

# Prepregnancy Obesity as a Risk Factor for Structural Birth Defects

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**Objective:** To describe the relation between maternal obesity, overweight and underweight status, and 16 categories of structural birth defects.

**Design:** An ongoing multisite, case-control study. Clinical geneticists reviewed all of the cases, excluding those that had or were strongly suspected to have a single-gene disorder or chromosomal abnormality. Mothers with preexisting diabetes were also excluded. Body mass index was based on maternal report of height and weight prior to pregnancy.

**Setting:** Eight participating states in the United States.

**Participants:** Mothers enrolled in the National Birth Defects Prevention Study who had index pregnancies between October 1, 1997, and December 31, 2002.

**Main Exposure:** Maternal obesity.

**Main Outcome Measures:** Crude and adjusted odds ratios.

**Results:** Mothers of offspring with spina bifida, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele were significantly more likely to be obese than mothers of controls, with odds ratios ranging between 1.33 and 2.10. Mothers of offspring with gastroschisis were significantly less likely to be obese than mothers of controls.

**Conclusions:** To our knowledge, this is the first population-based study of its scale to examine prepregnancy obesity and a range of structural birth defects. These results suggest a weak to moderate positive association of maternal obesity with 7 of 16 categories of birth defects and a strong inverse association with gastroschisis. The mechanisms underlying these associations are not yet understood but may be related to undiagnosed diabetes.

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**T**HE DRAMATIC INCREASE in the prevalence of overweight and obese women of childbearing age is of great public health concern because they are at increased risk for chronic disease,<sup>1</sup> infertility,<sup>2</sup> menstrual irregularities,<sup>3,4</sup> pregnancy complications,<sup>5</sup> and adverse pregnancy outcomes,<sup>6-8</sup> including birth defects.<sup>9-12</sup> Data from the 2003-2004 National Health and Nutrition Examination Survey<sup>13</sup> indicate that 51% of nonpregnant women aged 20 to 39 years are classified as overweight (body mass index [BMI] [calculated as the weight in kilograms divided by the height in meters squared]  $\geq 25.0$  and  $< 30.0$ ) or obese (BMI  $\geq 30.0$ ). A strong association has been demonstrated between a woman's prepregnancy BMI and risk for offspring with certain birth defects, particularly anencephaly and spina bifida.<sup>9-12</sup> The potential relation between obesity and other birth defects remains less certain, as those studies that have examined a range of dif-

ferent birth defects did not have sufficient numbers of cases to generate precise odds ratios.<sup>9,14,15</sup>

Given the paucity of data regarding prepregnancy obesity and the occurrence of birth defects, we conducted an analysis of data from the National Birth Defects Prevention Study (NBDPS),<sup>16</sup> an ongoing multisite, population-based, case-control study of more than 30 different categories of structural birth defects. Our study assessed whether maternal prepregnancy obesity, overweight status, and underweight status were associated with an increased risk for 16 categories of structural birth defects.

## METHODS

Infants in the NBDPS who were born on or after October 1, 1997, and had an estimated date of delivery on or before December 31, 2002, were eligible for the current analyses. Eight states participated in this analysis, and each state interviewed approximately 300 eligible case

**Table 1. Demographic Characteristics of Cases and Controls From the National Birth Defects Prevention Study, 1997-2002**

Characteristic	Cases, No. (%) (n = 10 249)	Controls, No. (%) (n = 4065)
Maternal age, y		
< 18	427 (4.2)	172 (4.2)
18-24	3130 (30.5)	1161 (28.6)
25-29	2497 (24.4)	1054 (25.9)
30-34	2592 (25.3)	1102 (27.1)
≥ 35	1603 (15.6)	576 (14.2)
Maternal ethnicity		
Non-Hispanic white	6230 (60.8)	2439 (60.0)
Black	1047 (10.2)	487 (12.0)
Hispanic	2394 (23.4)	925 (22.8)
Other	555 (5.4)	203 (5.0)
Missing	23 (0.2)	11 (0.3)
Education		
< High school	1853 (18.1)	671 (16.5)
High school	2732 (26.7)	1022 (25.1)
Some college	2709 (26.4)	1095 (26.9)
College graduate	2944 (28.7)	1269 (31.2)
Missing	11 (0.1)	8 (0.2)
Body mass index <sup>a</sup>		
Thin, < 18.5	620 (6.0)	233 (5.7)
Normal, ≥ 18.5 to < 25.0	5343 (52.1)	2241 (55.1)
Overweight, ≥ 25.0 to < 30.0	2166 (21.1)	858 (21.1)
Obese, ≥ 30.0	1740 (17.0)	572 (14.1)
Missing	380 (3.7)	161 (4.0)
Parity		
First birth	4448 (43.4)	1625 (40.0)
≥ Second birth	5796 (56.6)	2438 (60.0)
Missing	5 (0.0)	2 (0.0)
Current smoker <sup>b</sup>		
No	8020 (78.3)	3298 (81.1)
Yes	2225 (21.7)	766 (18.8)
Missing	4 (0.0)	1 (0.0)
Supplemental folic acid intake <sup>c</sup>		
No	7085 (69.1)	2809 (69.1)
Yes	3164 (30.9)	1256 (30.9)
Pregnancy outcome		
Live birth	9888 (96.5)	4065 (100.0)
Fetal death	159 (1.6)	0
Pregnancy termination	193 (1.9)	0
Missing	9 (0.0)	0

