Maternal Obesity and Risk for Birth Defects

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ABSTRACT. *Objective.* **Several studies have shown an increased risk for neural tube defects associated with prepregnancy maternal obesity. Because few recent studies have examined the relation between maternal prepregnancy obesity and overweight and other birth defects, we explored the relation for several birth defects and compared our findings with those of previous studies.**

Methods. **We conducted a population-based case-control study of several selected major birth defects using data from the Atlanta Birth Defects Risk Factor Surveillance Study. Mothers who delivered an infant with and without selected birth defects in a 5-county metropolitan Atlanta area between January 1993 and August 1997 were interviewed. Maternal body mass index (BMI) was calculated from self-reported maternal prepregnancy weight and height. Women with known preexisting diabetes were excluded. The risks for obese women (BMI ≥30) and overweight women (BMI 25.0–29.9) were compared with those for average-weight women (BMI 18.5–24.9).**

Results. **Obese women were more likely than average-weight women to have an infant with spina bifida (unadjusted odds ratio [OR]: 3.5; 95% confidence interval [CI]: 1.2–10.3), omphalocele (OR: 3.3; 95% CI: 1.0–10.3), heart defects (OR: 2.0; 95% CI: 1.2–3.4), and multiple anomalies (OR: 2.0; 95% CI: 1.0–3.8). Overweight women were more likely than average-weight women to have infants with heart defects (OR: 2.0; 95% CI: 1.2–3.1) and multiple anomalies (OR: 1.9; 95% CI: 1.1–3.4).**

Conclusions. **Our study confirmed the previously established association between spina bifida and prepregnancy maternal obesity and found an association for omphalocele, heart defects, and multiple anomalies among infants of obese women. We also found an association between heart defects and multiple anomalies and being overweight before pregnancy. A higher risk for some birth defects is yet another adverse pregnancy outcome associated with maternal obesity. Obesity prevention efforts are needed to increase the number of women who are of healthy weight before pregnancy.** ***Pediatrics*** **2003;111:1152–1158;** ***obesity, body mass index, pregnancy, neural tube defect, congenital anomaly, birth defect.***

ABBREVIATIONS. BMI, body mass index; BDRFSS, Birth Defects Risk Factor Surveillance Study; OR, odds ratio; CI, confidence interval.

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The prevalence of obesity (defined as body mass index [BMI] ≥30 kg/m^2) in the United States is increasing at an alarming rate, from 12.0% in 1991[1] to 19.8% in 2000,[2] based on a survey using self-reported height and weight. Obesity prevalence based on actual measured weights is likely to be even higher.[3] Obesity is associated with pregnancy complications and adverse reproductive outcomes,[4,5] including an increased risk for birth defects. Several recent studies have shown an increased risk for neural tube defects associated with maternal obesity,[6–11] but the relation between maternal obesity and other birth defects is not as well defined (Table 1). In some studies, obese women have been shown to have an elevated risk for abdominal wall defects,[6,12] certain types of congenital heart defects,[6,13] and orofacial clefts,[12,14] but these findings have not been consistent among different studies.[9] Several other defects have been found to be increased in obese women in at least 1 study, including eye and internal urogenital defects, esophageal atresia, Potter sequence,[14] other intestinal defects,[6] and clubfoot.[12] Most recently, Shaw et al[15] showed an increased risk for multiple congenital anomalies among offspring of obese women. We studied the relation between maternal obesity and overweight and several types of birth defects using the Atlanta Birth Defects Risk Factor Surveillance Study (BDRFSS), a case-control study of major birth defects during 1993–1997, and we compared our findings with those in previous studies.

METHODS

Approval for the BDRFSS was obtained from the Centers for Disease Control and Prevention's Institutional Review Board. Infants with birth defects (cases) were ascertained using the population-based Metropolitan Atlanta Congenital Defects Program. This surveillance system uses active case finding among records of all birth hospitals in metropolitan Atlanta to identify affected infants (live births, stillbirths, and pregnancy terminations of ≥20 weeks' gestation) and includes a clinical review of each case record.[23] Cases are also ascertained at the 2 pediatric referral hospitals in Atlanta, at 2 cytogenetics laboratories, at a clinic that specializes in pediatric cardiology, and from vital records.

