delivered via cesarean. Children with ADHD were more likely to be boys, to be born early preterm, of very low birth weight, and by cesarean delivery. Their mothers were more likely to have lower educational achievement; to be black; to be widowed, divorced, or separated from husband; to be obese; and

TABLE 1 Characteristics of TD Children and Children With ASD, ID, ADHD, and Other DD

Characteristics	TD, *n* = 1748		ASD, *n* = 102		ID, *n* = 137		ADHD, *n* = 301		Other DD, *n* = 864		ASD Versus TD	ID Versus TD	ADHD Versus TD	Other DD Versus TD
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*	*P*	*P*	*P*
Child gender											<.001	<.001	<.001	<.001
Girls	976	55.8	27	26.5	42	30.7	91	30.2	325	37.6				
Boys	772	44.2	75	73.5	95	69.3	210	69.8	539	62.4				
Mother's age, y											.009	<.001	.31	.18
≤25	600	34.3	20	19.6	25	18.2	117	38.9	271	31.4				
26–35	844	48.3	61	59.8	74	54.0	136	45.2	422	48.8				
≥36	304	17.4	21	20.6	38	27.7	48	15.9	171	19.8				
Gravity											.55	.11	.27	.06
1	498	28.5	25	24.5	28	20.4	76	25.2	208	24.1				
2	425	24.3	29	28.4	34	24.8	68	22.6	219	25.3				
≥3	825	47.2	48	47.1	75	54.7	157	52.2	437	50.6				
Parity											.06	.04	.62	.48
0	750	42.9	39	38.2	44	32.1	124	41.2	354	41.0				
1	510	29.2	41	40.2	46	33.6	85	28.2	271	31.4				
≥2	486	27.8	22	21.6	47	34.3	92	30.6	238	27.5				
(Unknown)	2	0.1	0	0.0	0	0.0	0	0.0	1	0.1				
Mother's education											.20	.32	.05	.81
Less than high school	503	28.8	22	21.6	33	24.1	93	30.9	249	28.8				
High school	617	35.3	34	33.3	56	40.9	119	39.5	311	36.0				
College or above	615	35.2	43	42.2	45	32.8	83	27.6	291	33.7				
(Unknown)	13	0.7	3	2.9	3	2.2	6	2.0	13	1.5				
Mother's race											.21	.59	.01	<.001
Black	1000	57.2	64	62.7	75	54.7	196	65.1	557	64.5				
White	147	8.4	4	3.9	10	7.3	21	7.0	47	5.4				
Hispanic	371	21.2	25	24.5	36	26.3	63	20.9	186	21.5				
Other	221	12.6	9	8.8	16	11.7	20	6.6	72	8.3				
(Unknown)	9	0.5	0	0.0	0	0.0	1	0.3	2	0.2				
Mother's marital status											.29	.72	.03	.70
Currently married	577	33.0	39	38.2	47	34.3	77	25.6	297	34.4				
Never married	44	2.5	4	3.9	2	1.5	11	3.7	23	2.7				
Widowed, divorced, or separated	1112	63.6	57	55.9	87	63.5	207	68.8	533	61.7				
(Unknown)	15	0.9	2	2.0	1	0.7	6	2.0	11	1.3				
Gestational age											<.001	<.001	<.001	<.001
Term birth	1316	75.3	61	59.8	81	59.1	196	65.1	569	65.9				
Late preterm birth	263	15.0	17	16.7	30	21.9	52	17.3	153	17.7				
Early preterm birth	169	9.7	24	23.5	26	19.0	53	17.6	140	16.2				
(Unknown)	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2				
Birth weight											.004	<.001	<.001	<.001
Normal	1328	76.0	71	69.6	79	57.7	198	65.8	591	68.4				
Low birth weight	331	18.9	18	17.6	39	28.5	69	22.9	178	20.6				
Very low birth weight	89	5.1	13	12.7	19	13.9	34	11.3	95	11.0				
Gestational weight specific birth weight percentile											.83	.03	.55	.48
Appropriate for gestational age	1301	74.4	78	76.5	88	64.2	218	72.4	625	72.3				
Large for gestational age	123	7.0	6	5.9	9	6.6	21	7.0	60	6.9				

