Body Mass Index and Birth Defects: Texas, 2005–2008

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Abstract Texas ranks 12th nationally in the proportion of adult residents who are obese; approximately 67 % of Texans are overweight or obese. Studies indicate that obesity is related to an increased risk for birth defects; however, small sample sizes have limited the scope of birth defects investigated, and only four levels of body mass index (BMI) are typically explored. Using six BMI levels, we evaluated the association between maternal BMI and birth defects in a population-based registry covering ~1.6 million births. Texas birth defect cases were linked to 2005–2008 vital records. Maternal BMI was calculated using self-reported prepregnancy weight and height from the vital record and categorized as follows: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), class I obese (BMI 30–34.9), class II obese (BMI 35–39.9) and class III obese (BMI ≥40). Prevalence ratios for specific birth defects for maternal BMI categories were estimated by using normal weight as the referent, adjusted for maternal age and race/ethnicity, and stratified by maternal diabetes status. Risk for certain birth defects increased with increasing BMI (i.e., atrial and ventricular septal defects, pulmonary valve atresia, patent ductus arteriosus, and clubfoot). Risk for birth defects was substantially increased among some obese mothers (BMI ≥30) (e.g., spina bifida, tetralogy of Fallot, cleft lip with or without cleft palate, hypospadias, and epispadias). Conversely, mothers with higher BMI had a lower risk for having an infant or fetus with gastroschisis (aPR = 0.35; 95 % CI = 0.12, 0.80). Given the increased risk for birth defects associated with obesity, preconception counseling should emphasize the importance of maintaining normal weight.

Keywords Body mass index · Obesity · Congenital abnormalities · Pregnancy · Diabetes complications

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Introduction

Texas ranks 12th nationally in the proportion of adult residents who are obese; approximately two-thirds of Texans are overweight or obese [1–3]. Obesity is associated with an increased risk for adverse pregnancy outcomes. A dozen studies have reported associations of obesity with certain birth defects; however, most of these studies relied only on cases whose mothers completed an interview, and/or they had limited sample sizes and sometimes heterogeneous groupings of birth defects. Furthermore, most did not consider the effect modification by gestational diabetes, some of which may be undiagnosed maternal diabetes [4–15]. Finally, very few have examined a summary effect of BMI on all birth defects combined.

The Texas Birth Defects Epidemiology and Surveillance Registry (TBDR) is a population-based active surveillance system. Pregnancy outcomes abstracted from birthing and tertiary facilities in Texas include: live births, fetal deaths, and elective pregnancy terminations. In Texas, approximately 17,000 babies each year are born with ≥1 congenital malformation [16]. Birth defects are a leading cause of death among infants [17]. The TBDR is linked to the Texas Vital Statistics birth, death, and fetal death certificates. Self-reported maternal prepregnancy height and weight measurements were added to the vital records birth certificates during 2005 and to fetal death certificates during 2006, which permitted the calculation of prepregnancy body mass index (BMI).

During 2005–2008, there were approximately 1.6 million births in the state of Texas, with a total of 69,081 birth defect cases available for this study. This information permitted a review of substantially more birth defects than have been analyzed previously, without necessitating combination into heterogeneous birth defect categories. Our number of cases for each of 49 birth defects permitted grouping into homogenous birth defect categories, expanded BMI categories, and maternal diabetes status. The objective of this cross sectional study was to use prevalence ratios to examine the association between maternal BMI and the 49 reported birth defects (BPA 740.000–758.200) in Texas during 2005–2008 [16]. Finally, since the TBDR ascertains all major structural malformations, we were able to generate prevalence estimates for "any infant or fetus with any monitored birth defect" and examined the relationship between BMI and this grouped outcome. The TBDR provided a rare opportunity to examine a large number of births and birth defect cases without necessitating the exclusion of cases without maternal interviews or the grouping of somewhat related but ultimately heterogeneous defects.

Methods

The primary sources of information for this study were the TBDR and Texas vital records. The TBDR is a population-based active surveillance system for major structural malformations and chromosomal anomalies. Trained program staff routinely visit medical facilities to review unit logs, hospital discharge lists, and medical records to identify potential cases of birth defects identified before the first birthday. If the fetus or infant has any of the birth defects reported by the registry and the mother resided in Texas at the time of delivery, the medical record is abstracted. Numerous quality control checks are conducted, including review of the majority of cases by a board-certified clinical geneticist to ensure that cases are definitively diagnosed.

Individuals with more than one birth defect are coded for each birth defect and counted once in their respective categories. The category called "Infants and fetuses with any monitored birth defect" is the number of individuals, with each baby counted only once [16].