Defects included in the BDRFSS, either as isolated defects or as one of multiple anomalies, were anencephaly, spina bifida, holoprosencephaly, oral clefts, intestinal atresia, renal agenesis/hypoplasia, urinary tract obstruction, esophageal atresia, diaphragmatic hernia, limb deficiencies, omphalocele, gastroschisis, choanal atresia, bladder exstrophy, cloacal exstrophy, hydrocephaly, hydranencephaly, anotia/microtia, anophthalmia/microphthalmia, conotruncal heart defects, Ebstein's anomaly, flow-related heart defects, endocardial cushion defects, amniotic band sequence, and porencephaly. In addition, infants with 2 or more unrelated major birth defects (multiple congenital anomalies) were included in the study, even when the defects were not on the specified inclusion list above. Case infants with chromosomal

TABLE 1. Summary of Previous Studies of Maternal Obesity and Birth Defects

Reference	Study Design	Site, Year of Birth	BMI (mg/kg^2) for Risk and Referent Group	Defect(s) Studied	Findings
Richards, 1969[16]	Case-control	South Wales, 1964–1966	Not given	Anencephaly	Maternal weight heavier than controls ($P < .05$)
Haddow et al, 1982[17]	Cohort	US, years of birth not given	Not given	Anencephaly and spina bifida	No significant differences in mean maternal weights between cases and controls
Wald et al, 1981[18]	Cohort	United Kingdom, 1972–1980	Not given	Anencephaly and spina bifida	Median maternal weight for NTDs less than for unaffected pregnancies
Johnson et al, 1990[19]	Cohort	US, years of birth not given	Not given	Open spina bifida	No significant differences in median weight between mothers of NTDs and of unaffected pregnancies
Naeye, 1990[20]	Cohort	US, 1959–1966	BMI >30 vs BMI = 20–24	Major congenital malformations	PR† = 1.24 (95% CI:1.09–1.40)
Waller et al, 1994[6]	Case-control	US, 6/85-4/87 (IL) and 8/85-4/87 (CA)	BMI ≥31 vs BMI = 19–27	NTDs	AOR = 1.8 (95% CI:1.1–3.0)
				Anencephaly	AOR = 1.5 (95% CI:0.8–3.0)
				Spina bifida	AOR = 2.6 (95% CI:1.5–4.5)
				Encephalocele	AOR = 0.8 (95% CI:0.2–3.7)
				Other neural tube	AOR = 4.2 (95% CI:1.2–14.6)
				Other CNS	AOR = 4.2 (95% CI:1.2–14.6)
				Heart, septal closure	AOR = 2.1 (95% CI:0.7–6.4)
				Great vessels	AOR = 6.2 (95% CI:1.4–27.4)
				Other heart	AOR = 0.8 (95% CI:0.2–3.5)
				Other intestinal	AOR = 4.2 (95% CI:1.2–14.6)
				Diaphragmatic hernia	AOR = 2.6 (95% CI: 0.3–20.7)
				Ventral wall	AOR = 2.5 (95% CI:1.1–6.0)
				Renal agenesis	AOR = 1.4 (95% CI:0.2–11.3)
				Multiple anomalies	AOR = 2.2 (95% CI:0.3–17.7)
Shaw et al, 1996[7]	Case-control	US, 6/1989–5/1991	BMI >29 vs BMI ≤29	Neural tube defects	OR = 1.9 (95% CI:1.3–2.9)
Watkins et al, 1996[10]	Case-control	US, 1968–1980	BMI >29 vs BMI = 19.8–26	Spina bifida or anencephaly	AOR * = 1.92 (95% CI:1.08–3.40)
Werler et al, 1996[8]	Case-control	1988–1994, US and Canada	BMI ≥29 vs BMI = 19–23.9	Neural tube defects	AOR = 2.0 (95% CI:1.0–4.0)
Kallen, 1998[11]	Cohort	Sweden, 1983–1989 & 1992–1993	BMI >26 vs BMI ≤26	NTDs	AOR = 1.35 (95% CI 1.00–1.83)
Queisser-Luft et al, 1998[14]	Case-control	Germany, 2/1990–1/1995	BMI ≥30 vs BMI <30	Major malformations	OR = 1.3 (95% CI:1.0–1.7)
				Malformations of	
				internal urogenital system	OR = 1.7 (95% CI:1.1–2.8)
				cardiovascular system	OR = 0.8 (95% CI:0.3–1.9)
				gastrointestinal tract	OR = 1.3 (95% CI:0.5–3.3)
				central nervous system	OR = 1.5 (95% CI:0.5–3.9)
				orofacial clefts	OR = 2.8 (95% CI:1.0–8.9)
				eyes	OR = 5.0 (95% CI:1.3–20.0)
				encephalocele	OR = 7.3 (95% CI:1.7–50.6)
				truncus arteriosus	OR = 6.3 (95% CI:1.6–24.8)
				transposition great arteries	OR = 4.4 (95% CI:1.1–17.7)
				Potter sequence	OR = 6.3 (95% CI:1.6–24.8)
				renal agenesis	OR = 4.1 (95% CI:1.3–12.9)
				ectopic kidney	OR = 4.1 (95% CI:1.2–16.4)
				esophageal atresia	OR = 4.0 (95% CI:1.0–16.1)
				an-microphthalmia	OR = 5.0 (95% CI:1.3–20.0)
Shaw et al, 2000[9]	Case-control	US, 6/89–5/91 (study 1)	BMI ≥29 vs BMI ≤29	NTDs (study 1)	OR† = 1.9 (95% CI:1.3–2.9)
		US, 1/87–12/88 (study 2)		NTDs (study 2)	OR† = 1.8 (95% CI:1.1–3.0)
		US, 1/87–12/89 (study 2–clefts)		Conotruncal defects	OR = 1.0 (95% CI:0.6–1.8)
				Limb anomalies	OR = 0.8 (95% CI:0.4–1.6)
				Cleft lip/palate (isolated)	OR = 1.0 (95% CI:0.6–1.6)
				Cleft palate (isolated)	OR = 1.1 (95% CI:0.6–2.0)
				Cleft lip/palate (multiple)	OR = 1.0 (95% CI:0.5–2.1)
				Cleft palate (multiple)	OR = 1.6 (95% CI: 0.8–3.4)