TABLE 1 Continued

Characteristics	TD, *n* = 1748		ASD, *n* = 102		ID, *n* = 137		ADHD, *n* = 301		Other DD, *n* = 864		ASD Versus TD	ID Versus TD	ADHD Versus TD	Other DD Versus TD
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*	*P*	*P*	*P*
Small for gestational age	301	17.2	16	15.7	35	25.5	60	19.9	165	19.1				
(Unknown)	23	1.3	2	2.0	5	3.6	2	0.7	14	1.6				
Delivery type											.08	.005	.03	.001
Cesarean delivery	585	33.5	43	42.2	62	45.3	120	39.9	346	40.0				
Vaginal delivery	1149	65.7	59	57.8	74	54.0	177	58.8	512	59.3				
(Unknown)	14	0.8	0	0.0	1	0.7	4	1.3	6	0.7				
Prepregnancy BMI											.01	.006	.05	.009
Normal/underweight	845	48.3	39	38.2	56	40.9	129	42.9	368	42.6				
Overweight	477	27.3	30	29.4	34	24.8	93	30.9	251	29.1				
Obese	343	19.6	33	32.4	43	31.4	75	24.9	205	23.7				
(Unknown)	83	4.7	0	0.0	4	2.9	4	1.3	40	4.6				
Diabetes											.001	<.001	.43	.07
No diabetes	1602	91.6	83	81.4	113	82.5	272	90.4	770	89.1				
GDM	78	4.5	9	8.8	11	8.0	12	4.0	45	5.2				
PGDM	66	3.8	10	9.8	13	9.5	16	5.3	48	5.6				
(Unknown)	2	0.1	0	0.0	0	0.0	1	0.3	1	0.1				
Preeclampsia											.27	.60	.85	.06
No	1562	89.4	94	92.2	120	87.6	267	88.7	751	86.9				
Yes	180	10.3	7	6.9	16	11.7	32	10.6	110	12.7				
(Unknown)	6	0.3	1	1.0	1	0.7	2	0.7	3	0.3				
Chronic hypertension											.92	.38	.43	.38
No	1634	93.5	95	93.1	125	91.2	283	94.0	799	92.5				
Yes	108	6.2	6	5.9	11	8.0	15	5.0	61	7.1				
(Unknown)	6	0.3	1	1.0	1	0.7	3	1.0	4	0.5				
Smoking during pregnancy											.38	.07	.06	.82
No	1557	89.1	88	86.3	115	83.9	257	85.4	767	88.8				
Yes	191	10.9	14	13.7	22	16.1	44	14.6	97	11.2				
Alcohol use during pregnancy											.21	.85	.04	.01
No	1584	90.6	89	87.3	124	90.5	282	93.7	805	93.2				
Yes	157	9.0	13	12.7	13	9.5	16	5.3	53	6.1				
(Unknown)	7	0.4	0	0.0	0	0.0	3	1.0	6	0.7				
Drug use during pregnancy											.66	.74	.58	.98
No	1425	81.5	82	80.4	111	81.0	240	79.7	701	81.1				
Yes	310	17.7	20	19.6	26	19.0	57	18.9	152	17.6				
(Unknown)	13	0.7	0	0.0	0	0.0	4	1.3	11	1.3				