All registry records are linked to their corresponding vital records to provide or supplement sociodemographic data (e.g., maternal education, indication of diabetes, and maternal birthplace). Self-reported maternal prepregnancy height and weight became available on the Texas Vital Statistics Unit's 2005–2008 birth certificates as well as the 2006–2008 fetal death certificates. The TBDR annually reports data on 49 birth defects (BPA 740.000–758.200) so this was the population cross section we analyzed by BMI for delivery years 2005–2008, during which 1,597,541 live births were reported. Live births from the vital records were used as the denominator, and 69,081 infants or fetuses with a birth defect and BMI data were ascertained by the TBDR during 2005–2008. Maternal BMI was calculated (BMI = weight [lb] × 703/height [in]^2) from the reported prepregnancy weight and height measurements from the birth or fetal death certificates. Outliers were considered to be mothers with values <3 feet or >7 feet in height, and were excluded from the analyses. Because we had a sufficient sample size, we utilized the expanded WHO categories as follows to more fully explore the effect of obesity: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), class I obese (BMI 30–34.9), class II obese (BMI 35–39.9), and class III obese (BMI ≥40) [18]. Because birth defects are rare events and follow a Poisson distribution, we used Poisson regression to assess the overall association of BMI with each birth defect and to estimate stratum-specific crude prevalence ratios and 95 % confidence intervals (CI) by using normal weight as the referent in each diabetes category. Prevalence ratios approximate relative risk for rare occurrences like birth defects. All prevalence ratios in this analysis were further adjusted by maternal age (as a continuous variable) and by race/ethnicity (e.g. Non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic other). Because diabetes is a risk factor for many birth defects we stratified by the presence of any maternal diabetes and no indication of diabetes as recorded in the vital record [4, 5, 8, 10, 11, 19]. We did not distinguish between gestational and prepregnancy diabetes because of evidence of misclassification between prepregnancy and gestational diabetes [4, 8–10, 20, 21]. Furthermore, our primary interest was the BMI-birth defects relationship in the absence of any diabetes. We used Breslow-Day test to examine differences in the association between BMI and birth defects by diabetes status and ran a test for linear trend to determine if there was a dose–response in the relationship between BMI and birth defects. The Bonferroni method was used to adjust for

multiple comparisons. Data were analyzed by using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA). Only those findings with significant prevalence ratios and p values were shown.

Results

During the 4-year period, TBDR ascertained 69,792 infants or fetuses diagnosed with ≥ 1 birth defects, of which 711 (1 %) were missing maternal height or weight. The latter group was excluded because BMI could not be calculated. Of 1,597,541 live births, there were 5 mothers who were removed because of obvious outlier values for height, comprising 0.03 % of the total number of mothers in the denominator (there were no outliers among case mothers). This left 69,081 infants or fetuses with complete data and who had at least one of the 49 defects of interest.

Table 1 displays the distribution of maternal characteristics by BMI category. BMI increased with maternal age. The prevalence of obesity was highest among non-Hispanic American Indians/Alaska Natives (30 %), non-Hispanic blacks (28 %), and Hispanics (24 %). Non-Hispanic American Indians/Alaska Natives had the highest prevalence of class I and II obesity, whereas non-Hispanic blacks had the highest prevalence of class III obesity. Twenty-one percent of non-Hispanic whites were obese, and Asian/Pacific Islanders had the lowest prevalence of obesity (6 %). Obesity percentage did not vary by education level. Approximately 45 % of mothers with diabetes were obese, compared with 21 % of mothers without diabetes. Overall, 6 % (4,090/69,081) of mothers had pregestational or gestational diabetes in vital records; 883/4,090 (21.6 %) had prepregnancy diabetes and 3,207/4,090 (78.4 %) had gestational diabetes.

Table 2 displays significant p values and aPR estimates for the association between BMI and any individual infant or fetus with any birth defect stratified by diabetes status. Among mothers without diabetes, those who were obese class II or III had a higher prevalence of having an infant or fetus with any birth defect, compared with their normal weight counterparts. The prevalence was more pronounced for the more obese mothers. Mothers with class II obesity had an 11 % higher prevalence and those with class III obesity had a 22 % higher prevalence of having an infant or fetus with any birth defect, compared with normal weight mothers. Obese mothers with diabetes had a higher prevalence of having an infant or fetus with any birth defect, compared with normal weight mothers with diabetes. Among mothers with diabetes, the prevalence of having an infant or fetus with any birth defect was 15, 17, and 38 % higher for classes I, II, and III obesity, respectively, compared with normal weight diabetic mothers. The association between BMI and having any birth defect was

stronger among mothers with an indication of diabetes compared to their nondiabetic counterparts (Breslow-Day $p = 0.0083$). The trend of increasing prevalence of birth defects overall with increasing BMI was statistically significant for both diabetic and nondiabetic mothers ($p < 0.0001$).

Table 3 displays the six heart defects, stratified by diabetes status, that had a statistically significant association with BMI ($p < 0.05$). However, for two of these six (tetralogy of Fallot and coarctation of the aorta), this was observed only among non-diabetic mothers. For three of these six (patent ductus arteriosis (PDA), ventricular septal defect (VSD), and pulmonary valve atresia/stenosis), the association was strengthened further among diabetic mothers (Breslow-Day $p < 0.05$). Finally, the prevalence of these six heart defects increased with increasing BMI category (trend $p < 0.05$). However, for two of these six (tetralogy of Fallot and coarctation of the aorta), the significant trend was observed only among non-diabetic mothers.

Compared with normal weight mothers, all classes of obesity had higher risks for PDA, atrial septal defect (ASD), and VSD. The risk for VSD among mothers with class III obesity was significantly more pronounced among those who also had diabetes (aPR = 2.09; 95 % CI 1.58, 2.74) compared to those without diabetes (aPR = 1.34; 95 % CI 1.18, 1.50). No other heart defect demonstrated this pattern.

Table 4 displays statistically significant aPRs and p values for maternal BMI and non-heart birth defects in the TBDR, stratified by maternal diabetes. BMI was positively associated with clubfoot, cleft palate, hypospadias, and episadias, but only among non-diabetic mothers ($p < 0.05$). For spina bifida and cleft lip, the prevalence was statistically elevated only among the non-diabetic mothers with class 3 obesity (aPRs = 1.85; 95 % CI 1.07, 3.01 and 1.55; 95 % CI 1.14, 2.07, respectively). BMI was negatively and strongly associated with gastroschisis ($p < 0.0001$) and small intestinal atresia/stenosis ($p = 0.0058$), but only among non-diabetic mothers. BMI was not associated with any non-heart defects among diabetic mothers ($p > 0.05$; data not shown).