TABLE 1. Continued

Reference	Study Design	Site, Year of Birth	BMI (mg/kg^2) for Risk and Referent Group	Defect(s) Studied	Findings
Moore et al, 2000[12]	Cohort	US, 10/1984–6/1987	BMI ≥28 vs BMI <28	Major nonchromosomal defects	adjusted PR* = 0.95 (95% CI:0.62–1.5)
				NTDs	PR*† = 0.74 (95% CI:0.23–2.37)
				Hydrocephaly	PR*† = 2.22 (95% CI:0.49–10.10)
				Orofacial clefts	PR*† = 3.69 (95% CI:1.19–11.44)
				Club foot	PR*† = 3.02 (95% CI: 1.1–6.0)
				Abdominal wall defects	PR*† = 2.46 (95% CI:0.53–11.38)
				Septal closure defects	PR*† = 1.95 (95% CI:0.57–6.66)
				Hypoplastic left heart	PR*† = 1.11 (95% CI:0.14–8.65)
				Renal agenesis	PR*† = 0.00 (95% CI:indeterminate)
				Lower limb reduction	PR*† = 0.00 (95% CI:indeterminate)
Hendricks et al, 2001[21]	Case-control	US-Mexico border, 1995–2000	BMI ≥30 vs BMI <30	NTDs	OR = 1.73 (95% CI:1.03–2.92)
					AOR = 1.40 (95% CI:0.80–2.47)
					OR adjusted for hyperinsulinemia only = 1.45 (95% CI:0.84–2.51)
Watkins and Botto, 2001[22]	Case-control	US, 1968–1980	BMI >26 vs BMI 19.9–22.7	Congenital heart defects	AOR* = 1.36 (95% CI:0.95–1.93)
Shaw et al., 2002[15]	Case-control	US, 1/1993–7/1996	BMI >29 vs BMI ≤29	Multiple congenital anomalies (2 or more major unrelated congenital anomalies affecting >1 organ system)	OR = 2.4 (95% CI:1.2–4.9)
					OR* = 2.3 (95% CI:1.1–5.2)
					AOR = 3.2 (95% CI 1.4–7.8)
Mikhail et al, 2002[13]	Retrospective cohort	US, 1981–1994, black women	BMI ≥27 vs BMI <27	Congenital heart defects	OR* = 6.5 (95% CI:1.2–34.9) (excluded high-risk mothers)

NTD indicates neural tube defect; AOR, adjusted odds ratio; PR, prevalence ratio
* Excludes diabetic mothers.
† Calculated from extracted data.