<sup>a</sup>Body mass index is calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup>Smoked cigarettes in the month prior to conception.

<sup>c</sup>Intake of any supplemental folic acid in the month prior to conception.

mothers and 100 control mothers annually. Cases had 1 or more of 30 eligible birth defects. Infants recognized or strongly suspected to have single-gene conditions or chromosomal abnormalities were excluded from the NBDPS. Controls were unmatched and were live-born infants without birth defects randomly selected from birth certificates (Arkansas, Iowa, Massachusetts, New Jersey, and Georgia [2001-2002]) or from birth hospitals (California, Georgia [1997-2000], New York, and Texas) to represent the population from which cases were derived. This study was approved by the institutional review boards of the participating study centers and the Centers for Disease Control and Prevention.

Among the birth defect categories included in the NBDPS, we selected only those for which 150 or more eligible cases with completed interviews were available, as those categories with fewer eligible cases would not have generated sufficiently precise odds

ratios (ORs). A total of 16 birth defect categories met this criterion. After all of the cases were aggregated across states, they were further reviewed by clinical geneticists associated with the NBDPS and classified based on the nature of accompanying congenital anomalies into 1 of 3 categories: isolated, multiple (infants with ≥ 2 major unrelated birth defects),<sup>17</sup> or complex sequence (infants with ≥ 2 birth defects believed to be pathogenetically related but for which the underlying defect is not clear).

Microtia and anotia included dysplastic or absent ear pinna or stenosis or atresia of the external auditory canal. Infants with well-defined major congenital heart defects and eligible for inclusion in the NBDPS<sup>16</sup> were analyzed in aggregate in this study. Some heart defects were excluded from the NBDPS because they were very rare, not well ascertained in infancy, preterm-related birth defects (patent ductus arteriosus and patent foramen ovale), minor defects of unclear significance (eg, insufficiency of the tricuspid, mitral, or pulmonary valves), and vascular defects rather than true malformations of the heart (eg, vascular rings and aberrant subclavian artery). Muscular ventricular septal defects were ascertained only in the early years of the study; therefore, we chose to exclude them from this analysis. All of the cases with cardiovascular defects were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy.<sup>16</sup> Oral clefts were classified into 2 groups that have been established by previous epidemiologic studies to have different risk factors: cleft lip with or without cleft palate and cleft palate only.<sup>18</sup> Only cases of second- or third-degree hypospadias were included in the NBDPS because first-degree hypospadias is less likely to be consistently ascertained.<sup>19</sup>

Maternal interviews were conducted using a standardized computer-based interview, primarily by telephone, in English or Spanish, no earlier than 6 weeks after the infant's estimated date of delivery, and no later than 24 months after delivery. During the study period (October 1, 1997, to December 31, 2002), participation rates for the interview were 71.4% among case mothers and 67.9% among control mothers. Interviews were completed within an average of 11 months from the estimated date of delivery for cases and 9 months for controls. A total of 1.1% (122 of 10 655) of cases and 1.2% (49 of 4143) of controls were excluded because the mothers did not complete the interview. To ensure that any associations we observed between maternal obesity and birth defects were not confounded by preexisting diabetes, we also excluded an additional 2.7% of cases (n=284) and 0.7% of controls (n=29) whose mothers reported having diabetes prior to conception or did not answer the question on preexisting diabetes. After these exclusions, 10 249 cases and 4065 controls remained in our initial analyses (**Table 1**).