Among mothers without diabetes, the prevalence of having an infant or fetus with clubfoot increased with each increasing category of obesity, from 23 % for class I, to 37 % for class II, to 55 % higher prevalence for class III obese mothers, compared with normal weight mothers (trend $p = 0.0005$). Also, the prevalence of any hypospadias was 21 and 39 % higher among mothers with class II and class III obesity, respectively, compared with normal weight mothers without diabetes (trend $p < 0.0001$). Spina bifida also demonstrated a positive but less dramatic trend (trend $p = 0.0018$), also among non-diabetic mothers, and negative trends were observed for gastroschisis ($p < 0.0001$) and small intestinal atresia/stenosis ($p = 0.0227$).

Table 1 Distribution of birth defect cases by maternal demographic characteristics and BMI[a] category, Texas, 2005–2008

	Under weight (<18.5) No. of cases	Normal weight (18.5 to 24.9) No. of cases	Over weight (25.0 to 29.9) No. of cases	Obese class I (30.0 to 34.9) No. of cases	Obese class II (35.0 to 39.9) No. of cases	Obese class III (40.0+) No. of cases	Total No. of cases	%
Maternal age (years)								
<20	766	5,339	1,813	723	243	103	8,987	13.0
20–24	1,092	8,945	4,398	2,193	971	712	18,311	26.5
25–29	667	8,379	4,470	2,490	1,220	892	18,118	26.2
30–34	395	6,455	3,598	1,903	920	693	13,964	20.2
35–39	164	3,444	2,013	1,077	573	416	7,687	11.1
40+	53	843	581	286	146	105	2,014	2.9
Maternal race/ethnicity								
Non-Hispanic white	1,362	13,139	5,666	2,871	1,428	1,007	25,473	36.9
Non-Hispanic black	299	3,078	1,941	1,056	546	493	7,413	10.7
Hispanic	1,228	15,618	8,800	4,595	2,045	1,400	33,686	48.8
Non-Hispanic Asian/ Pacific Islander	221	1,351	353	91	30	9	2,055	3.0
Non-Hispanic American Indian/Alaska Native	7	48	35	22	12	5	129	0.2
Non-Hispanic Other	20	169	77	37	12	7	322	0.5
Maternal education								
<High school	1,099	9,577	5,317	2,551	1,006	648	20,198	29.3
High school	901	9,171	4,340	2,431	1,265	879	18,987	27.5
>High school	1,134	14,620	7,193	3,684	1,801	1,391	29,823	43.2
Maternal diabetes status								
Yes	70	1,155	1,014	860	502	489	4,090	5.9
No[b]	3,067	32,250	15,859	7,812	3,571	2,432	64,991	94.1
Total	3,137	33,405	16,873	8,672	4,073	2,921	69,081	100.0
Percent (%)	4.5	48.4	24.4	12.6	5.9	4.2	100.0	

[a] Body mass index

[b] Includes both prepregnancy and gestational diabetes as indicated on the vital record

Discussion

We confirmed that BMI is associated with a number of birth defects, some of which demonstrated a dose–response pattern. In contrast with previous studies, we were able to examine a wider range of birth defects (including "birth defects overall") and several levels of obesity, in both the absence and presence of self-reported maternal diabetes.

BMIs were initially analyzed by using 3 different categorization methods as follows: age and sex adjusted BMI, the National Institutes of Health (NIH) standard 4 BMI categories, and the expanded World Health Organization (WHO) 6 BMI categories. Because 13 % of the TBDR Registry mothers were aged <20 years, we explored using the age and sex adjusted BMI as outlined by the National Center for Health Statistics 2000 CDC Growth Charts, which adjusted for juvenile maternal age of <20 years [22], but found no differences from that of the NIH 4 standard

categories [23]. Because we had sufficient numbers, we analyzed BMI by using the expanded WHO categories, which permitted more detailed analysis of the classes of obesity.

Studies of BMI and birth defects have been conducted using different methods of categorizing BMI. Certain studies have had ≤25 % of their samples missing BMI data [13], whereas we only had approximately 1 % of BMI data missing. Many studies have had limited sample sizes, which necessitated the grouping of heterogeneous birth defects. Certain study populations reported lower prevalence of obesity; Sweden had a 10 % prevalence of obesity [6], compared with the 23 % prevalence of obesity among mothers in this study. Some studies did not stratify by maternal diabetes, although others excluded either any indication of diabetes or only prepregnancy diabetes in their analyses [5, 7, 10, 15]. This variability of study methodology made comparing results difficult. The

Table 2 Infants and fetuses with any monitored birth defect by BMI[a] category—Texas, 2005–2008

BMI[a] group	Mothers without diabetes* (n = 64,991; $p < 0.0001$; $p_{trend} < 0.0001$)			Mothers with any diabetes*,[b] (n = 4,090; $p < 0.0001$; $p_{trend} < 0.0001$; $p_{Breslow-Day} = 0.0083$)		
	Adjusted prevalence ratio[c]	95 % Confidence interval for prevalence ratio		Adjusted prevalence ratio[c]	95 % Confidence interval for prevalence ratio	
Underweight (BMI <18.5)	1.05	1.01	1.10	1.04	0.81	1.32
Normal weight (BMI 18.5–24.9)	1.0 (ref)			1.0 (ref)		
Overweight (BMI 25–29.9)	1.00	0.98	1.02	1.01	0.93	1.10
Obese class I (BMI 30–34.9)	1.03	0.99	1.06	**1.15**	**1.05**	**1.26**
Obese class II (BMI 35–39.9)	**1.11**	**1.06**	**1.16**	**1.17**	**1.05**	**1.30**
Obese class III (BMI ≥40)	**1.22**	**1.16**	**1.28**	**1.38**	**1.24**	**1.53**

