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Maternal overweight and obesity and risk of congenital heart defects in offspring

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Abstract

Objective—Obesity is a risk factor for congenital heart defects (CHD), but whether risk is independent of abnormal glucose metabolism is unknown. Data on whether overweight status increases risk is also conflicting.

Research Design and Methods—We included 121815 deliveries from a cohort study, the Consortium on Safe Labor, after excluding women with pregestational diabetes as recorded in the electronic medical record. CHD were identified via medical record discharge summaries. Adjusted odds ratios (OR) for any CHD were calculated for prepregnancy body mass index (BMI) categories of overweight (25 to <30 kg/m^2), obese (30 to <40 kg/m^2), and morbidly obese (≥40 kg/m^2) compared to normal weight (18.5 to <25 kg/m2) women, and for specific CHD with obese groups combined (≥30 kg/m^2). A sub-analysis adjusting for oral glucose tolerance test (OGTT) results where available was performed as a proxy for potential abnormal glucose metabolism present at the time of organogenesis.

Results—There were 1388 (1%) infants with CHD. Overweight (OR=1.15 95% CI: 1.01–1.32), obese (OR=1.26 95% CI: 1.09, 1.44), and morbidly obese (OR=1.34 95% CI: 1.02–1.76) women had greater odds of having a neonate with CHD than normal weight women (*P*< 0.001 for trend). Obese women (BMI ≥30 kg/m^2) had higher odds of having an infant with conotruncal defects (OR=1.34 95%CI: 1.04–1.72), atrial septal defects (OR =1.22 95% CI: 1.04–1.43), and ventricular

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Duality of interest

The authors report no conflicts of interest.

septal defects (OR=1.38 95% CI: 1.06–1.79). Being obese remained a significant predictor of CHD risk after adjusting for OGTT.

Conclusion—Increasing maternal weight class was associated with increased risk for CHD. In obese women, abnormal glucose metabolism did not completely explain the increased risk for CHD; the possibility that other obesity-related factors are teratogenic requires further investigation.

Keywords

Prepregnancy BMI; Obesity; Congenital Heart Defects

Background and Significance

The majority of studies have found an association between maternal obesity and congenital heart defects (CHD).[1–9] It is not clear whether the association between obesity and CHD can be explained by maternal diabetes, a known teratogen, because previous studies have not had detailed information on maternal glucose status. It is also not known whether mild elevations in maternal glucose could be responsible for the excess in CHD seen in offspring of obese women. This hypothesis is reasonable given that other adverse birth outcomes such as macrosomia have a linear association with maternal blood glucose even below the level that meets the criteria for a diagnosis of gestational diabetes.[10, 11] Thus, data are needed to clarify whether obesity is in fact a risk factor for CHD independent of blood glucose level.

The literature is also conflicting regarding whether overweight status increases CHD risk.[2, 3, 5, 6] Moreover, most studies have had insufficient numbers of subjects to investigate the relationship between obesity or overweight and classes of cardiac defects or individual defects.[7]

Using data from the Consortium on Safe Labor (CSL), a large United States cohort study, we investigated the association between prepregnancy body mass index (BMI) and odds of congenital cardiac defects overall and for specific defects where enough cases were available. In a subset of women with diabetes-screening data available, we also investigated the odds of CHD by weight status after adjusting for blood glucose levels.

Methods

Study Design and Methods

The Consortium on Safe Labor (CSL) was an observational study of medical records with prospectively entered data conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at 12 clinical centers (19 hospitals). It was designed to study contemporary obstetric management as well as maternal, obstetric, and neonatal outcomes given the changing maternal socio-demographics in regard to increased maternal age and body mass index (BMI).[12, 13] Information on maternal demographic characteristics (including height, prepregnancy weight, race, educational attainment, insurance status, and age); medical, reproductive, and prenatal history (including pregestational diabetes status, parity, and smoking and alcohol use during pregnancy); pregnancy complications including

development of gestational diabetes mellitus (GDM); and labor, delivery, postpartum, and newborn outcomes was abstracted from electronic medical records. Information from the neonatal intensive care units (NICU) was linked to the newborn records. Maternal and newborn discharge summaries, in International Classification of Diseases-9 (ICD-9) codes, were linked to each delivery. CHD status for each infant was obtained via discharge record ICD-9 codes (Appendix A). Infants with isolated and multiple defects were examined together. Congenital heart defects were categorized as previously described[14], and infants with more than one cardiac defect were categorized in a hierarchical fashion. Infants who had more than one cardiac defect were analyzed in each group. CHD cases related to aneuploidy were excluded.