Mothers were asked to report their height and prepregnancy weight using either English or metric units. Case and control mothers with invalid or missing values of BMI (3.7% and 4.0%, respectively) were excluded from the analyses presented in **Table 2** and **Table 3**. We used the BMI analytic categories currently recommended by the National Heart, Lung, and Blood Institute and the World Health Organization (underweight, < 18.5; normal [reference], ≥ 18.5 to < 25.0; overweight, ≥ 25.0 to < 30.0; and obese, ≥ 30.0).<sup>20</sup> As only male infants are at risk for hypospadias, all of the analyses for hypospadias were conducted limiting controls to mothers of male infants. Logistic regression was used to examine crude and adjusted ORs for the association between maternal prepregnancy BMI and the frequency of the 16 different categories of birth defects included in this study. All of the ORs were adjusted for maternal race/ethnicity (white, black, Hispanic, or other), maternal age (< 18, 18-24, 25-29, 30-34, or ≥ 35 years), maternal educational level (< 12, 12, 13-15, or ≥ 16 years), parity (0 or ≥ 1 previous births), smoking in the month prior to conception (yes or no), and any intake of vitamins containing

**Table 2. Adjusted Odds Ratios for the Association Between Maternal Body Mass Index and Selected Birth Defects<sup>a</sup>**

Birth Defect	Cases, No.	Thin, BMI < 18.5		Overweight, 25.0 ≤ BMI < 30.0		Obese, BMI ≥ 30.0	
		Cases, No.	OR (95% CI)	Cases, No.	OR (95% CI)	Cases, No.	OR (95% CI)
Anencephaly	193	10	0.82 (0.42-1.59)	42	0.94 (0.65-1.36)	30	0.96 (0.62-1.48)
Spina bifida	425	20	0.91 (0.56-1.46)	84	1.03 (0.78-1.34)	117	2.10 (1.63-2.71)
Hydrocephaly	156	10	1.06 (0.54-2.09)	35	1.14 (0.76-1.71)	28	1.36 (0.87-2.12)
Microtia and anotia	216	11	0.82 (0.43-1.56)	46	0.86 (0.60-1.23)	35	1.10 (0.74-1.65)
Heart defects <sup>b</sup>	4128	255	1.12 (0.93-1.36)	939	1.13 (1.01-1.26)	784	1.40 (1.24-1.59)
Cleft palate	592	33	0.92 (0.62-1.36)	125	1.03 (0.82-1.28)	104	1.26 (0.99-1.61)
Cleft lip and cleft palate <sup>c</sup>	1064	92	1.35 (1.04-1.76)	215	0.97 (0.81-1.15)	165	1.13 (0.92-1.38)
Esophageal atresia	278	17	1.07 (0.63-1.82)	57	1.01 (0.74-1.39)	41	1.20 (0.84-1.73)
Small-intestinal atresia <sup>d</sup>	163	11	1.20 (0.63-2.31)	36	1.04 (0.70-1.56)	30	1.29 (0.83-1.99)
Anorectal atresia	380	17	0.81 (0.48-1.36)	90	1.19 (0.92-1.55)	75	1.46 (1.10-1.95)
Second- or third-degree hypospadias <sup>e</sup>	793	43	1.04 (0.71-1.52)	188	1.25 (1.01-1.54)	122	1.33 (1.03-1.72)
Limb reduction defects	509	32	1.08 (0.73-1.61)	123	1.22 (0.97-1.54)	90	1.36 (1.05-1.77)
Craniosynostosis	422	22	1.07 (0.67-1.70)	105	1.28 (1.00-1.64)	69	1.26 (0.94-1.68)
Diaphragmatic hernia	286	15	0.85 (0.49-1.47)	55	0.91 (0.66-1.26)	55	1.42 (1.03-1.98)
Omphalocele	177	9	0.98 (0.48-1.98)	48	1.50 (1.04-2.17)	34	1.63 (1.07-2.47)
Gastroschisis	400	41	0.85 (0.58-1.23)	68	0.69 (0.50-0.92)	12	0.19 (0.10-0.34)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio.

<sup>a</sup>The ORs are adjusted for maternal age, ethnicity, education, parity, smoking in the month prior to conception, and supplemental folic acid intake in the month prior to conception. There were 3904 controls: 233 controls in the thin group, 858 controls in the overweight group, 572 controls in the obese group, and 2241 controls in the reference group (18.5 ≤ BMI < 25.0).

<sup>b</sup>All heart defects.

