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## Maternal Diagnosis of Obesity and Risk of Cerebral Palsy in the Child

Mary D. Crisham Janik, BA<sup>1</sup>, Thomas B. Newman, MD, MPH<sup>2,3</sup>, Yvonne W. Cheng, MD, PhD<sup>4</sup>, Guibo Xing, PhD<sup>5</sup>, William M. Gilbert, MD<sup>6</sup>, and Yvonne W. Wu, MD, MPH<sup>1,3</sup>

<sup>1</sup>Department of Neurology, UCSF, San Francisco, CA

<sup>2</sup>Department of Epidemiology and Biostatistics, UCSF, San Francisco, CA

<sup>3</sup>Department of Pediatrics, UCSF, San Francisco, CA

<sup>4</sup>Department of Obstetrics and Gynecology, UCSF, San Francisco, CA

<sup>5</sup>Department of Obstetrics and Gynecology, UC Davis, Sacramento, CA

<sup>6</sup>Department of Obstetrics and Gynecology, Sutter Medical Center, Sacramento, CA

### Abstract

**Objective**—To examine the association between maternal hospital diagnoses of obesity and risk of cerebral palsy (CP) in the child.

**Study design**—For all California hospital births from 1991–2001, we linked infant and maternal hospitalization discharge abstracts to California Department of Developmental Services records of children receiving services for CP. We identified maternal hospital discharge diagnoses of obesity (ICD-9 646.1, 278.00 or 278.01) and morbid obesity (ICD-9 278.01), and performed logistic regression to explore the relationship between maternal obesity diagnoses and CP.

**Results**—Among 6.2 million births, 67,200 (1.1%) mothers were diagnosed with obesity, and 7878 (0.1%) with morbid obesity; 8798 (0.14%) children had CP. A maternal diagnosis of obesity (RR 1.30, 95% CI 1.09–1.55) or morbid obesity (RR 2.70, 95% CI 1.89–3.86) was associated with increased risk of CP. In multivariable analysis adjusting for maternal race, age, education, prenatal care, insurance status and infant sex, both obesity (OR 1.27, 95% CI 1.06 – 1.52) and morbid obesity (OR 2.56, 95% CI 1.79 – 3.66) remained independently associated with CP. On stratified analyses, the association of obesity (RR 1.72, 95% CI 1.25 – 2.35) or morbid obesity (RR 3.79, 95% CI 2.35 – 6.10) with CP was only significant among women who were hospitalized prior to the birth admission. Adjusting for potential comorbidities and complications of obesity did not eliminate this association.

**Conclusions**—Maternal obesity may confer an increased risk of CP in some cases. Further studies are needed to confirm this finding.

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Corresponding Author: Yvonne Wu, MD, MPH, UCSF Department of Child Neurology, Box 0137, 350 Parnassus Ave, Suite 609, San Francisco, CA 94143-0137, wuy@neuropeds.ucsf.edu, Phone: (415) 353-3678, Fax: (415) 353-2400.

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## Keywords

cerebral palsy; maternal obesity; inflammation; epidemiology

Cerebral palsy (CP) refers to a heterogeneous group of disorders of the development of movement and posture caused by non-progressive lesions occurring in the developing fetal or infant brain.<sup>1</sup> It is one of the most common motor disabilities in childhood, occurring in two to four per 1,000 live births.<sup>2</sup> Etiologic studies have largely focused on the role of perinatal factors, such as chorioamnionitis and hypoxic-ischemic encephalopathy. However, it is estimated that brain injury occurring during the perinatal and post-natal periods accounts for the minority of cases of CP.<sup>3,4</sup> Moreover, despite improvements in perinatal care in recent decades, most studies have failed to demonstrate any significant decline in the prevalence of CP.<sup>5,6,7</sup> These findings suggest that prenatal factors, including maternal conditions that are present before the onset of labor, may contribute to the pathogenesis of CP in a significant proportion of cases.