The CSL study included 208695 women with 228562 deliveries at 23 weeks of gestation or later, occurring between 2002 and 2008. Women were excluded if they had multiple gestations (n=3234), were missing pre-pregnancy BMI information (n=76952), or had pregestational diabetes (n=18786). One site was excluded because it did not report pregestational diabetes status (n=7877). Women with missing BMI data had a higher percentage of neonates with CHD, compared to those with known BMI (1.7% versus 1.1%, $p<0.01$ by Chi-squared test). The critical period for most heart defects is 14 to 60 days after conception.[2] Because gestational diabetes is usually not diagnosed until later in pregnancy around 24 – 28 weeks of gestation,[15] we included women with gestational diabetes in the main analysis. However, since some women diagnosed as having gestational diabetes may have had undiagnosed diabetes during organogenesis, we performed a sensitivity analysis excluding all women with pregnancies complicated by gestational diabetes.

Statistical Analysis

Potential confounders were identified by comparing the distribution of baseline characteristics among women with infants with and without any type of CHD. For categorical factors, chi-squared tests were used. For continuous factors, t-tests were used. All factors with $P \leq 0.05$ were then included in a multivariable model. We adjusted for site to account for the potential differences in diagnoses by the different institutions. We adjusted for race and age because the Baltimore Washington Infant Heart Study reported race and age differences for some defects.[16] The multivariable model related the odds ratio of having an infant with a CHD to categories of BMI (underweight: BMI < 18.5 kg/m^2; normal weight: BMI 18.5 to < 25 kg/m^2; overweight: BMI 25 to < 30 kg/m^2; obese: BMI 30 to < 40 kg/m^2; morbidly obese: BMI ≥ 40 kg/m^2), while adjusting for each of the selected confounders, site, age, race, insurance, and maternal smoking. Women with multiple deliveries were accounted for in the model through a common random effect using PROC GENMOD of SAS.[17] All reported tests were two-sided with $P \leq 0.05$ taken as statistically significant. SAS (SAS Institute Inc, Cary, NC) version 9.1 was used for the statistical analysis.

Additional models combined all obese subjects into a single group: BMI ≥ 30. Further models examined specific types of CHD where n >50, decided a priori. For each model a test for trend was obtained by replacing the categorical BMI with a continuous BMI term.

Oral glucose tolerance test (OGTT) results were available at one site (n=5131). We performed a sub-analysis additionally adjusting for continuous OGTT results as a proxy for potential abnormal glucose metabolism present at the time of organogenesis.

Results

After the exclusions noted above, the study sample consisted of 121815 singleton births from 114819 women. There were 1388 cases of any type of CHD, 1.1% of the study population. Table 1 presents maternal characteristics. Mean maternal BMI was higher for women who had a neonate with any type of CHD compared to women whose neonates did not have CHD (26.3 kg/m^2 versus 25.5 kg/m^2, respectively, P<0.001). Compared to women who did not give birth to an infant with CHD, women who gave birth to infants with CHD were more likely to be overweight (25.4% compared to 23.7%) or obese (BMI ≥ 30 kg/m^2) (22.6% versus 19.6%). Women whose infants had CHD were also less likely to be privately insured, and more likely to smoke during pregnancy and be diagnosed with gestational diabetes mellitus (GDM).

Increasing prepregancy BMI was associated with an increased odds for having an infant with CHD: 1.18-fold for overweight, 1.25-fold for obese, and 1.36-fold for morbidly obese women (P<0.001 for trend) (Table 2). These results remained significant but were slightly attenuated after adjusting for site, age, race, insurance, and maternal smoking. There was no association of CHD with underweight.

GDM complicated 2.2% of pregnancies of normal weight, 4.5% of overweight, and 8% of all obese women (≥ 30 kg/m^2). Women who were diagnosed with GDM had significantly higher odds (OR=2.12 95% CI: 1.73, 2.59) of having a baby with any type of CHD. Because some women who developed GDM also might have had undiagnosed pregestational diabetes, we performed sensitivity analyses excluding all women who developed GDM. When women who developed GDM were excluded from the analytic population, the association between maternal BMI and infant CHD was attenuated but remained significant for the combined obesity categories (BMI ≥ 30 kg/m^2) in the fully adjusted model: OR=1.18 (95%CI: 1.02–1.36) (data not shown). The association was in the same direction but was no longer significant for overweight women: OR= 1.09 (95% CI: 0.95 – 1.25).