<sup>c</sup>Cleft lip with or without cleft palate.

<sup>d</sup>Includes jejunal, ileal, and multiple small-intestinal atresias.

<sup>e</sup>The control group for this birth defect was limited to mothers of male infants.

**Table 3. Adjusted Odds Ratios for the Association Between Maternal Body Mass Index and Selected Birth Defects Stratified by Isolated and Multiple Defects<sup>a</sup>**

Birth Defect	Overweight, 25.0 ≤ BMI < 30.0				Obese, BMI ≥ 30.0			
	Isolated		Multiple		Isolated		Multiple	
	Cases, No.	OR (95% CI)	Cases, No.	OR (95% CI)	Cases, No.	OR (95% CI)	Cases, No.	OR (95% CI)
Anencephaly	39	0.97 (0.66-1.42)	3	0.61 (0.17-2.24)	27	1.00 (0.64-1.56)	3	0.62 (0.13-2.88)
Spina bifida	73	0.99 (0.74-1.31)	11	1.32 (0.63-2.76)	110	2.19 (1.69-2.85)	7	1.24 (0.52-2.97)
Hydrocephaly	28	1.33 (0.84-2.11)	7	0.81 (0.34-1.92)	18	1.27 (0.74-2.19)	10	1.70 (0.78-3.70)
Microtia and anotia	38	0.96 (0.64-1.44)	8	0.58 (0.27-1.28)	25	1.06 (0.66-1.70)	9	1.04 (0.49-2.21)
Heart defects <sup>b</sup>	753	1.08 (0.96-1.22)	171	1.50 (1.22-1.85)	627	1.33 (1.17-1.52)	137	1.80 (1.43-2.26)
Cleft palate	98	0.97 (0.76-1.25)	27	1.27 (0.80-2.04)	86	1.27 (0.98-1.66)	18	1.22 (0.70-2.11)
Cleft lip and cleft palate <sup>c</sup>	190	0.95 (0.79-1.14)	25	1.07 (0.66-1.74)	140	1.07 (0.86-1.32)	25	1.67 (1.03-2.73)
Esophageal atresia	25	1.15 (0.71-1.85)	32	0.92 (0.61-1.39)	19	1.41 (0.83-2.40)	22	1.07 (0.66-1.73)
Small-intestinal atresia <sup>d</sup>	30	0.97 (0.63-1.50)	6	1.63 (0.59-4.49)	25	1.20 (0.75-1.92)	5	1.93 (0.65-5.73)
Anorectal atresia	40	1.20 (0.81-1.77)	49	1.19 (0.84-1.68)	37	1.68 (1.12-2.52)	38	1.32 (0.89-1.94)
Second- or third-degree hypospadias <sup>e</sup>	174	1.24 (1.00-1.54)	14	1.31 (0.68-2.54)	106	1.25 (0.96-1.63)	16	2.43 (1.26-4.67)
Limb reduction defects	96	1.24 (0.96-1.61)	27	1.18 (0.74-1.88)	64	1.26 (0.93-1.71)	26	1.72 (1.06-2.78)
Craniosynostosis	96	1.33 (1.02-1.72)	9	0.91 (0.42-1.95)	63	1.31 (0.96-1.77)	6	0.86 (0.35-2.14)
Diaphragmatic hernia	41	0.82 (0.57-1.17)	13	1.30 (0.66-2.54)	39	1.20 (0.82-1.76)	15	2.37 (1.24-4.56)
Omphalocele	24	1.27 (0.78-2.09)	21	1.83 (1.04-3.24)	17	1.42 (0.81-2.51)	16	2.03 (1.08-3.81)
Gastroschisis	63	0.69 (0.51-0.94)	5	0.63 (0.23-1.67)	11	0.19 (0.10-0.35)	1	0.19 (0.03-1.42)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio.

<sup>a</sup>The ORs are adjusted for maternal age, ethnicity, education, parity, smoking in the month prior to conception, and supplemental folic acid intake in the month prior to conception.

<sup>b</sup>All heart defects.

<sup>c</sup>Cleft lip with or without cleft palate.

<sup>d</sup>Includes jejunal, ileal, and multiple small-intestinal atresias.

<sup>e</sup>The control group for this birth defect was limited to mothers of male infants.

folic acid in the month prior to conception (yes or no). We stratified our analyses according to whether the infant was classified as having isolated or multiple birth defects. A total of 1.1%

of all of the cases (110 of 10 249 cases) were classified as complex sequences. As they were too rare to examine separately, these cases were excluded from this analysis.