TABLE 2 Associations of Maternal Obesity and Diabetes With DDs in the Offspring

Characteristics	ASD, n = 102, Versus TD, n = 1664			ID, n = 133, Versus TD			ADHD, n = 296, Versus TD			Other DD, n = 821, Versus TD		
	HR	(95% CI)	P	HR	(95% CI)	P	HR	(95% CI)	P	HR	(95% CI)	P
BMI												
Normal/underweight	Ref.			Ref.			Ref.			Ref.		
Overweight	1.05	(0.65–1.71)	.84	0.87	(0.56–1.34)	.52	1.13	(0.82–1.56)	.47	0.99	(0.84–1.17)	.89
Obese	1.92	(1.20–3.07)	.007	1.64	(1.09–2.45)	.02	1.26	(0.88–1.80)	.21	1.22	(1.03–1.45)	.02
Diabetes												
No diabetes	Ref.			Ref.			Ref.			Ref.		
GDM	1.86	(0.92–3.76)	.08	1.71	(0.91–3.23)	.10	0.99	(0.50–1.94)	.98	1.11	(0.82–1.51)	.50
PGDM	2.25	(1.14–4.42)	.02	2.26	(1.25–4.09)	.007	1.56	(0.86–2.84)	.15	1.31	(0.96–1.77)	.09
BMI and diabetes												
Not obese, no diabetes	Ref.			Ref.			Ref.			Ref.		
Not obese, GDM	1.44	(0.51–4.02)	.49	1.54	(0.61–3.86)	.36	0.88	(0.32–2.40)	.81	0.98	(0.63–1.53)	.93
Not obese, PGDM	1.32	(0.41–4.29)	.64	1.66	(0.66–4.18)	.28	2.00	(1.00–4.00)	.05	1.15	(0.75–1.76)	.52
Obese, no diabetes	1.54	(0.93–2.53)	.09	1.54	(1.00–2.36)	.05	1.25	(0.87–1.78)	.22	1.18	(0.99–1.40)	.07
Obese, GDM	3.04	(1.21–7.63)	.02	2.31	(1.00–5.36)	.05	1.20	(0.49–2.93)	.70	1.34	(0.89–2.02)	.17
Obese, PGDM	3.91	(1.76–8.68)	<.001	3.63	(1.73–7.61)	<.001	1.06	(0.34–3.36)	.92	1.63	(1.07–2.49)	.02

Adjusted for child year of birth, child gender, maternal age, parity, smoking during pregnancy, and preterm birth. Ref., reference.

to have used alcohol during pregnancy. Children with other DD had the similar child characteristics as children with ADHD; their mothers were more likely to be black, obese prepregnancy, and to have used alcohol during the pregnancy.

Adjusting for demographic variables, the risk of ASD was meaningfully associated (defined as $P \leq 0.1$) with early preterm birth, very low birth weight, maternal obesity, PGDM, and smoking during pregnancy, respectively (see Supplemental Table 4). Very low birth weight was not considered an independent confounder, as it was not associated with risk of ASD after controlling for preterm birth status.

Table 2 shows the relationship between maternal obesity/diabetes and the risk of DDs after adjusting for potential confounders. Irrespective of whether they had diabetes, mothers who were obese had an almost twofold risk of having a child with ASD compared with normal weight or underweight mothers (95% confidence interval [CI] 1.20–3.07). Regardless of obesity status, mothers with PGDM had more than a twofold risk of having a child with ASD relative to those without diabetes (95% CI 1.14–4.42). However, the association for GDM did not reach significance (hazard ratio [HR] 1.86, 95% CI 0.92–3.76). Evaluated jointly, obesity without diabetes and also diabetes without obesity were each associated with slightly increased risk ($P > .05$) of ASD in children compared with the group with neither condition, whereas the combination of obesity and GDM (HR 3.04, 95% CI 1.21–7.63) or obesity and PGDM (HR 3.91, 95% CI 1.76–8.68) were associated with substantially higher risk of ASD in children (see Fig 1). Risk of ID relative to maternal obesity and diabetes shared similar patterns