Regarding specific categories and types of CHD, the combined obesity group (BMI ≥ 30 kg/m^2) had significantly increased odds for conotruncal defects (OR=1.33 95% CI: 1.03–1.72), ventricular septal defects (OR=1.38 95% CI: 1.06–1.79), and atrial septal defects (OR=1.22 95% CI: 1.04–1.43) (Table 3). There was no association between underweight or overweight status for any specific type of CHD in either crude or adjusted models.

To determine whether the association between pre-pregnancy BMI and CHD persisted after adjusting for glucose concentration later in pregnancy, we performed a sub-analysis restricted to the site that reported the results of 1-hour oral glucose tolerance test (OGTT) for more than 85% of women. This site had fewer women with missing BMI than the overall study population, and CHD incidence at this site was 0.92% (47 defects), which was similar to the 1.15% rate of CHD at sites that did not report OGTT values. We found after we

adjusted for OGTT as a linear predictor, there was a 6% increased odds of CHD with one unit increase in maternal BMI (adjusted OR=1.06, 95% CI 1.02 – 1.10) (Table 4). Among all women at the site with OGTT results (n=5131), obese women (BMI ≥ 30 kg/m^2) had an OR for giving birth to an infant with any type of CHD of 1.96 (95% CI: 1.01, 3.80) (*P*=.045) in the crude model and 2.38 (95% CI: 1.02, 3.76) (*P*=.023) after adjusting for age and OGTT level. Moreover, the test for trend between increasing BMI and OR for congenital heart defects remained significant (*P*=.015) after adjusting for OGTT levels.

Discussion

In this large U.S. cohort study, obese and overweight women were more likely than normal weight women to deliver an infant with any CHD and among obese women, conotruncal, ventricular septal or atrial septal defects in particular. Increasing maternal BMI had a "dose-response" effect on CHD risk. Obesity remained a significant risk factor for CHD after adjusting for glycemic status as measured by oral glucose tolerance test (OGTT).

Women with BMIs above the normal range are more likely to have pre-gestational diabetes mellitus (DM), and diabetes is an established teratogen.[18] Therefore, DM has been put forth as a possible explanation for the observed increased CHD risk in obese mothers.[19] However, several studies have found the association persisted even after diabetic women were excluded.[2, 4, 6, 8] One possible explanation might be obese and overweight women are more likely to have higher glucose concentrations that don't meet the threshold for a diagnosis of diabetes. [6, 7] No study to date has been able to test this hypothesis. We used OGTT tests as a method of identifying possible glucose abnormalities during organogenesis. Even after adjusting for glucose status, increasing BMI was associated with increasing risk of CHD, and obese women still had higher risk of CHD.

The fact that maternal obesity was associated with risk of CHD even after taking abnormal glucose metabolism (albeit evaluated later in pregnancy) into account suggests that abnormalities in glucose metabolism do not fully explain the increased risk for CHD found in obese women. Furthermore, obesity remained a significant risk factor for CHD after we excluded all subjects with GDM (or undiagnosed pregestational diabetes), providing additional support for the hypothesis that other factors contribute to the increased risk for CHD in obese women. Obesity is associated with a wide range of metabolic abnormalities, but little is known about their potential teratogenicity. Our results raise important questions for future investigation. It has been hypothesized mothers with high pre-pregnancy BMI may be at higher risk of giving birth to an infant with CHD because obese women may be more likely to be dieting when they conceive;[19] may have reduced folate levels;[20] or may have more-difficult-to-read ultrasound scans, resulting in fewer terminations of pregnancy for fetal anomaly and therefore increased prevalence at birth.[1, 7]

Most studies have found that obesity was a risk factor for CHD, with similar effect sizes to our study. [2, 4–7] The data are much less consistent, however, regarding the risk associated with being overweight. Two prior case-control studies [2, 3] and two studies using birth certificate data with inherent limitations[5, 6] did not find overweight to be associated with

CHD while other studies did, [1, 4, 8, 9] including a meta-analysis.[7] Our study found overweight status had a modest effect on CHD risk after accounting for other factors.