The NBDPS interview asked participants whether they had a history of physician-diagnosed gestational diabetes but did not determine during which pregnancy the diagnosis was made. Similar to previous studies, we did not exclude women who reported a history of gestational diabetes from our main analysis. Retaining these women allowed us to assess the total risk associated with maternal obesity, including the risk among obese women who develop gestational diabetes. We also conducted an analysis assessing the risk associated with maternal obesity after excluding women with a history of gestational diabetes.

## RESULTS

Control mothers were slightly older, more educated, more likely to be black, and more likely to have had a previous birth than case mothers (Table 1). Controls were also less likely to be smokers or to be obese compared with case mothers (Table 1). Among cases, 96.5% were live born, 1.6% were fetal deaths ( $\geq 20$  weeks' gestation), and 1.9% were pregnancy terminations.

Because crude and adjusted ORs were very similar, we chose to present only adjusted ORs. Maternal obesity was associated with significantly increased risk for offspring with spina bifida, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele, with ORs ranging from 1.33 to 2.10 (Table 2). Maternal obesity was also associated with a borderline increase in risk for cleft palate and a strong and significantly decreased risk for gastroschisis (adjusted OR, 0.19; 95% confidence interval [CI], 0.10-0.34). Maternal overweight status was associated with a significantly increased risk for heart defects, hypospadias, and omphalocele (ORs ranging from 1.13-1.50) and a borderline increase in risk for craniosynostosis (adjusted OR, 1.28; 95% CI, 1.00-1.64). Mothers who were underweight had no significant increase or decrease in the risk for these birth defects, except for a modest increase in risk for cleft lip with or without cleft palate (adjusted OR, 1.35; 95% CI, 1.04-1.76).

After excluding case and control mothers with gestational diabetes from the analysis, the adjusted ORs for the 7 birth defects that had been positively associated with maternal obesity were decreased slightly toward the null (spina bifida: OR, 2.09; 95% CI, 1.63-2.70; heart defects: OR, 1.26; 95% CI, 1.11-1.43; anorectal atresia: OR, 1.21; 95% CI, 0.89-1.63; hypospadias: OR, 1.21; 95% CI, 0.93-1.58; limb reduction defects: OR, 1.16; 95% CI, 0.89-1.52; diaphragmatic hernia: OR, 1.41; 95% CI, 1.01-1.97; and omphalocele: OR, 1.27; 95% CI, 0.83-1.96). However, the adjusted OR for gastroschisis remained about the same (OR, 0.20; 95% CI, 0.11-0.37).

In Table 3, adjusted ORs are presented for the association between maternal BMI and the 16 birth defect categories, stratified by isolated and multiple birth defects. For most of the categories of birth defects, the percentages of cases with multiple birth defects were less than 25%, except for esophageal atresia (59.7%), anorectal atresia (54.7%), and omphalocele (42.9%) (Table 3). Although there was some loss of precision owing to this stratification, the same pattern as described earlier was observed among infants with isolated birth defects, ie, a positive association between maternal obesity and the 7 categories of birth defects described earlier and a strong

inverse association between maternal obesity and gastroschisis. Based on differences in the ORs of 25% or more, 8 of the 16 birth defect categories had higher ORs for obesity among the subgroup with multiple birth defects, 5 had higher ORs among the subgroup with isolated birth defects, and 3 had no meaningful difference in the magnitude of the ORs across these subgroups.

## COMMENT

The current study and 7 large case-control studies<sup>9-12,21-23</sup> were remarkably consistent in observing that obese mothers have an approximately 2-fold increase in the risk of offspring affected by spina bifida compared with nonobese mothers. This study also confirmed the observations of 2 large studies by Watkins and Botto<sup>24</sup> and Cedergren and Källén<sup>25</sup> that obese or overweight women have a modest increase in the risk of all heart defects in aggregate (adjusted OR, 1.36; 95% CI, 0.95-1.93; and adjusted OR, 1.18; 95% CI, 1.09-1.27, respectively). Our finding of a modest increase in the risk of cleft palate is similar to that of a large prospective study by Cedergren and Källén<sup>26</sup> that included 610 cases of cleft palate and observed a borderline increase in the risk of cleft palate among obese women (adjusted OR, 1.28; 95% CI, 0.98-1.67). Based on 104 cases, a previous case-control study<sup>27</sup> of overweight mothers (BMI > 28.3) and gastroschisis observed a decreased OR (adjusted OR, 0.20; 95% CI, 0.05-0.90) remarkably similar to the OR we observed.