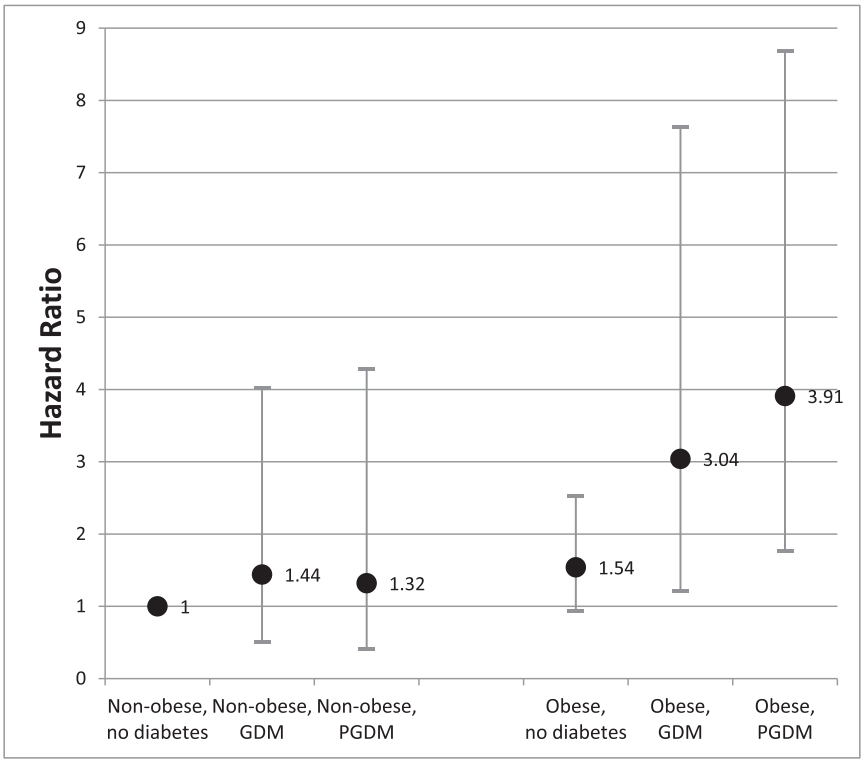

FIGURE 1
Adjusted HR and 95% CI for ASD associated with maternal obesity and diabetes. The models adjusted for child year of birth, child gender, maternal age, parity, smoking during pregnancy, and preterm birth.

of risk of ASD, evaluated alone (obesity: HR 1.64, 95% CI 1.09–2.45; PGDM: HR 2.26, 95% CI 1.25–4.09) or jointly (obesity without diabetes: HR 1.54, 95% CI 1.00–2.36; obesity with GDM: HR 2.31, 95% CI 1.00–5.36; obesity with PGDM: HR 3.63, 95% CI 1.73–7.61). Risk for ADHD and other DD were slightly elevated and several were significant relative to maternal obesity and diabetes.

As shown in Table 3, compared with the group with neither condition, obesity without diabetes was associated with a slightly increased risk of ASD without ID (HR 2.05, 95% CI 1.06–3.97) in children. Obesity with GDM (HR 6.53, 95% CI 2.45–17.38) and obesity with PGDM (HR 9.73, 95% CI 4.07–23.27) were associated with a large increased risk of co-occurring ASD and ID.

Sensitivity analyses using more stringent criteria to identify ASD cases are shown in Supplemental Tables 5 and 6. The results were not substantively different from the main analyses.

DISCUSSION

This is a prospective birth cohort study: the first of its kind to examine the independent and combined association of maternal obesity and diabetes with the risk of ASD in children. We demonstrated that prepregnancy obesity and PGDM each were associated with a slightly increased risk of ASD, but the associations were most pronounced when mothers had both conditions. This pattern of risk was observed for children with ID, but not ADHD and other DDs. Furthermore, our results suggested that the association of maternal obesity and diabetes with ASD and ID may be entirely due to those cases with co-occurring ASD and ID.