abnormalities, single gene conditions, or other recognized genetic syndromes were excluded from the study, even when they had defects that were included. Control infants were a stratified random sample of births at the 18 birth hospitals included in the Metropolitan Atlanta Congenital Defects Program, with the number of controls selected from each hospital based on the proportion of metropolitan Atlanta births that occurred in each birth hospital. Controls were selected among births in the same time period as the cases and were limited to infants with no major birth defects. To be eligible for inclusion as either a case or a control, infants had to be born between January 1993 and August 1997 and the mother had to be a resident of 1 of 5 metropolitan Atlanta counties (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) at the time of delivery. There were approximately 40 000 births per year to residents of these counties during this time period.

All mothers of case and control infants completed a telephone interview with questions on maternal health and medication use, pregnancy history and fertility, demographics, family history, nutrition, occupational and environmental exposures, tobacco and alcohol use, and substance abuse. The interviews were conducted in either English or Spanish. Mothers who did not speak either English or Spanish were excluded from the study. An outline of the planned study methods was published earlier.[24]

Heart defect cases were reviewed by one of us with heart defect expertise (L.D.B.). These cases were classified into several major categories, according to the main structural cardiac anomaly, and also into isolated (only 1 major primary malformation) or multiple (at least 1 other major unrelated malformation in a different organ system) categories. All other cases were reviewed by a clinical geneticist (C.A.M. or S.A.R.) and were classified as either isolated or multiple, using the same criteria. We limited our analyses to the subset of defects that contained at least 10 cases (Table 2). We also analyzed as a group all infants who were classified as having multiple congenital anomalies.

Maternal BMI was based on the mother's self-reported height and prepregnancy weight obtained during the telephone interview. BMI was calculated as weight (kg) divided by height (m) squared. We followed the National Institutes of Health BMI classification system with the following definitions: underweight (<18.5), average weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0).[25] Average-weight women were used as the referent group for all analyses. Some cases were missing data on maternal height or weight, resulting in a few case groups with fewer than 10 cases in the analyses. Recognizing the association between preexisting diabetes and birth defects, and diabetes and obesity, we excluded from the analyses infants whose mothers reported preexisting diabetes. Because defects showing a relation with obesity could share a common mechanism, we also combined defects that had an elevated risk (odds ratio [OR]: ≥1.5) associated with obesity into an aggregate, to perform additional stratified analyses.

All data were analyzed using SAS 8.01 (SAS Institute Inc, Cary, NC). Adjusted ORs for BMI category (adjusted for maternal age, education, alcohol use, smoking, periconceptional vitamin use, and race) were similar to the unadjusted ORs; therefore, only unadjusted estimates from stratified analyses are presented. All 95% confidence intervals (CIs) were calculated in SAS using the Mantel-Haenszel method.

RESULTS

The distribution of maternal and infant characteristics among cases and controls was similar, except that case mothers were more likely to have fewer than 12 years of education (Table 3). Compared with average-weight women, obese women were more likely to have an infant with a neural tube defect, especially spina bifida (OR: 3.5, 95% CI: 1.2–10.3), omphalocele (OR: 3.3; 95% CI: 1.0–10.3), heart defects in the aggregate (OR: 2.0; 95% CI: 1.2–3.4), or multiple anomalies (OR: 2.0; 95% CI: 1.0–3.8) than were average-weight women (Table 2). Overweight women also more likely to have an infant with a heart defect (OR: 2.0; 95% CI: 1.2–3.1), especially left

TABLE 2. Unadjusted OR* for Selected Defects by BMI Category (Referent = Average Weight, BMI 18.5–24.9), Atlanta Birth Defects Risk Factor Surveillance Study, 1993–1997