The obesity epidemic is a critical public health issue in the United States.<sup>8</sup> Among women of childbearing age (20 to 44), nearly half are overweight or obese.<sup>9</sup> Maternal obesity is associated with adverse outcomes in both mother and child, including gestational diabetes, preeclampsia, increased rates of cesarean delivery, stillbirth, birth defects and neonatal encephalopathy.<sup>10,11,12</sup> A growing literature suggests that maternal obesity also detrimentally affects the fetal brain.<sup>13,14</sup> Furthermore, obesity induces a chronic inflammatory state, and maternal inflammatory conditions such as chorioamnionitis are known to contribute to CP.<sup>15,16</sup>

Studies addressing maternal obesity and CP have produced conflicting results. In Australia, one study found a 3.5-fold increased risk of CP among term infants born to obese mothers,<sup>17</sup> whereas two others reported no significant association.<sup>18,19</sup> A recent study in Sweden reported a marginally significant association between increased maternal weight at 34 weeks and CP (OR 1.02, 95% CI 1.00 – 1.03).<sup>20</sup> In a large California population, we sought to determine whether a maternal hospital diagnosis of obesity during pregnancy is associated with increased risk of moderate to severe CP in the child.

## METHODS

We conducted a population-based study of all infants born in California hospitals during the eleven-year period from January 1, 1991 to December 31, 2001. Data were retrieved from three statewide sources: (1) the Office of Statewide Health Planning and Development Patient Discharge Abstracts; (2) the Department of Health Services Linked Vital Statistics Birth and Infant Death file; and (3) the California Department of Developmental Services. Linkage of these three sources was performed using probabilistic record linkage technique with 98% linkage accuracy.<sup>21</sup> All study procedures were approved by the California Protection of Human Subjects Committee and by the institutional review boards at the California Office of Statewide Health Planning and Development, the University of California, San Francisco and the University of California, Davis.

The California Office of Statewide Health Planning and Development (OSHPD) maintains a database of discharge abstracts for all admissions to nonfederal hospitals, representing 96% (571 of 594) of all hospitals in the state. According to the 1991–1998 California natality figures from the Centers for Disease Control and Prevention, 96.7% of all live births in California were recorded in the OSHPD hospital discharge dataset. Maternal hospitalization discharge diagnoses from one year before delivery through the birth hospitalization are

included, as are infant discharge diagnoses from the birth hospitalization. Each record contains information regarding a single mother-infant pair. Therefore, individual women who gave birth to more than one child during this time period are represented more than once in the study population.

From the linked California Department of Health Services' Vital Statistics Birth files, we extracted maternal and infant sociodemographic characteristics including maternal age at delivery, race, ethnicity, education, level of prenatal care and parity; multiple gestation; and infant sex, birth weight and gestational age. We determined the source of payment for the birth hospitalization as an indicator of socioeconomic status; women who were publicly insured or uninsured were categorized as having low insurance status, whereas women with private or managed care insurance were categorized as having high insurance status.

The California Department of Developmental Services (DDS) sponsors a statewide program that provides occupational and physical therapy and social services for residents of the state who have a substantive disability related to CP, regardless of income. CP is defined as a non-progressive lesion or disorder in the brain occurring during intrauterine life or the perinatal period and characterized by paralysis, spasticity or abnormal control of movement or posture that is manifest before two years of age. Each year, individuals who receive services from the DDS receive a comprehensive evaluation by a staff physician who records data regarding medical diagnoses including CP. We identified study subjects who qualified for DDS services for CP before November 30, 2006. Thus, all children in our study were at least five years old at the time of CP ascertainment. We excluded children with known postnatal causes of CP, including child abuse ( $n = 272$ ), motor vehicle and other injuries ( $n = 213$ ) and near drowning ( $n = 72$ ).

We searched the OSHPD database for maternal hospitalization records that contained the following discharge diagnoses related to obesity, as coded by the International Statistical Classification of Diseases, ninth Revision (ICD-9): obesity of pregnancy (646.1), unspecified obesity (278.0) and morbid obesity (278.01). We categorized maternal obesity diagnoses into two separate time periods: (1) "prenatal," indicating diagnoses made during a maternal hospitalization in the twelve months prior to the birth hospitalization, and (2) "perinatal," indicating diagnoses made during the birth hospitalization. We calculated bivariate relative risks (RR) and 95% confidence intervals (95% CI) to compare CP rates in children of women with and without obesity diagnoses.

We used logistic regression to calculate odds ratios (OR) and 95% CIs to determine whether CP prevalence in children of women with and without obesity diagnoses remained statistically different after adjusting for the following sociodemographic risk factors: maternal race, age, educational attainment, prenatal care, insurance status and infant sex. We considered two sets of maternal obesity diagnoses in our multivariate analysis: a specific diagnosis of morbid obesity, or any diagnosis of obesity including morbid obesity, unspecified obesity or obesity of pregnancy. All ORs closely approximate the RR given the low prevalence of CP. Analyses were performed using Stata statistical package (version 12.0; Stata Corporation, College Station, TX).