We also examined the relationship between specific types of CHD and prepregnancy BMI and found that obese women were at an increased risk of having a neonate with conotruncal, ventricular septal, and atrial septal defects. Our findings are consistent with prior studies that found an association between obesity or morbid obesity and atrial and ventricular septal defects.[2, 4, 6, 7, 19] Although our numbers of specific defects were small, our finding that overweight women were not at risk for giving birth to an infant with atrial or ventricular septal defects is similar to prior reports.[4, 6, 7] Results have been more mixed for conotruncal defects. One study found an increased risk in obese mothers for conotruncal defects in general.[4] In contrast, several studies have found no association between prepregnancy BMI for obese or overweight mothers and conotruncal defects in general[5, 21, 22] or tetralogy of Fallot specifically.[2, 7, 21, 22]

Some limitations of our study should be noted. BMI data were not available on all women. However, CHD prevalence was somewhat higher in women with missing BMI data (1.68%) than those in the analytic population (1.15%). We did not have data on potential teratogens such as drugs, although they account for a small percentage of CHD. Cases not identified in the nursery or cases terminated prenatally were not available for study. Many cases of CHD, particularly atrial septal defects, ventricular septal defects, and Coarctation of aorta, may not be diagnosed before discharge after birth, and we did not have full clinical data on infants outside of ICD-9 discharge codes. Finally we were unable to account for any misclassification of ICD-9 coding, despite the fact classification for congenital heart disease has been shown to be inaccurate for certain types of defects, particularly tetralogy of Fallot, where the sensitivity was 83% based on ICD-9 reports.[23]

A major strength of our study was the ability to examine the role of potentially impaired glucose tolerance. Our study also had a large sample size, comprehensive maternal and infant demographic and delivery characteristics, and reliable, uniform data collection from medical charts. Because data were gathered prospectively from the medical records, several types of measurement error and bias, particularly recall bias, were greatly minimized.

Our findings have important public health implications considering that approximately two-thirds of American women 20–39 are overweight or obese according to the 2009–2010 National Health and Nutrition Examination Survey (NHANES) and are at greater risk of giving birth to a child with CHD.[24] A simulation conducted by Honein et al. demonstrated that pre-pregnancy obesity may contribute to 2850 (95% CI: 1035–5065) CHD cases each year in the U.S. Worldwide, the burden of overweight and obesity is increasing, particularly in Latin America and the Caribbean, where 23% of women 20–29 are overweight and 11% are obese.[25]

Conclusion

In summary, women who were obese when they conceived were at increased risk of having an infant with a congenital heart defect. Abnormalities in glucose metabolism likely did not

completely explain the increased risk in obese women. Other obesity-related factors should be investigated as potential teratogens. Women should be counseled prior to conception that obesity increases the risk for CHD and that weight reduction may decrease their risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the Consortium on Safe Labor (CSL) study population women by congenital heart disease (CHD) status in offspring*

	CHD (n=1388)	No CHD (n=120427)	p-value
BMI (kg/m^2)	26.30 (6.88)	25.53 (6.21)	<0.001
BMI categories, n (%)			0.007
Underweight <18.5 kg/m^2	72 (5.2)	6196 (5.2)	
Normal weight 18.5–<25 kg/m^2	651 (47.0)	62162 (51.7)	
Overweight 25–<30 kg/m^2	352 (25.4)	28519 (23.7)	
Obese 30–<40 kg/m^2	255 (18.4)	19463 (16.2)	
Morbidly obese 40+ kg/m^2	58 (4.2)	4087 (3.4)	
All obese 30+ kg/m^2	313 (22.6)	23550 (19.6)	
Insurance, n (%)			<0.001
Private	713 (55.4)	67973 (61.5)	
Public/self-pay	569 (44.2)	42395 (38.4)	
Other	6 (0.47)	139 (0.13)	
Race, n (%)			<0.001
White	635 (45.8)	62083 (51.6)	
Black	330 (23.8)	24158 (20.1)	
Hispanic	305 (22.0)	23294 (19.3)	
Asian/Pacific Islander	34 (2.5)	3527 (3.0)	
Multi-racial/Other	42 (3.1)	2985 (2.6)	
Maternal age (years)	27.43 (6.23)	27.11 (5.91)	0.048
Parity, n (%)			0.878
0	46889 (38.9)	541 (39.0)	
1	35721 (29.7)	404 (29.1)	
2+	37817 (31.4)	443 (31.9)	

	CHD (n=1388)	No CHD (n=120427)	p-value
Smoking during pregnancy, n (%)			0.017
No/unknown	1274 (91.8)	112464 (93.4)	
Yes	114 (8.2)	7963 (6.6)	
Alcohol during pregnancy, n (%)			0.199
No/unknown	1356 (97.7)	118212 (98.1)	
Yes	32 (2.3)	2215 (1.8)	
History of depression, n (%)			0.541
No/unknown	1330 (95.8)	114982 (95.5)	
Yes	58 (4.2)	5445 (4.5)	
Gestational diabetes, n (%)			<0.001
No/unknown	1282 (92.4)	115899 (96.2)	
Yes	106 (7.6)	4528 (3.8)	