	Total	Average (BMI 18.5–24.9)	Underweight (BMI <18.5)		Overweight (BMI 25–29.9)		Obese (BMI ≥30)	
		n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Controls	330	212	27		55		36	
Hydrocephaly	14	8	1	1.0 (0.1–8.2)	3	1.5 (0.4–5.6)	2	1.5 (0.3–7.2)
NTDs	43	22	3	1.1 (0.3–3.8)	8	1.4 (0.6–3.3)	10	2.7 (1.2–6.1)
Anencephaly	12	6	1	1.3 (0.2–11.3)	2	1.3 (0.3–6.5)	3	2.9 (0.7–12.3)
Spina bifida	22	10	2	1.6 (0.3–7.6)	4	1.5 (0.5–5.1)	6	3.5 (1.2–10.3)
Encephalocele	9	6	0	-	2	1.3 (0.3–6.5)	1	1.0 (0.1–8.4)
Anencephaly and spina bifida	34	16	3	1.5 (0.4–5.4)	6	1.5 (0.5–3.9)	9	3.3 (1.4–8.1)
Oral clefts	90	59	5	0.7 (0.3–1.8)	18	1.2 (0.6–2.2)	8	0.8 (0.4–1.8)
Cleft palate	30	22	1	0.4 (0.1–2.8)	5	0.9 (0.3–2.4)	2	0.5 (0.1–2.4)
Cleft lip	26	16	3	1.5 (0.4–5.4)	5	1.2 (0.4–3.4)	2	0.7 (0.2–3.3)
Cleft lip + palate	34	21	1	0.4 (0.1–2.9)	8	1.5 (0.6–3.5)	4	1.1 (0.4–3.5)
Heart defects	195	95	20	1.7 (0.9–3.1)	48	2.0 (1.2–3.1)	32	2.0 (1.2–3.4)
LVOTO	42	19	3	1.2 (0.3–4.5)	16	3.3 (1.6–6.7)	4	1.2 (0.4–3.9)
HLH	22	13	1	0.6 (0.1–4.8)	7	2.1 (0.8–5.5)	1	0.5 (0.1–3.6)
Coarctation of aorta	12	5	0	-	5	3.9 (1.1–13.8)	2	2.4 (0.4–12.6)
RVOTO	25	13	4	2.4 (0.7–7.9)	5	1.5 (0.5–4.3)	3	1.4 (0.4–5.0)
Severe RVOTO†	14	6	3	3.9 (0.9–16.6)	3	1.9 (0.5–8.0)	2	2.0 (0.4–10.1)
ASD	12	4	3	5.9 (1.3–27.7)	3	2.9 (0.6–13.3)	2	2.9 (0.5–16.7)
VSD	43	23	3	1.0 (0.3–3.6)	9	1.5 (0.7–3.4)	8	2.1 (0.9–4.9)
ASD or VSD	55	27	6	1.8 (0.7–4.6)	12	1.7 (0.8–3.6)	10	2.2 (1.0–4.9)
Outflow tract defects	50	25	6	1.9 (0.7–5.0)	11	1.7 (0.8–3.7)	8	1.9 (0.8–4.5)
TOF	19	10	2	1.6 (0.3–7.6)	4	1.5 (0.5–5.1)	3	1.8 (0.5–6.7)
D-TGA	25	13	4	2.4 (0.7–7.9)	5	1.5 (0.5–4.3)	3	1.4 (0.4–5.0)
Esophageal atresia	20	13	1	0.6 (0.1–4.8)	1	0.3 (0.0–2.3)	5	2.3 (0.8–6.7)
Omphalocele	18	9	1	0.9 (0.1–7.2)	3	1.3 (0.3–4.9)	5	3.3 (1.0–10.3)
Gastroschisis	23	16	1	0.5 (0.1–3.9)	6	1.5 (0.5–3.9)	0	-
Small intestinal atresia	9	5	0	-	3	2.3 (0.5–10.0)	1	1.2 (0.1–10.4)
Large intestinal atresia	32	19	0	-	9	1.8 (0.8–4.3)	4	1.2 (0.4–3.9)
Limb deficiencies	45	29	4	1.1 (0.4–3.3)	8	1.1 (0.5–2.5)	4	0.8 (0.3–2.5)
Transverse	33	22	2	0.7 (0.2–3.2)	5	0.9 (0.3–2.4)	4	1.1 (0.4–3.3)
Longitudinal	13	7	2	2.2 (0.4–11.4)	3	1.7 (0.4–6.6)	1	0.8 (0.1–7.0)
Amniotic band sequence	12	10	0	-	1	0.4 (0.1–3.1)	1	0.6 (0.1–4.7)
Renal anomalies	106	74	8	0.9 (0.4–2.0)	16	0.8 (0.5–1.5)	8	0.6 (0.3–1.4)
Renal agenesis	20	14	3	1.5 (0.4–5.4)	1	0.3 (0.0–2.1)	2	0.8 (0.2–3.9)
Renal multicystic dysplasia	30	19	1	0.4 (0.1–3.2)	7	1.4 (0.6–3.6)	3	0.9 (0.3–3.3)
Urinary obstruction	67	47	5	0.8 (0.3–2.3)	11	0.9 (0.4–1.9)	4	0.5 (0.2–1.5)
Hypospadias	21	13	2	1.2 (0.3–5.6)	5	1.5 (0.5–4.3)	1	0.5 (0.1–3.6)
Craniosynostosis	28	15	4	2.1 (0.7–6.8)	7	1.8 (0.7–4.6)	2	0.8 (0.2–3.6)
Diaphragmatic hernia	17	11	2	1.4 (0.3–6.8)	3	1.1 (0.3–3.9)	1	0.5 (0.1–4.3)
Multiple congenital anomalies	96	48	8	1.3 (0.6–3.1)	24	1.9 (1.1–3.4)	16	2.0 (1.0–3.8)