* p value remains statistically significant after Bonferroni correction for multiple comparisons

[a] Body mass index

[b] Includes both prepregnancy and gestational diabetes as indicated on the vital record

[c] Adjusted by maternal age and maternal race/ethnicity; statistically significant categories in bold font

n case number, p p value for Poisson regression (association between BMI and the defect), p_{trend} p value for trend; $p_{Breslow-Day}$ p value for Breslow-Day

reported aPRs varied among studies and part of the variability might be attributable to the rarity of birth defects and the subsequent small numbers of cases available for analysis.

Obesity is associated with an increased risk for certain birth defects. A British study used the standard 4 BMI categories and reported maternal obesity to be associated with VSD, cleft lip, and eye anomalies; whereas, maternal underweight was associated with ASD, hypospadias, and genital anomalies. They reported an approximate ninefold increased risk for hypospadias for underweight mothers (BMI ≤18) [13]. Although we did not find an association among underweight mothers for hypospadias, we report a 21–39 % increased prevalence of hypospadias among mothers with class II and III obesity and an approximate threefold increased prevalence of epispadias among mothers with class II obesity.

Consistent with the Waller et al. case–control study, which used the standard 4 BMI categories, we report an approximate twofold increased prevalence of spina bifida, but only among the most obese mothers (class III) [14]. A number of studies and a meta-analysis also documented an association between obesity and spina bifida [5, 14, 15, 24–26]. Waller et al. [14] reported that BMI ≥30 was substantially associated with an increased risk for other defects (e.g., all heart defects combined, omphalocele, limb reduction defects, second- and third-degree hypospadias, and diaphragmatic hernia and anorectal atresia) and a decreased risk for gastroschisis. Although an association was seen in the crude analysis between class II obesity and reduction of birth defects of the upper arms, this association became nonsignificant after adjustment (data not

shown). In contrast to other defects, gastroschisis prevalence decreased with higher BMI, with obese mothers having a 65–83 % decreased prevalence, compared with normal weight mothers. This inverse association replicates the findings of other studies [6, 14].

We also report that among mothers without diabetes, those who were underweight were 50 % more likely, and those who were overweight were 26 % less likely to have an infant or fetus with stenosis or atresia of the small intestine, compared with their normal weight counterparts without diabetes. This is the first time this association has been reported. We did not find an association between BMI and either diaphragmatic hernia or omphalocele. Previous studies have reported that even in the absence of diabetes, obese mothers had higher risks for having an infant or fetus with hydrocephaly, clubfoot, orofacial clefts, abdominal wall defects, and cardiac septal defects [12].

The association between BMI and birth defects varied by diabetes status in our analysis and analyses by others [4, 5, 8, 9, 12]. We report that among mothers with diabetes, obese mothers had an increasing prevalence of having an infant with any type of congenital anomaly for each increase in BMI class, which ranged from 15 % higher for class I obesity to 38 % higher for class III obesity, compared with normal weight mothers with diabetes (Table 2). Our findings are consistent with previous studies that reported an increasing prevalence of birth defects with increasing BMI [7, 10, 15] and those reporting an increased prevalence among mothers who were both obese and had diabetes [4, 5, 8–10, 12, 27].

A case–control study with similar BMI classifications to ours but excluding mothers with prepregnancy diabetes and

Table 3 Association of selected heart defects[a] by expanded WHO[b] adult BMI[c] categories for mothers—Texas, 2005–2008