In line with a recent meta-analysis, our study confirms a slightly increased ASD risk associated with maternal diabetes.[6] However, whether and how the effects of GDM and PGDM differ is still debatable. Although the 2 studies differentiating PGDM and GDM in the meta-analysis both reported larger odds ratios (ORs) for PGDM than GDM,[15,16] Xiang et al[17] found that only GDM diagnosed before 26 weeks, but not GDM diagnosed

TABLE 3 Associations of Maternal Obesity and Diabetes With ASD Without ID, Co-occurring ASD and ID, and ID Without ASD in the Offspring

Characteristics	ASD w/o ID, *n* = 53, Versus TD, *n* = 1664			Co-occurring ASD and ID, *n* = 49 Versus TD			ID w/o ASD, *n* = 84 Versus TD		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Not obese, no diabetes	Ref.		Ref.			Ref.			
Not obese, GDM	0.67	(0.09–4.95)	.69	1.60	(0.37–6.99)	.53	1.09	(0.26–4.57)	.90
Not obese, PGDM	0.92	(0.12–6.91)	.94	0.99	(0.13–7.44)	.99	1.13	(0.27–4.75)	.87
Obese, no diabetes	2.05	(1.06–3.97)	.03	1.06	(0.43–2.61)	.89	1.69	(0.96–2.97)	.07
Obese, GDM	—[a]	—[a]	—[a]	6.53	(2.45–17.38)	<.001	0.73	(0.10–5.29)	.75
Obese, PGDM	—[a]	—[a]	—[a]	9.73	(4.07–23.27)	<.001	1.07	(0.15–7.84)	.95

Ref., reference category; w/, with; w/o, without.
[a] No children in the ASD w/o ID group have mothers who are obese and have GDM/PGDM. Adjusted for child year of birth, child gender, maternal age, parity, smoking during pregnancy, and preterm birth.

after 26 weeks or PGDM, was significantly associated with risk for ASD. If the effect of early GDM is due to untreated hyperglycemia during early critical brain developmental windows, as Xiang et al[17] suspected, it is possible that women with PGDM in our sample did not have well-controlled blood glucose levels, contributing to the increased risk of ASD in children.

Our study also supports a slightly increased risk of ASD associated with maternal obesity. Among the few studies on this topic, the population-based case-control study by Krakowiak et al[7] reported a significant OR (1.7), similar to ours. A clinical cohort study of 62 very preterm children by Reynolds et al[9] reported a large increased OR (9.9) for a positive Modified Checklist for Autism in Toddlers screen, a proxy for ASD risk.[18] Another population-based cohort study by Moss et al[8] found no direct effect; however, the prepregnancy BMI was reported 9 months after delivery, and autism was defined by parental report of diagnosis, where misclassification due to recalling/reporting errors may have biased the finding toward the null. A population-based cohort study by Surén et al[10] found an increased OR (2.1) associated with maternal obesity that disappeared after adjusting for paternal obesity. Although potential confounding from paternal obesity was not testable in our study, the strong and consistent association between the co-occurring maternal obesity/diabetes and ASD/ID suggest contrary to a simple confounding artifact.

We found that only the combination of obesity and diabetes was associated with significant risk of ASD, whereas each condition without the other was not. Although the sample size is too small to formally test for effect modification, our study suggests potential synergistic effects between maternal obesity and diabetes, and that omission of 1 condition may result in biased estimates for the effect of the other. So far, very few studies have considered the 2 conditions in combination. Xiang et al[17] focused on maternal diabetes and reported no confounding from maternal obesity, but this was tested only among a subcohort that was followed 0 to 3 years, when most of their ASD cases were not yet diagnosed. Krakowiak et al[7] considered maternal obesity, diabetes, and hypertension within 1 group (metabolic syndrome), but no confounding or effect modification was tested.