LVOTO indicates left ventricular outflow tract obstruction; HLH, hypoplastic left heart; RVOTO, right ventricular outflow tract obstruction; ASD, atrial septal defect; VSD, ventricular septal defect; TOF, tetralogy of Fallot; D-TGA, dextro transposition of the great arteries.

* Cases with preexisting diabetes excluded from analysis.

† Includes infants with tricuspid atresia, pulmonary atresia with intact ventricular septum, and hypoplastic right heart

ventricular outflow tract defects (OR: 3.3; 95% CI: 1.6–6.7), or multiple anomalies (OR: 1.9; 95% CI: 1.1–3.4). With the exception of atrial septal defects, there were no significant associations between birth defects and underweight status; however, there was a low prevalence of underweight in this population. For each of the defects for which there was an association among obese women, the ORs for obese and overweight women were greater than that for underweight women.

We combined defect groups in which there was an elevated OR (≥1.5) to evaluate whether the strength of the association varied by several characteristics (Table 4). The OR for this aggregate group was 1.8 (95% CI: 1.1–2.9) for obese women and 1.7 (95% CI: 1.1–2.5) for overweight women. For this group, the magnitude of the obesity-related birth defect effect tended to be greater among women who were white, smoked, were primigravidas, were periconceptional multivitamin users, had fewer years of education, and did not report gestational diabetes, although none of the interactions was statistically significant. The heaviest obese women (BMI >35) tended to have a stronger association (OR: 2.1; 95% CI: 1.0–4.3) than moderately obese women (BMI 30–35; OR: 1.6; 95% CI: 0.9–2.9) or overweight women (OR: 1.7; 95% CI: 1.1–2.5), although again this was based on small numbers. To assess this possible dose-response relation further, we evaluated BMI as a continuous variable. The OR per incremental unit increase in BMI for women who were of average weight or heavier (BMI ≥18.5) was 1.07 (95% CI: 1.03–1.10; $P = .0001$).

DISCUSSION

Our study, although small, confirmed the previously observed elevated risk for spina bifida[6–11] among obese women. The risk estimates of 3.5 for spina bifida and 3.3 for spina bifida or anencephaly

TABLE 3. Characteristics of Subjects by Case/Control Status, Atlanta Birth Defects Risk Factor Surveillance Study, 1993–1997

	Cases *N* (%)	Controls *N* (%)	*P* Value
Race			
White	378 (59)	183 (55)	.35
Other	267 (41)	147 (45)	
Gravidity			
Primigravid	194 (30)	106 (32)	.52
Multigravid	450 (70)	224 (68)	
Education			
<12 y	87 (14)	27 (8)	.04
12 y	134 (21)	66 (20)	
>12 y	421 (66)	235 (72)	
Maternal age			
≤ 29 y	380 (59)	197 (60)	.77
> 29 y	263 (41)	131 (40)	
Cigarette smoking*			
Yes	133 (21)	53 (16)	.08
No	511 (79)	277 (84)	
Alcohol use*			
Yes	320 (50)	160 (48)	.74
No	325 (50)	170 (52)	
Gestational diabetes†			
Yes	44 (7)	19 (6)	.52
No	601 (93)	311 (94)	
Periconceptional multivitamin use‡			
Yes	110 (17)	48 (15)	.31
No	535 (83)	282 (85)	
BMI (kg/m^2)			
Underweight (<18.5)	50 (8)	27 (8)	.81
Average weight (18.5–24.9)	391 (61)	212 (64)	.27
Overweight (25.0–29.9)	131 (20)	55 (17)	.17
Obese (≥30.0)	73 (11)	36 (11)	.85

* Any during 3 months before or during pregnancy.
† One control and 10 cases with preexisting diabetes were excluded from analyses.
‡ Regular use 1 month before through third month of pregnancy.

were higher than previously reported, but wide CIs limit the conclusions possible. If future studies confirm these higher risk estimates, then it might be because the average weight of women in the obese category has increased over time. Consistent with this potential explanation, we found increasing risk with increasing BMI for the aggregate of defects with ORs ≥1.5. This suggests a dose response; for every incremental unit increase in BMI, the risk increased 7%.