For 3 categories of birth defects, our results differed from those of previous studies. Based on 1069 cases of cleft lip with or without cleft palate, Cedergren and Källén<sup>26</sup> observed that obese women had a modest increase in the risk for this birth defect (adjusted OR, 1.31; 95% CI, 1.07-1.60), whereas based on a similar number of cases of this birth defect, we observed no significant increase in risk (adjusted OR, 1.13; 95% CI, 0.92-1.38). The lack of an association between maternal obesity and anencephaly in this study is inconsistent with 4 large case-control studies<sup>9,10,12,21</sup> that reported elevations in the risk for anencephaly with adjusted ORs ranging from 1.40 to 2.30. Also, the lack of a significant association between maternal obesity and hydrocephaly in this study conflicts with 2 previous studies<sup>21,28</sup> in which an increased risk for this birth defect among obese women was observed. The failure of our study to confirm previous reports of an association between maternal obesity and these 3 birth defects may be explained by chance. The numbers of cases of hydrocephaly (n = 156) and anencephaly (n = 200) in our study were relatively low; therefore, statistical power to detect weak to moderate associations for these 2 birth defects was more limited compared with most of the categories of birth defects in this study.

To our knowledge, this is the first study to report associations between maternal obesity and anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele based on sufficient sample sizes, ie, 150 cases or more. Hence, these associations should be interpreted cautiously until confirmed by additional studies.

The NBDPS has a number of important strengths. It was designed to use well-defined, state-of-the-art proce-



dures for case definition, clinical review, and classification of birth defects—which are often complex and difficult to classify. In addition, for many types of birth defects, it provides much greater statistical precision than has been previously possible. The NBDPS provides excellent statistical power to examine maternal obesity and heart defects. As classification of heart defects is quite complex and varies across studies, we chose to limit the analyses to heart defects in aggregate. The association between maternal obesity and specific types of heart defects will be examined in depth in a forthcoming article.

Potential limitations of this study include the fact that we did not ascertain all of the cases of birth defects in which elective termination occurred. This could have introduced bias into this study, as women who have prenatal diagnosis and choose to terminate their pregnancies are known to have a different demographic profile from those who do not.<sup>29</sup> Also, fetuses of obese women may be less likely to be diagnosed by prenatal ultrasonography, as obesity interferes with the quality of the technique.<sup>30</sup> Three study sites (Massachusetts, New Jersey, and New York) did not ascertain birth defects among pregnancy terminations for all (Massachusetts and New Jersey) or part (New York) of the study period. However, after excluding these states, our results were unchanged (data not shown). It is also possible that, to some extent, all of the states participating in the NBDPS could have underascertained cases in which elective termination occurred. This would most likely affect results for birth defects in which more than 10% are typically terminated, ie, anencephaly, spina bifida, and omphalocele.<sup>29</sup> To test the effect of such a bias, we calculated crude ORs for these 3 birth defects assuming that the proportion of cases electively terminated was double the number we observed. The frequency of maternal obesity was assumed to be equal among cases with elective termination that were enrolled and those that were not enrolled. Crude ORs were slightly decreased for anencephaly (crude ORs, 0.97-0.94) and spina bifida (crude ORs, 2.25-2.12) and slightly increased for omphalocele (crude ORs, 1.55-1.66). Thus, bias from underascertainment of elective abortions is unlikely to have an important impact on these findings.

Other potential limitations of this study include the use of self-reported height and prepregnancy weight and the possibility of recall bias for these variables. Studies that have compared self-reported height and weight with measurements of height and weight among US adults are consistent in observing small differences. For example, Nieto-García et al<sup>31</sup> observed that women of childbearing age underestimate their weight by 0.64% to 0.83% and overestimate their height by 0.40% to 0.42% and that obese women underestimate their weight by a larger amount, ie, 1.5%. In our study, women were asked to recall their weight prior to becoming pregnant, about 18 to 20 months before their interview. To the extent that errors in reporting are similar among case mothers and control mothers, nondifferential misclassification may have been introduced into our estimates, resulting in a bias toward the null. Differential misclassification of BMI probably did not occur, as case mothers would be un-

likely to overestimate or underestimate their prepregnancy weight compared with control mothers.