Defect	BMI category[c]	Mothers without diabetes			Mothers with any diabetes[d]		
		Adjusted prevalence ratio[e]	95 % Confidence interval for prevalence ratio		Adjusted prevalence ratio[e]	95 % Confidence interval for prevalence ratio	
Patent ductus arteriosus* (n = 8,709;	1	1.12	0.98	1.29	0.43	0.14	1.00
$p < 0.0001$; $p_{trend} < 0.0001$;	2	1.0 (ref)			1.0 (ref)		
$p_{Breslow-Day} = 0.0151$)	3	**1.11**	**1.03**	**1.19**	1.20	0.97	1.48
	4	**1.20**	**1.10**	**1.30**	**1.60**	**1.30**	**1.98**
	5	**1.38**	**1.23**	**1.55**	**1.75**	**1.37**	**2.22**
	6	**1.67**	**1.46**	**1.90**	**2.02**	**1.58**	**2.58**
Atrial septal defect* (n = 10,102;	1	1.14	1.00	1.30	0.85	0.41	1.54
$p < 0.0001$; $p_{trend} < 0.0001$)	2	1.0 (ref)			1.0 (ref)		
	3	**1.11**	**1.04**	**1.19**	1.09	0.89	1.33
	4	**1.23**	**1.13**	**1.33**	**1.54**	**1.26**	**1.88**
	5	**1.43**	**1.28**	**1.60**	**1.63**	**1.29**	**2.06**
	6	**1.55**	**1.35**	**1.76**	**1.64**	**1.28**	**2.10**
Ventricular septal* (n = 9,434; $p < 0.0001$;	1	**1.22**	**1.09**	**1.35**	0.74	0.28	1.55
$p_{trend} < 0.0001$; $p_{Breslow-Day} = 0.0056$)	2	1.0 (ref)			1.0 (ref)		
	3	1.01	0.96	1.07	1.17	0.92	1.49
	4	**1.13**	**1.06**	**1.22**	**1.38**	**1.08**	**1.76**
	5	**1.16**	**1.04**	**1.28**	**1.61**	**1.22**	**2.12**
	6	**1.34**	**1.18**	**1.50**	**2.09**	**1.58**	**2.74**
Pulmonary valve atresia or stenosis* [nondiabetic only]	1	0.91	0.68	1.20	2.76	0.88	6.75
(n = 1,546; $p < 0.0006$; $p_{trend} = 0.0171$;	2	1.0 (ref)			1.0 (ref)		
$p_{Breslow-Day} = 0.0275$)	3	1.09	0.96	1.24	1.02	0.61	1.69
	4	1.18	1.00	1.39	1.24	0.73	2.09
	5	**1.56**	**1.26**	**1.92**	0.92	0.44	1.77
	6	**1.58**	**1.21**	**2.03**	**2.89**	**1.72**	**4.84**
Tetralogy of Fallot (n = 609;	1	0.95	0.60	1.42	1.31	0.06	7.05
$p_{nondiabetic only} = 0.0007$;	2	1.0 (ref)			1.0 (ref)		
$p_{trend-nondiabetic only} < 0.0001$)	3	1.01	0.82	1.24	0.62	0.22	1.58
	4	1.08	0.82	1.39	0.83	0.30	2.14
	5	**1.43**	**1.01**	**1.97**	1.43	0.51	3.68
	6	**2.21**	**1.55**	**3.06**	1.67	0.59	4.32
Coarctation of the aorta (n = 823;	1	1.13	0.75	1.64	–	–	–
$p_{trend-nondiabetic only} = 0.0040$)	2	1.0 (ref)			1.0 (ref)		
	3	1.11	0.90	1.35	0.71	0.42	1.18
	4	**1.43**	**1.12**	**1.80**	0.82	0.47	1.38
	5	1.03	0.68	1.49	0.72	0.34	1.36
	6	1.53	1.00	2.25	0.99	0.49	1.84

—, No cases in this stratum, thus no calculations. *n* case number, *p* *p* value for Poisson regression (association between BMI and the defect), p_{trend} *p* value for trend, $p_{Breslow-day}$ *p* value for Breslow-day

* *p* value remains statistically significant after Bonferroni correction for multiple comparisons

[a] Only those birth defects with statistical significant results (95 % confidence interval does not include 1.0)

[b] World Health Organization

[c] Body mass index and type: (1) underweight BMI <18.5; (2) normal weight BMI 18.5–24.9; (3) overweight BMI 25–29.9; (4) obese class I BMI 30–34.9; (5) obese class II BMI 35–39.9; (6) obese class III BMI ≥40

[d] Includes both prepregnancy and gestational diabetes as indicated on the vital record

[e] Adjusted by maternal age and maternal race/ethnicity; statistically significant categories in bold font

Table 4 Association of selected nonheart birth defects[a] by expanded WHO[b] adult BMI[c] categories for mothers—Texas, 2005–2008

Defect	BMI category[c]	Mothers without diabetes		Mothers with any diabetes[d]	
		Adjusted prevalence ratio[e]	95 % Confidence interval for prevalence ratio	Adjusted prevalence ratio[e]	95 % Confidence interval for prevalence ratio
Talipes equinovarus or clubfoot (n = 2,272; $p_{\text{nondiabetic only}} = 0.0264$; $p_{\text{trend}} < 0.0049$)	1	1.16	0.84 1.55	0.58	0.04 2.54
	2	1.0 (ref)		1.0 (ref)	
	3	1.07	0.91 1.25	0.95	0.58 1.56
	4	**1.23**	**1.01 1.50**	1.26	0.76 2.06
	5	**1.37**	**1.03 1.78**	1.25	0.68 2.20
	6	**1.55**	**1.11 2.11**	**1.90**	**1.09 3.24**
Hypospadias (cases and prevalence among males) (n = 4,546; $p_{\text{nondiabetic only}} = 0.0002$; $p_{\text{trend-nondiabetic only}} < 0.0001$)	1	0.93	0.80 1.08	1.40	0.47 3.25
	2	1.0 (ref)		1.0 (ref)	
	3	1.06	0.98 1.14	1.02	0.68 1.51
	4	1.06	0.96 1.16	1.19	0.78 1.80
	5	**1.21**	**1.06 1.38**	0.87	0.49 1.47
	6	**1.39**	**1.18 1.61**	**1.78**	**1.13 2.78**
Spina bifida without anencephaly (n = 522; $p_{\text{trend-nondiabetic only}} = 0.0018$)	1	0.89	0.46 1.54	–	– –
	2	1.0 (ref)		1.0 (ref)	
	3	1.11	0.84 1.45	1.04	0.26 4.17
	4	1.31	0.93 1.81	0.67	0.10 3.23
	5	1.46	0.90 2.26	1.57	0.30 6.96
	6	**1.85**	**1.07 3.01**	1.94	0.37 8.60
Cleft lip with or without cleft palate (n = 1,659; $p_{\text{trend}} < 0.0090$)	1	0.94	0.69 1.26	0.59	0.04 2.62
	2	1.0 (ref)		1.0 (ref)	
	3	1.06	0.91 1.22	1.17	0.70 1.98
	4	1.13	0.93 1.36	**1.72**	**1.03 2.89**
	5	1.12	0.84 1.46	1.29	0.65 2.45
	6	**1.55**	**1.14 2.07**	1.84	0.96 3.40
Cleft palate alone (without cleft lip) (n = 950; $p_{\text{nondiabetic only}} = 0.0073$; $p_{\text{trend-nondiabetic only}} = 0.0003$)	1	1.10	0.74 1.58	3.73	0.39 17.76
	2	1.0 (ref)		1.0 (ref)	
	3	**1.28**	**1.06 1.53**	2.22	0.89 6.06
	4	**1.46**	**1.16 1.83**	**2.97**	**1.19 8.14**
	5	1.33	0.94 1.83	1.80	0.50 5.95
	6	1.49	0.98 2.17	2.15	0.59 7.10
Epispadias (n = 142; $p_{\text{nondiabetic only}} = 0.0018$; $p_{\text{trend-nondiabetic only}} = 0.0277$)	1	0.70	0.22 1.67	–	– –
	2	1.0 (ref)		1.0 (ref)	
	3	1.25	0.84 1.86	2.11	0.42 14.61
	4	0.57	0.26 1.10	0.68	0.03 6.80
	5	**2.79**	**1.60 4.61**	–	– –
	6	1.56	0.62 3.27	1.18	0.06 11.91
Gastroschisis* [nondiabetic only] (n = 864; $p_{\text{nondiabetic only}} < 0.0001$; $p_{\text{trend}} < 0.0001$)	1	1.02	0.72 1.41	–	– –
	2	1.0 (ref)		1.0 (ref)	
	3	**0.64**	**0.50 0.81**	0.46	0.15 1.24
	4	**0.35**	**0.22 0.53**	**0.21**	**0.03 0.84**
	5	**0.17**	**0.05 0.40**	–	– –
	6	**0.35**	**0.12 0.80**	–	– –