Although Waller et al[6] found a 2.5-fold obesity-related risk for ventral wall defects, our study is the first to evaluate omphalocele and gastroschisis separately, finding a risk elevation for omphalocele (OR: 3.3) but not for gastroschisis, consistent with the pathogenetic heterogeneity suspected for these 2 defects.[26] Previous studies of obesity and heart defects have been inconsistent and often difficult to compare because of variation in classification schemes. Whereas 1 study[9] reported no risk elevation for conotruncal heart defects, others report risk elevations for truncus arteriosus and transposition of the great arteries[14] and defects of the great vessels[6] (Table 1). We reported a modestly elevated risk among obese women for aggregate heart defects in an earlier Atlanta study (OR: 1.4; 95% CI: 1.0–1.9),[22] and a recent study found a 6.5-fold risk elevation for aggregate cardiac defects among black women.[13] Our current study is the first to report a significant 2-fold increased risk for an aggregate group of heart defects among both obese and overweight women. Our finding of a 2-fold risk for having an infant with multiple defects among both obese and overweight women adds evidence to a similar finding reported by Shaw et al.[15] We did not observe an elevated risk for orofacial clefts, consistent with 1 study,[9] but inconsistent with 2 other studies that found ORs of 2.8 and 3.0 (Table 1).[12,14]

The mechanism for the observed association between obesity and birth defects is not known, but several possible explanations have been proposed.[6,12] One explanation might be that obese women have metabolic alterations, such as hyperglycemia or elevated insulin or estrogen levels, that increase their risk for birth defects. Hyperinsulinemia has been shown to be an independent risk factor for neural tube defects, but even after adjustment for hyperinsulinemia, obesity continued to be a modest risk factor.[21] Another explanation is that women who are obese might have diabetes, a known risk factor for birth defects.[27] In previous studies, the relation between obesity and neural tube defects persisted, even when women with known diabetes were excluded or when adjustment was made for diabetes; however, some women with diabetes might be unrecognized. Women who are obese also might have nutritional deficits, resulting from dieting behaviors or poor-quality diets,[28] that increase their risk for congenital anomalies. Previous studies have shown that multivitamin[7,10] and folic acid intake[7] is similar among obese and nonobese women; however, other nutrients, currently not recognized as causing birth defects, might play a role. Another explanation is that women who are obese might have an increased requirement for certain nutrients (eg, folic acid) known to be protective against birth defects. The study by Werler et al[8] provides some evidence for this hypothesis: the reduction in neural tube defect risk typically associated with folic acid was not observed among heavier women.

Strengths of our study include that it was population based and that careful case classification was performed. However, small numbers limited our ability to assess the relation between obesity and less common birth defects and to evaluate extensively whether the obesity-related birth defect risk varied by demographic and behavioral characteristics, which could provide clues to the mechanisms involved. Although we combined several defects with ORs ≥1.5 into an aggregate, we had limited power to detect interactions and found no significant ones. An additional limitation was that our BMI calculations were based on self-reported weight and height, which tend to underreport BMI compared with measured weights.[3] However, it is unlikely that obese case women reported their prepregnancy weights differently from obese control mothers, making a systematic bias unlikely. Biological measurements early in pregnancy (eg, insulin levels, glucose levels) would be informative in determining whether the obesity-related risk is related to hyperglycemia, hyperinsulinemia, or some other metabolic abnormality. Hendricks et al[21] found a relation between post-

TABLE 4. Unadjusted ORs for Combined Positive-Association Group of Defects* by BMI Category by Maternal Characteristic (Referent = Average Weight, BMI 18.5–24.9), Atlanta Birth Defects Risk Factor Surveillance Study, 1993–1997