* data presented are mean and standard deviation or N(%) when indicated

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for congenital heart defects by categories of body mass index (BMI) among 121815 pregnancies in the Consortium on Safe Labor

	Total (n)	Cases (n)	Crude		Multivariable *	
			OR (95%CI)	P value	OR (95% CI)	*P* value
			p-value for trend test=<.001		p-value for trend test=<.001	
Underweight						
<18.5kg/m^2	6268	72	1.11 (0.87–1.42)	0.405	1.08 (0.85–1.38)	0.529
Normal Weight						
18.5–<25 kg/m^2	62813	651	1.00 (ref)	n/a	1.00 (ref)	n/a
Overweight						
25–<30 kg/m^2	28871	352	1.18 (1.03–1.34)	0.014	1.15 (1.01–1.32)	0.033
Obese						
30–<40 kg/m^2	19718	255	1.25 (1.08–1.45)	0.003	1.24 (1.07–1.44)	0.005
Morbidly Obese						
40+kg/m^2	4145	58	1.36 (1.03–1.78)	0.028	1.34 (1.02–1.76)	0.036
All Obese						
30+kg/m^2	23863	313	1.27 (1.11, 1.45)	0.001	1.26 (1.09–1.44)	0.001

* adjusted for site, age, race, insurance, maternal smoking

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Table 3

Odds ratios (OR)* and 95% confidence intervals (CI) for the effect of pre-pregnancy body mass index (BMI) on risk of types of congenital heart defects**

	Conotruncal p-value for trend test: 0.050			**Ventricular Septal p-value for trend test: 0.029**			**Atrial Septal p-value for trend test: 0.021**		
	OR* (95% CI)	**Total Cases**	***P* value**	**OR* (95% CI)**	**Total Cases**	***P* value**	**OR* (95% CI)**	**Total N Cases**	***P* value**
	p-value for trend test: 0.050			**p-value for trend test: 0.029**			**p-value for trend test: 0.021**		
Underweight (n=6268)									
<18.5kg/m^2	1.04 (0.66–1.67)	20	0.842	0.99 (0.60–1.64)	17	0.974	0.99 (0.74–1.32)	51	0.929
Normal Weight (n=62813)									
18.5–<25 kg/m^2	1.00 (ref)	187	n/a	1.00 (ref)	169	n/a	1.00 (ref)	505	n/a
Overweight (n=28871)									
25–<30 kg/m2	1.18 (0.92–1.51)	101	0.186	1.15 (0.89–1.49)	89	0.286	1.12 (0.96–1.30)	267	0.145
Obese (n=19718)									
30–<40 kg/m^2	1.35 (1.03–1.77)	77	0.030	1.39 (1.05–1.83)	71	0.021	1.19 (1.01–1.42)	191	0.042
Morbidly Obese (n=4145)									
40+kg/m^2	1.21 (0.70–2.10)	14	0.492	1.36 (0.79–2.34)	14	0.272	1.37 (1.00–1.86)	46	0.048
All Obese (n=23863)									
30+kg/m^2	1.33 (1.03–1.72)	91	0.031	1.38 (1.06–1.79)	85	0.016	1.22 (1.04–1.43)	237	0.014
N=		399			360			1060	

* adjusted for site, age, race, insurance, maternal smoking

** Sample sizes (n<50) too small for all other CHD types

Table 4

Odds of congenital heart disease by pre-pregnancy BMI category at site where OGTT results known (n=5131).

	Total (n)	Cases (n)	Crude		Age-adjusted		Adjusted for age and OGTT **	
			OR (95% CI)	P value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
BMI *:								
Normal Weight								
18.5–24.9	2226	16	1.00 (ref)	n/a	1.00 (ref)	n/a	1.00 (ref)	n/a
Overweight								
25–29.9	1272	10	1.10 (0.50–2.42)	0.8219	1.09 (0.49–2.42)	0.8261	0.83 (0.33–2.05)	0.686
Obese								
30–39.9	1115	12	1.50 (0.71–3.19)	0.2884	1.50 (0.71–3.16)	0.2877	2.04 (0.90–4.62)	0.088
Morbidly Obese								
40+	311	8	3.65 (1.55- 8.58)	0.0030	3.63 (1.55- 8.51)	0.0030	3.63 (1.33- 9.91)	0.021
All Obese								
30+	1426	20	1.96 (1.01–3.80)	0.0451	1.95 (1.02–3.76)	0.0445	2.38 (1.12–5.05)	0.023

* Underweight category had an insufficient number of cases (n)=1.

** Oral glucose tolerance test