Table 4 continued

Defect	BMI category[c]	Mothers without diabetes		Mothers with any diabetes[d]	
		Adjusted prevalence ratio[e]	95 % Confidence interval for prevalence ratio	Adjusted prevalence ratio[e]	95 % Confidence interval for prevalence ratio
Stenosis or atresia of the small intestine (n = 529; $p_{nondiabetic\ only}$ = 0.0058; $p_{trend-nondiabetic\ only}$ = 0.0227)	1	**1.50**	**1.04** **2.11**	–	– –
	2	1.0 (ref)		1.0 (ref)	
	3	**0.74**	**0.58** **0.93**	0.98	0.21 4.14
	4	0.74	0.53 1.00	2.01	0.54 7.98
	5	0.99	0.65 1.45	2.30	0.49 9.99
	6	0.80	0.44 1.34	2.07	0.36 9.83

— , No cases in this stratum, thus no calculations. *n* case number, *p* *p* value for Poisson regression (association between BMI and the defect), p_{trend} *p* value for trend, $p_{Breslow-day}$ *p* value for Breslow-day

* *p* value remains statistically significant after Bonferroni correction for multiple comparisons

[a] Only those birth defects with statistical significant results (95 % CI does not include 1.0)

[b] World Health Organization

[c] Body mass index and type: (1) underweight BMI <18.5; (2) normal weight BMI 18.5–24.9; (3) overweight BMI 25–29.9; (4) obese class I BMI 30–34.9; (5) obese class II BMI 35–39.9; (6) obese class III BMI ≥40

[d] Includes both prepregnancy and gestational diabetes as indicated on the vital record

[e] Adjusted by maternal age and maternal race/ethnicity; statistically significant categories in bold font

infants with genetic anomalies reported an association among BMI ≥25 and heart defects [9]. Because this is a spectrum paper of 69,081 infants or fetuses, we did not clinically review and exclude birth defect cases with additional genetic anomalies. However, we reported a substantial association between BMI and 6 heart defects (Table 3), 3 of which demonstrated a dose–response effect with increasing BMI (PDA, VSD, and ASD). Furthermore, the presence of diabetes appeared to increase the prevalence of 3 out of 6 of these defects in the corresponding BMI group (Table 3). Another study which used the expanded WHO BMI categories noted that the overall risk for heart defects increased with increasing maternal obesity. However, they did not exclude or stratify by diabetes status, and it is unclear if the observed associations were related to BMI or diabetes [6].

Gilboa et al. [9] documented an additive interaction between obesity and gestational diabetes for tetralogy of Fallot and left ventricular outflow tract malformations. Other studies reported a multiplicative interaction between gestational diabetes and obesity (class II and class III) on the risk for central nervous system defects [5, 8]. Correa et al. [8] reported that pregestational diabetes was associated with tetralogy of Fallot, dextrotransposition of the great arteries, VSD, ASD, aortic stenosis, outflow tract obstructions, anencephaly, craniorachischisis, hydrocephaly, anotia or microtia, cleft lip with or without cleft palate, anorectal atresia, bilateral renal agenesis or hypoplasia, and longitudinal limb defects. Conversely, they reported weaker associations among

gestational diabetes and tetralogy of Fallot, pulmonary valve stenosis, ASD, oral clefts, and anorectal atresia and that these associations were limited to BMI ≥25. Most notably, they reported that diabetics with good glycemic control had birth defect prevalences similar to the general population.