	N	Average (BMI 18.5–24.9)	Underweight (BMI <18.5)		Overweight (BMI 25–29.9)		Obese† (BMI ≥30)	
		N	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)
Controls	330	212	27		55		36	
Combined group (anencephaly, spina bifida, omphalocele, esophageal atresia, hydrocephaly, hearts, and all multiples)	302	158	27	1.3 (0.8–2.4)	69	1.7 (1.1–2.5)	48	1.8 (1.1–2.9)
Maternal smoking	70	35	4	0.6 (0.2–2.4)	17	1.6 (0.6–3.9)	14	2.6 (0.8–7.9)
No maternal smoking	232	123	23	1.6 (0.8–3.0)	52	1.7 (1.1–2.7)	34	1.6 (0.9–2.7)
Primigravid	87	48	8	1.2 (0.4–3.3)	20	1.8 (0.9–3.8)	11	2.8 (1.0–8.0)
Multigravid	215	110	19	1.4 (0.7–2.8)	49	1.6 (1.0–2.7)	37	1.6 (0.9–2.7)
Maternal alcohol use	146	80	11	1.4 (0.6–3.4)	36	2.5 (1.4–4.7)	19	1.6 (0.8–3.2)
No maternal alcohol use	156	78	16	1.3 (0.6–2.7)	33	1.2 (0.7–2.1)	29	2.0 (1.0–3.7)
Periconceptional vitamin use	53	29	8	1.5 (0.5–4.7)	8	1.3 (0.4–3.9)	8	2.9 (0.7–12.2)
No periconceptional vitamin use	249	129	19	1.3 (0.7–2.4)	61	1.8 (1.1–2.8)	40	1.7 (1.0–2.8)
Maternal education								
<12 y	43	19	6	—	8	1.6 (0.4–5.8)	10	3.3 (0.8–14.0)
12 y	64	27	6	1.7 (0.5–6.1)	16	1.5 (0.6–3.5)	15	2.6 (1.0–7.1)
>12 y	195	112	15	0.9 (0.5–1.9)	44	1.7 (1.0–2.9)	23	1.3 (0.7–2.5)
Maternal age #29 y	181	86	19	1.5 (0.7–3.0)	48	1.6 (1.0–2.7)	28	2.3 (1.2–4.5)
Maternal age >29 y	121	72	8	1.1 (0.4–3.0)	21	1.9 (0.9–3.9)	20	1.4 (0.7–2.8)
Reported gestational diabetes	23	9	0	—	6	2.7 (0.4–17.2)	8	0.9 (0.2–3.5)
No gestational diabetes	279	149	27	1.4 (0.8–2.5)	63	1.6 (1.1–2.5)	40	2.0 (1.2–3.3)
Race/ethnicity white	172	98	17	1.7 (0.8–3.6)	33	2.5 (1.3–4.7)	24	2.1 (1.0–4.1)
Race/ethnicity other	130	60	10	1.0 (0.4–2.4)	36	1.2 (0.7–2.2)	24	1.5 (0.8–3.0)
Combined group-isolated cases only	207	110	19	1.4 (0.7–2.5)	45	1.6 (1.0–2.5)	33	1.8 (1.0–3.0)

* Anencephaly, spina bifida, omphalocele esophageal atresia, hydrocephaly, hearts, and all multiples.
† All *P* values for interaction not significant, >.20 (χ^2, Breslow-Day test for homogeneity of ORs).

partum insulin levels and neural tube defects and suggested that obesity-related risk may be explained by hyperinsulinemia. However, postpartum insulin levels might not be representative of early pregnancy levels. Biological measurements obtained prospectively at the time of teratogenesis are obviously more desirable and would be possible in a prospective study, although such a study would have to be large to assess relatively rare outcomes such as birth defects. The proposed National Children's Study would allow this type of assessment (nationalchildrensstudy.gov/).

Our study adds more evidence to the link between maternal obesity and birth defects. Although the biological mechanism(s) behind obesity and birth defects is unknown, efforts to ensure that reproductive-aged women are of healthy weight before pregnancy should not await the elucidation of the mechanisms. There is growing recognition of the many reproductive problems associated with maternal obesity and the importance of evaluation and treatment in this population.[29] Weight loss during pregnancy is not recommended.[30] However, many of the general initiatives to control the obesity epidemic and its associated morbidities[25] in the general population can help prevent obesity in reproductive-aged women before they become pregnant. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults,[25] as well as in children and adolescents,[31] are available.

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