A total of 3.7% of cases and 4.0% of controls were missing values for BMI. Seventy-one percent of these missing values were the result of mothers reporting weight but not height. Of those women who did not report height, 87.7% were non-US-born Hispanic women. Very few women failed to report their prepregnancy weight (1.2% of cases and 1.1% of controls), again suggesting that differential reporting of weight is probably not an important concern in this study. Also, the fact that large prospective studies, which are not susceptible to recall bias, observed associations of very similar magnitude to ours for maternal obesity and all of the birth defects in aggregate,<sup>8</sup> spina bifida,<sup>32,33</sup> heart defects,<sup>25</sup> and oral clefts<sup>26</sup> suggests that the associations we observed for these birth defects are not explained by recall bias.

Our findings for gastroschisis remained the same after adjustment for maternal age, a known risk factor for gastroschisis.<sup>34</sup> The fact that both younger maternal age and lower BMI are strong risk factors for gastroschisis suggests that the etiology of gastroschisis may differ substantially from the etiology of birth defects that are positively associated with maternal obesity.

The reasons for an association between maternal obesity and a spectrum of structural birth defects are unknown. Both animal studies and human studies provide substantial evidence that alterations in glycemic control are responsible for an increased risk of a range of structural birth defects among women who have diabetes prior to becoming pregnant.<sup>35,36</sup> Thus, a similar mechanism to that occurring in women with diabetes may be responsible for the associations observed between maternal obesity and specific categories of birth defects. Confining our analysis to women without a history of gestational diabetes attenuated many of the ORs but did not substantially explain the general pattern of risk. This may be explained by the fact that it was not possible to exclude those mothers who had undiagnosed or subclinical cases of gestational diabetes or type 2 diabetes. Alternatively, it may point to other reasons for some or all of the associations observed between maternal obesity and birth defects.

This study and previous studies adjusted findings for supplementation with vitamins containing folic acid. Thus, differences between obese and nonobese women in daily multivitamin use prior to conception do not explain the effects observed for obesity. Two recent studies have linked other health behaviors with an increased risk for neural tube defects. Carmichael et al<sup>37</sup> observed that physically active women had a 30% to 50% lower risk for neural tube defect-affected pregnancies independent of maternal obesity. In a subsequent study, Carmichael et al<sup>38</sup> observed that when present during the first trimester of pregnancy, diets to lose weight, fasting diets, and eating disorders were associated with an increased risk of delivering offspring affected by neural tube defects independent of maternal obesity. They suggested that food restriction might increase the risk of neural tube defects via decreased availability of micronutrients or via ketosis, which accompanies reduced food intake and fasting.

Our study supports previous evidence as well as provides new evidence for the associations between mater-

nal obesity and particular categories of birth defects. Future inquiries are needed to unravel the underlying reasons for these associations.