Hyperinsulinemia and obesity might act synergistically to increase the risk for birth defects [28]. Uncontrolled diabetes has a generalized teratogenic action affecting multiple organ systems early during gestation [19]. Gestational diabetes accounts for approximately 90 % of diabetes reported during pregnancy and is usually diagnosed during the second trimester after embryogenesis [10]. One study noted that the majority of the defects reported among offspring of mothers who had gestational diabetes were of blastogenetic origin, which provides evidence that some of the gestational diabetes diagnoses were actually previously undiagnosed prepregnancy diabetes [10]. Mothers with undiagnosed diabetes would have no warning to modify their diets to protect their unborn children at this vulnerable stage of formation. A recent cross sectional study concluded that the increase in birth defects among neonates was not due to obesity but to diabetes [29].

Strengths and Limitations

This study's greatest strength is that Texas has one of the largest active birth defects surveillance systems in the world. Texas residents delivered approximately 1.6 million

live-born infants during 2005–2008. This population provided sufficient power to conduct this analysis of expanded BMI categories for selected birth defects. Another strength is that only about 1 % of BMI data were missing. Furthermore, we had the ability to evaluate six levels of BMI which included expanded classes of obesity. Finally, Texas is one of the few systems that ascertain all structural malformations. Therefore, we were able to demonstrate the public health impact of BMI on all infants or fetuses with structural birth defects, particularly among women in the higher levels of obesity.

A limitation is that some significant findings may be due to chance because of the issue of multiple comparisons. For 49 defects, 5 BMI categories, and two diabetes strata, we would expect approximately 25 statistically significant findings due to chance alone ($p < 0.05$). In this analysis, we actually found 54 statistically significant findings. However, even after adjustment for multiple comparisons using Bonferroni adjustments, several birth defects remained statistically significant as indicated by an asterisk in Tables 2, 3, 4. Defects that remained statistically significant for both diabetic and nondiabetic mothers included: ventricular septal defect, atrial septal defect, patent ductus arteriosus as well as infants and fetuses with any monitored birth defect (which is individuals with any birth defect overall). Defects that remained statistically significant among mothers without diabetes include: pulmonary valve atresia or stenosis and gastroschisis. Another limitation is that not all of the 69,081 records were clinically reviewed for syndromes. Some of the defect categories may be more heterogeneous than others. Potentially, the increased prevalence of birth defects among obese mothers might be artifactual because of detection bias. Dashe et al. [30] noted that ultrasound detection of anomalous fetuses decreased with increasing BMI from 66 % in normal weight women to as low as 48, 42, and 25 % in class I, II, and III obesity, respectively. This might create a bias, whereby birth defects are more likely to be detected prenatally and terminated in normal weight mothers. However, a study in England that had complete ascertainment of all pregnancy outcomes also reported that increased BMI was associated with an increase in congenital anomalies without any evidence of differences in termination rates by BMI category [13].

Although the effect of possible covariates is very interesting, this was a spectrum study and as such we did not examine the effect of all possible covariates. However, we did examine the effect of education and smoking on the prevalence of having an infant or fetus with any birth defect and found that neither smoking nor education was a confounder of the association between BMI and birth defects. In addition, there was no interaction between BMI and smoking or education on the prevalence of having an

infant or fetus with any birth defect. Therefore, we adjusted for variables that are known to have associations with birth defects, namely maternal race/ethnicity and maternal age. Future studies can conduct more targeted defect-specific analyses, particularly for heart defects, to examine the effects of other possible covariates and effect modifiers.

A substantial limitation is that vital records were the sole source of maternal height, weight and diabetes information. Birth certificates have been documented to underascertain many factors such as diabetes, and hypertension status [30]. However, this is the only source of data that we have for all live births. We do agree however that self-reported height and weight for both cases and all live-births is most likely underreported based on findings from other studies that have examined this issue. The effect of this bias would be to reduce the size of the observed association between BMI and birth defects. Therefore, the size of the association between BMI and birth defects is likely larger than what was detected in this study. A Washington state study comparing medical records to birth certificates, reported that birth certificates only recorded 53 % of the gestational diabetes and 38 % of the prepregnancy diabetes described in the medical records [31]. They also reported that when diabetes was listed on the birth certificate, a <1 % chance existed that it was false. Because we used the same data source for diabetes information, we expect the misclassification to be similar between cases and unaffected live births. Therefore, we are underascertaining diabetes prevalence by using vital records and thereby likely underestimating the effect of diabetes on birth defects prevalence. Finally, because of the relatively small numbers of mothers with diabetes, it was not possible to examine the separate effects of gestational versus prepregnancy diabetes on birth defects prevalence.

Conclusion

We report a significant association between obesity and a number of birth defects. The prevalence of certain birth defects increased with increasing categories of BMI, especially among some heart defects. In the absence and presence of diabetes, obesity was associated with an increased risk for certain birth defects. Similar to national trends, obesity is increasing at a substantial rate in Texas [1]. The obesity epidemic may have implications for current and subsequent generations. Preconception counseling should emphasize the importance of maintaining a normal weight and controlling diabetes. Further research is needed to distinguish the effects of gestational and pregestational diabetes.

identifying, and abstracting potential cases of birth defects. We also thank the medical facilities that provided access to their hospital discharge lists and log books, and Vital Statistics Unit for providing us with birth and fetal death vital records to supplement sociodemographic data. This project was supported in part by the CDC-funded Texas Center for Birth Defects Research and Prevention (#U01DD000494) through a cooperative agreement with the Texas Department of State Health Services (DSHS) as well as the Title V office at DSHS.