In order to investigate factors that might mediate the association between maternal obesity and CP, we identified maternal and infant complications that were associated with both maternal obesity and CP and adjusted for these potential mediators in a logistic regression model. We analyzed the following discharge diagnoses: pregestational diabetes (ICD-9 648.0), gestational diabetes (648.8), preeclampsia (642.4–5 and 642.7), eclampsia (642.6), hypertension (ICD-9 401 – 405), hypertension of pregnancy (ICD-9 642), chorioamnionitis (658.4), any perinatal infection (646.6, 647.9, 659.3 and 670), placental abruption (641.2),

obstructed labor (660.0–9), cord prolapse (663.0), uterine rupture (665.1), medical induction of labor (73.4) and surgical induction of labor (73.1), prematurity (765), birth defects (740 – 759), birth trauma (767), severe birth asphyxia (768.5) and any birth asphyxia (768.5–9). Parity, instrumental delivery, artificial rupture of membranes and other factors which were not significantly associated with both maternal obesity and CP were not included in the model. Birthweight was not included because it was collinear with prematurity.

## RESULTS

Among 6,221,001 infants born in California hospitals between 1991 and 2001, we identified 8,397 cases of CP. Population prevalence of CP was 1.4 per 1,000 live births. Among all mother-baby pairs in the birth population, maternal obesity was diagnosed in 67,200 (1.10%), and maternal morbid obesity was diagnosed in 7878 (0.13%). Compared with white women, black women were more likely to have a diagnosis of morbid obesity (RR 2.47, 95% CI 2.32 – 2.63), whereas Asian (RR 0.11, 95% CI 0.09 – 0.13) and Hispanic women (RR 0.82, 95% CI 0.78 – 0.86) were less likely (Table I). Similar racial differences existed among women diagnosed with obesity of pregnancy or unspecified obesity. Obesity diagnoses were more common in women age 35 years or older, women who had not graduated from college, women with private insurance coverage and women receiving prenatal care.

A maternal diagnosis of obesity at any time was associated with a 30% increased risk of delivering a child with CP (RR 1.30, 1.09–1.55). The risk of CP was even higher among infants born to a mother who was diagnosed with morbid obesity at any time (RR 2.70, 95% CI 1.89–3.86). The highest risk of CP (Table II) was seen in infants born to a mother who was diagnosed with morbid obesity during a prenatal hospitalization (RR 5.76, 95% CI 2.75–12.05).

In a multivariate logistic regression controlling for maternal race, age and education, prenatal care, private insurance coverage and infant sex, women with a diagnosis of morbid obesity at any time had significantly increased risk of having a child with CP after adjusting for these factors (OR 2.56, 95% CI 1.79 – 3.66). Similarly, any maternal diagnosis of obesity (morbid obesity, unspecified obesity or obesity of pregnancy) at any time period was an independent risk factor for delivering a child with CP (OR 1.27, 95% CI 1.06 – 1.52). Other independent risk factors for CP included maternal age > 35 years, no college graduation, lack of prenatal care and male sex (Table III).

Each of the following medical complications, diagnosed at any time, was significantly associated with maternal obesity (Table IV), as well as with increased risk of CP: maternal diabetes, pre-eclampsia, eclampsia, maternal hypertension, chorioamnionitis, perinatal infection, placental abruption, uterine rupture, cord prolapse, obstructed labor, low birth weight, preterm delivery, birth trauma, and birth defects. When each of these potential mediators was added individually into the multivariate model, little appreciable change was seen in the association between maternal obesity and CP. Adding all of the above factors together into the multivariate model attenuated but did not eliminate the association between morbid obesity (OR 2.02, 95% CI 1.39 – 2.93) or any diagnosis of obesity (OR 1.26, 95% CI 1.05 – 1.52) with CP. Infants who were large for gestational age (i.e. > 4500 grams) had a *reduced* risk of CP (RR 0.70, 95% CI 0.58 – 0.85). Thus, although obese women were at higher risk of delivering large for gestational age babies (RR 2.9, 95% CI 2.80 – 3.00), the increased risk of CP associated with obesity diagnoses was not explained by the presence of larger babies.