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## REFERENCES

1. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol.* 1997;146(3):214-222.
2. Rich-Edwards JW, Goldman MB, Willett WC, et al. Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol.* 1994;171(1):171-177.
3. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. *Int J Obes.* 1979;3(1):57-73.
4. Diamanti-Kandarakis E, Bergiele A. The influence of obesity on hyperandrogenism and infertility in the female. *Obes Rev.* 2001;2(4):231-238.
5. Goldenberg RL, Tamura T. Prepregnancy weight and pregnancy outcome. *JAMA.* 1996;275(14):1127-1128.
6. Cnattingius S, Bergström R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. *N Engl J Med.* 1998;338(3):147-152.
7. Stephansson O, Dickman PW, Johansson A, Cnattingius S. Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. *Am J Obstet Gynecol.* 2001;184(3):463-469.
8. Naeye RL. Maternal body weight and pregnancy outcome. *Am J Clin Nutr.* 1990;52(2):273-279.
9. Waller DK, Mills JL, Simpson JL, et al. Are obese women at higher risk for producing malformed offspring? *Am J Obstet Gynecol.* 1994;170(2):541-548.
10. Watkins ML, Scanlon KS, Mulinare J, Khoury MJ. Is maternal obesity a risk factor for anencephaly and spina bifida? *Epidemiology.* 1996;7(5):507-512.
11. Werler MM, Louik C, Shapiro S, Mitchell AA. Prepregnant weight in relation to risk of neural tube defects. *JAMA.* 1996;275(14):1089-1092.
12. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. *JAMA.* 1996;275(14):1093-1096.
13. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA.* 2006;295(13):1549-1555.
14. Queisser-Luft A, Kieninger-Baum D, Menger H, Stolz G, Schlaefer K, Merz E. Does maternal obesity increase the risk of fetal abnormalities? analysis of 20 248 newborn infants of the Mainz birth register for detecting congenital abnormalities [in German]. *Ultraschall Med.* 1998;19(1):40-44.
15. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. *Pediatrics.* 2003;111(5, pt 2):1152-1158.
16. Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. *Public Health Rep.* 2001;116(suppl 1):32-40.
17. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA; National Birth Defects Prevention Study. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol.* 2003;67(3):193-201.
18. Mitchell LE. Mode of inheritance of oral clefts. In: Wyszynski DF, ed. *Cleft Lip and Palate From Origin to Treatment.* New York, NY: Oxford University Press; 2002:234-239.
19. Dolk H, Vrijheid M, Scott JE, et al. Toward the effective surveillance of hypospadias. *Environ Health Perspect.* 2004;112(3):398-402.
20. Kuczmarski RJ, Flegal KM. Criteria for definition of overweight in transition: background and recommendations for the United States. *Am J Clin Nutr.* 2000;72(5):1074-1081.
21. Anderson JL, Waller DK, Canfield MA, Shaw GM, Watkins ML, Werler MM. Maternal obesity, gestational diabetes, and central nervous system birth defects. *Epidemiology.* 2005;16(1):87-92.
22. Hendricks KA, Nuno OM, Suarez L, Larsen R. Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. *Epidemiology.* 2001;12(6):630-635.
23. Shaw GM, Todoroff K, Schaffer DM, Selvin S. Maternal height and prepregnancy body mass index as risk factors for selected congenital anomalies. *Pediatr Perinat Epidemiol.* 2000;14(3):234-239.
24. Watkins ML, Botto LD. Maternal prepregnancy weight and congenital heart defects in offspring. *Epidemiology.* 2001;12(4):439-446.
25. Cedergren MI, Källén BAJ. Maternal obesity and infant heart defects. *Obes Res.* 2003;11(9):1065-1071.
26. Cedergren M, Källén B. Maternal obesity and the risk for orofacial clefts in the offspring. *Cleft Palate Craniofac J.* 2005;42(4):367-371.
27. Lam PK, Torfs CP, Brand RJ. A low pregnancy body mass index is a risk factor for an offspring with gastroschisis. *Epidemiology.* 1999;10(6):717-721.
28. Moore LL, Singer MR, Bradlee ML, Rothman KJ, Milunsky A. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology.* 2000;11(6):689-694.
29. Waller DK, Pujazon MA, Canfield MA, Scheuerle AE, Byrne JL. Frequency of prenatal diagnosis of birth defects in Houston, Galveston and the lower Rio Grande Valley, Texas 1995. *Fetal Diagn Ther.* 2000;15(6):348-354.
30. Wolfe HM, Sokol RJ, Martier SM, Zador IE. Maternal obesity: a potential source of error in sonographic prenatal diagnosis. *Obstet Gynecol.* 1990;76(3, pt 1):339-342.
31. Nieto-García FJ, Bush TL, Keyl PM. Body mass definitions of obesity: sensitivity and specificity using self-reported weight and height. *Epidemiology.* 1990;1(2):146-152.
32. Källén K. Maternal smoking, body mass index, and neural tube defects. *Am J Epidemiol.* 1998;147(12):1103-1111.
33. Ray JG, Wyatt PR, Vermeulen MJ, Meier C, Cole DEC. Greater maternal weight and the ongoing risk of neural tube defects after folic acid flour fortification. *Obstet Gynecol.* 2005;105(2):261-265.
34. Haddow JE, Palomaki GE, Holman MS. Young maternal age and smoking during pregnancy as risk factors for gastroschisis. *Teratology.* 1993;47(3):225-228.
35. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics.* 1990;85(1):1-9.
36. Eriksson UJ, Cederberg J, Wentzel P. Congenital malformations in offspring of diabetic mothers: animal and human studies. *Rev Endocr Metab Disord.* 2003;4(1):79-93.
37. Carmichael SL, Shaw GM, Neri E, Schaffer DM, Selvin S. Physical activity and risk of neural tube defects. *Matern Child Health J.* 2002;6(3):151-157.
38. Carmichael SL, Shaw GM, Schaffer DM, Laurent C, Selvin S. Dieting behaviors and risk of neural tube defects. *Am J Epidemiol.* 2003;158(12):1127-1131.