References

1. *Texas Comptroller of Public Accounts. Gaining costs, losing time: The obesity crisis in Texas*. (2010). Available from: http://www.window.state.tx.us/specialrpt/obesitycost/. Accessed March 26, 2012.
2. *Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System. Prevalence and trends data: Overweight and obesity*. (2009). Available from: http://apps.nccd.cdc.gov/brfss/list.asp?cat=OB&yr=2009&qkey=4409&state=All. Accessed April 23, 2012.
3. *Texas Department of State Health Services. Texas overweight and obesity statistics*. (2008). Available from: www.dshs.state.tx.us/obesity/pdf/TxObesityData.doc. Accessed April 23, 2012.
4. Allen, V. M., et al. (2007). Teratogenicity associated with pre-existing and gestational diabetes. *Journal of Obstetrics and Gynaecology Canada, 29*(11), 927–944.
5. Anderson, J. L., et al. (2005). Maternal obesity, gestational diabetes, and central nervous system birth defects. *Epidemiology, 16*(1), 87–92.
6. Blomberg, M. I., & Kallen, B. (2010). Maternal obesity and morbid obesity: The risk for birth defects in the offspring. *Birth Defects Research, Part A: Clinical and Molecular Teratology, 88*(1), 35–40.
7. Cedergren, M. I., & Kallen, B. A. (2003). Maternal obesity and infant heart defects. *Obesity Research, 11*(9), 1065–1071.
8. Correa, A., et al. (2008). Diabetes mellitus and birth defects. *American Journal of Obstetrics and Gynecology, 199*(237), e1–237 e9.
9. Gilboa, S. M., et al. (2010). Association between prepregnancy body mass index and congenital heart defects. *American Journal of Obstetrics and Gynecology, 202*(1), 51 e1–51 e10.
10. Martinez-Frias, M. L., et al. (2005). Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabetic Medicine, 22*(6), 775–781.
11. Mills, J. L., et al. (2010). Maternal obesity and congenital heart defects: A population-based study. *American Journal of Clinical Nutrition, 91*(6), 1543–1549.
12. Moore, L. L., et al. (2000). A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology, 11*(6), 689–694.
13. Rankin, J., et al. (2010). Maternal body mass index and congenital anomaly risk: A cohort study. *International Journal of Obesity (London), 34*(9), 1371–1380.
14. Waller, D. K., et al. (2007). Prepregnancy obesity as a risk factor for structural birth defects. *Archives of Pediatrics and Adolescent Medicine, 161*(8), 745–750.
15. Watkins, M. L., et al. (2003). Maternal obesity and risk for birth defects. *Pediatrics, 111*(5 Part 2), 1152–1158.
16. *Texas Birth Defects Epidemiology and Surveillance Branch. Report of brith defects among 1999–2008 deliveries*. (2011). Available from: http://www.dshs.state.tx.us/birthdefects/Data/reports.shtm. Accessed April 23, 2012.
17. Petrini, J., et al. (2002). Contribution of birth defects to infant mortality in the United States. *Teratology, 66*(Suppl 1), S3–S6.
18. *World Health Organization. Global database on body mass index: BMI classification*. (2011). Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed April 23, 2012.
19. Mills, J. L. (1982). Malformations in infants of diabetic mothers. *Teratology, 25*(3), 385–394.
20. Ramadhani, T. A., et al. (2004). Medical records vs. interview responses: A comparative analysis of selected variables for linked birth defect cases. *Birth Defects Research, Part A: Clinical and Molecular Teratology, 70*(9), 592–596.
21. *Texas Diabetes Council. Texas diabetes fact sheet*. (2011). Available from: http://www.dshs.state.tx.us/diabetes/PDF/data/Texas-Diabetes-Fact-Sheet.pdf. Accessed April 23, 2012.
22. Kuczmarski, R. J., et al. (2002). 2000 CDC growth charts for the United States: Methods and development. *Vital and Health Statistics, 11*(246), 1–190.
23. *National Institutes of Health. Assessing your weight and health risk*. (2005). Available from: http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/risk.htm.
24. Shaw, G. M., et al. (2000). Spina bifida phenotypes in infants or fetuses of obese mothers. *Teratology, 61*(5), 376–381.
25. Shaw, G. M., Velie, E. M., & Schaffer, D. (1996). Risk of neural tube defect-affected pregnancies among obese women. *Journal of the American Medical Association, 275*(14), 1093–1096.
26. Stothard, K. J., et al. (2009). Maternal overweight and obesity and the risk of congenital anomalies: A systematic review and meta-analysis. *Journal of the American Medical Association, 301*(6), 636–650.
27. Biggio, J. R, Jr, et al. (2010). Fetal anomalies in obese women: The contribution of diabetes. *Obstetrics and Gynecology, 115*(2 Pt 1), 290–296.
28. Hendricks, K. A., et al. (2001). Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. *Epidemiology, 12*(6), 630–635.
29. Biggio, J. R, Jr, Chapman, V., Neely, C., Cliver, S. P., & Rouse, D. J. (2010). Fetal anomalies in obese women: The contribution of diabetes. *Obstetrics and Gynecology, 115*(21), 290–296.
30. Dashe, J. S., McIntire, D. D., & Twickler, D. M. (2009). Effect of maternal obesity on the ultrasound detection of anomalous fetuses. *Obstetrics and Gynecology, 113*(5), 1001–1007.
31. Lydon-Rochelle, M. T., et al. (2005). The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. *American Journal of Obstetrics and Gynecology, 193*(1), 125–134.