The likelihood of being diagnosed with obesity at any time in the twelve months leading up to and including the birth hospitalization was twice as high among women who were hospitalized during the prenatal period as compared with those without a prenatal hospitalization (2.04% vs. 1.01%,  $p < 0.001$ ). This was an anticipated difference given that women who were hospitalized more frequently would have more opportunities to have a documented hospital diagnosis of obesity. The risk of having a child with CP was also higher among women who required a prenatal hospitalization when compared with women who were not hospitalized before the birth admission (0.26% vs 0.13%,  $p < 0.001$ ). To address the concern for potential ascertainment bias, we conducted a stratified analysis.

Among the 7.12% of women who required a prenatal hospitalization, a diagnosis at any time of morbid obesity (RR 3.79, 95% CI 2.35 – 6.10) or any obesity (RR 1.72, 95% CI 1.25 – 2.35) was associated with increased risk of having a child with CP, compared with women who required prenatal hospitalization but did not have an obesity diagnosis. Adjusting for potential mediators (ie, maternal diabetes, pre-eclampsia, eclampsia, maternal hypertension, chorioamnionitis, perinatal infection, placental abruption, uterine rupture, cord prolapse, obstructed labor, low birth weight, preterm delivery, birth trauma and birth defects) did not eliminate this association. In contrast, obese pregnant women who did not require hospitalization before the birth admission did not exhibit an increased risk of CP (morbid obesity: RR 1.60, 95% CI 0.93 – 2.76; any obesity: RR 1.08, 95% CI 0.87 – 1.34).

## DISCUSSION

Maternal obesity increases the risk of several maternal and obstetrical complications, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia<sup>10,11</sup>, chorioamnionitis and cesarean delivery.<sup>22,23</sup> These complications can lead to prenatal hospitalizations and thus could potentially account for the increased risk of CP observed among obese mothers who were hospitalized in the prenatal period. However, adjusting for obesity related pregnancy and obstetric complications did not eliminate the observed association between obesity diagnoses and CP, suggesting that none of these known complications of obesity explain this finding.

Obesity-induced inflammation could explain how maternal obesity affects CP risk. Maternal inflammatory conditions such as chorioamnionitis have been associated with fetal inflammation,<sup>16</sup> a known risk factor for neonatal brain injury and CP.<sup>24,25</sup> In animal models of neonatal brain injury, the presence of maternal inflammatory mediators increases the susceptibility of the fetal brain to hypoxic-ischemic injury.<sup>26, 27,28</sup> It is possible that an obesity-associated inflammatory milieu could make the fetus more susceptible to hypoxic-ischemic insults that might otherwise have been tolerated, though this remains speculation.

Adipose tissue is a highly active endocrine organ and a source of pro-inflammatory mediators.<sup>29</sup> Obesity induces a state of chronic, low-grade inflammation characterized by elevated inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6 and IL-8.<sup>30</sup> When obesity complicates pregnancy, which is itself an inflammatory state marked by increased concentrations of cytokines and increased activation of maternal neutrophils and macrophages, an exaggerated state of inflammatory up-regulation results.<sup>31</sup> Serum levels of leptin, CRP and IL-6 are increased in obese pregnant women compared with non-obese pregnant women,<sup>32,33</sup> and CRP, IL-6, ICAM-1 and IL-10 levels are elevated in obese compared with lean pregnant women.<sup>34</sup> A localized placental inflammatory response has been described in obese pregnant women, with a two- to three-fold increase in placental macrophage expression of the pro-inflammatory cytokines IL-1, TNF and IL-6.<sup>35</sup> Alterations in plasma cytokine levels in obese women have also been associated with decreased placental function during the first trimester.<sup>33</sup>



The relationship between maternal obesity and CP has been studied previously in three Australian cohorts. Walstab et al found that maternal BMI > 25 was associated with a 3.5-fold (P= 0.02) increased risk of moderate to severe CP among term infants.<sup>17</sup> In contrast, two other studies reported no association between maternal weight and CP, though no point estimates were given<sup>18,19</sup>; these studies may not have had adequate power to detect an association. Other studies have investigated the association between maternal obesity and other neurodevelopmental problems in the child.<sup>36,37</sup> A recent population study found that children born to obese mothers had an increased risk of autism spectrum disorder and developmental delay.<sup>38</sup>

The association between maternal obesity diagnoses and CP was limited to the subset of women requiring prenatal hospitalization. This group comprised only 7% of the women in the study cohort. Thus, for the vast majority of women in our large population, having an obesity diagnosis did not put them at increased risk of having a child with CP. This may be reassuring for obese women who are able to remain healthy enough to avoid hospitalization during their pregnancy. Prenatal complications that require hospitalization, such as preterm labor and infection, often have an inflammatory component.<sup>39</sup> It is possible that the inflammation induced by maternal obesity may be particularly harmful in pregnancies that are already complicated by other underlying inflammatory conditions, especially in the preterm infant. Prospective studies of maternal obesity are needed to better understand how inflammatory prenatal conditions heighten a woman's risk of having a child with CP.