Growing evidence suggests that ASD may be related to immunologic and metabolic disturbances associated with maternal obesity and diabetes. Obesity increases circulating proinflammatory cytokines in pregnant women.[19,20] In rat models, maternal peripheral inflammation resulted from high-fat diet and obesity and can lead to offspring brain inflammation.[21] Maternal diabetes also induces proinflammatory environments in intrauterine tissues.[22] Both intrauterine inflammation and fetal brain inflammation are implicated in the development of ASD.[23–25] Diabetes also can lead to hyperglycemia. Maternal hyperglycemia triggers fetal hyperinsulinemia and increased oxygen consumption, inducing chronic intrauterine fetal tissue hypoxia.[26] Maternal hyperglycemia is also associated with an increased production of free radicals and oxidative stress.[27,28] Hypoxia[29] and oxidative stress[30] are also implicated as risk factors for ASD. Cooccurring obesity and diabetes may be "multiple hits" to the developing fetal brain, conferring an even higher risk of ASD in the offspring than a single condition. Future studies of a larger size are needed to formally test potential interactions between maternal obesity and diabetes.

In our study, maternal obesity and diabetes were associated with elevated risk of ID similar to that of ASD, whereas they were not clearly associated with risks of other DD and ADHD. The similarity between ASD and ID was mainly driven by cases with co-occurring ASD and ID. This suggests that co-occurring ASD and ID maybe an etiologically distinct group from the other 2 groups. In support of this hypothesis, we found that most Down syndrome ID cases, a condition clearly resulting from chromosomal rather than environmental causes, did not have co-occurring ASD (12 out of 14). Given the small sample size, this result needs to be confirmed in larger studies.

Our study has several limitations. First, ASD and DD were identified if they ever received such a diagnosis. This approach is subject to misclassification error, as conditions may be underdiagnosed or misdiagnosed as other conditions, and the diagnosis can be tentative. However, we expect this error to bias our estimate toward the null. In addition, in the main analyses, restricting ASD to only those diagnosed at least twice and ever diagnosed by the specialist did not alter our results. Second, this report analyzed a subset of the BBC children who continued to receive pediatric care at the BMC. Concern for selection bias may be somewhat ameliorated, as the baseline characteristics between our study sample and the remaining BBC sample are comparable. As well, associations between well-established risk factors such as maternal age, gender of the child, and preterm birth with ASD were replicated in our study sample. Third, postnatal visits before 2003 were

not captured in the EMR. However, our analyses took account of "late entry" into follow-up in the survival analysis; as ASD cases and non-ASD cases did not differ in late-entry status, therefore this was not likely to result in bias. Fourth, although we adjusted for well-recognized ASD risk factors, potential residual confounding, such as genetic susceptibility and other unknown risk factors, may still exist. Finally, caution is needed in generalizing our findings to other populations with different social, demographic, and clinical characteristics.

CONCLUSIONS

Our findings suggest that children whose mothers had a combination of obesity and diabetes during pregnancy may have an elevated risk of developing ASD and ID.

ACKNOWLEDGMENTS

We gratefully acknowledge many individuals who participated and helped the recruitment and follow-up of the Boston Birth Cohort, which has made this work possible.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
BBC: Boston Birth Cohort
BMC: Boston Medical Center
CI: confidence interval
DD: developmental disorders
EMR: electronic medical record
GDM: gestational diabetes
HR: hazard ratio
ID: intellectual disability
OR: odds ratio
PGDM: pregestational diabetes
TD: typically developing

manuscript; Ms Caruso, Ms Pearson, Ms Kiang, and Dr Hong coordinated subject recruitment and follow-up, collected the data, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-2206

Accepted for publication Nov 12, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The parent study was supported in part by the March of Dimes Prematurity Epidemiology Research Initiative grant (20-FY02–56), National Institute of Environmental Health Sciences (R21 ES011666), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (2R01 HD041702). The follow-up study is supported in part by the Ludwig Family Foundation, the National Institute of Allergy and Infectious Diseases (U01AI090727 and R21AI079872), and the Maternal and Child Health Bureau (R40MC27443). Ms Li is supported by the Josephine Kohn and Family Fund and the Bernard and Jane Guyer Scholarship in her current training. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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