Our study has several limitations. The prevalence of CP (1.4 per 1000) is lower than previously reported (2–4 per 1000).<sup>2</sup> The DDS provides services to more severely impaired children, and thus we are limited to establishing an association between maternal obesity and moderate to severe CP. The maternal discharge diagnoses are susceptible to coding errors; however, inaccuracies are likely to be non-differential with respect to CP and to bias the results towards the null, because the diagnoses were coded prior to knowledge of the child's future condition. Potential confounders not included in the hospital discharge data, such as history of infertility, could not be assessed in this study. Obesity is significantly under-ascertained in our dataset, and there are presumably many women in this population who are obese but were not diagnosed as such. However, women who were identified as obese in this study were likely to be definitively obese, suggesting that the observed association between obesity and CP is real. It is possible that mothers are more likely to be diagnosed with obesity if their baby suffers newborn complications, causing ascertainment bias for obesity. However, the association with CP was strongest for maternal obesity diagnosed *before* the birth hospitalization, suggesting that our findings are not due to bias arising from neonatal complications leading to enhanced coding for maternal obesity. Strengths of our study include the large study population and the lack of recall bias. Better understanding of the relationship between maternal obesity during pregnancy and risk of CP in the child may provide new opportunities for intervention.

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## Abbreviations

CP	cerebral palsy
CRP	C-reactive protein

<b>DDS</b>	Department of Developmental Services
<b>ICD-9</b>	International Statistical Classification of Diseases and Related Health Problems
<b>IL</b>	interleukin
<b>OSHPD</b>	Office of Statewide Health Planning and Development
<b>TNF</b>	tumor necrosis factor

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TABLE 1

Risk of maternal obesity and maternal morbid obesity diagnoses based on sociodemographic characteristics in a cohort of 6.2 million births in California, 1991 – 2001.<sup>a</sup>

	% of Cohort	Any Obesity (%)	Morbid Obesity (%)
Maternal age, years			
< 35	86	1.08	0.12
35	14	1.16	0.17
Maternal race/ethnicity			
White	35	1.28	0.13
Hispanic	46	0.87	0.11
Asian	10	0.87	0.01
Black	7	1.73	0.33
Other	1	1.93	0.30
Maternal education, years			
Primary school or none (0–5y)	5	0.44	0.05
Secondary school (6–11y)	28	0.77	0.10
High school graduate (12y)	29	1.36	0.17
Some college (13–15y)	20	1.44	0.17
College graduate (16y)	18	0.95	0.07
Insurance status			
Private coverage	49	1.39	0.14
Medicare/Medicaid/Self-Pay	49	0.79	0.12
Prenatal care <sup>b</sup>			
Any	99	1.10	0.13
None	1	0.46	0.09
Parity			
Multiparous	62	1.01	0.13
Nulliparous	38	1.19	0.12

<sup>a</sup>P < 0.001 for all comparisons unless otherwise noted.

<sup>b</sup>P < 0.005.

**TABLE 2**

Bivariate risk for CP associated with hospital diagnoses of maternal obesity.

	CP per 1,000	RR	95% CI	P value
Prenatal diagnosis <sup>a</sup>				
Obesity of pregnancy	4.3	3.04	1.45 – 6.38	0.002
Unspecified obesity	5.9	4.17	2.31 – 7.52	<0.001
Morbid obesity	8.1	5.76	2.75 – 12.05	<0.001
Any of the above	5.5	3.88	2.58 – 5.84	<0.001
No obesity diagnosis	1.4	1.00		Reference
Perinatal diagnosis <sup>b</sup>				
Obesity of pregnancy	1.3	0.90	0.69 – 1.18	0.44
Unspecified obesity	2.2	1.57	1.13 – 2.18	0.01
Morbid obesity	3.2	2.25	1.49 – 3.38	<0.001
Any of the above	1.7	1.22	1.01 – 1.47	0.04
No obesity diagnosis	1.4	1.00		Reference
Prenatal or perinatal diagnosis <sup>c</sup>				
Obesity of pregnancy	1.3	0.95	0.74 – 1.23	0.71
Unspecified obesity	2.5	1.75	1.30 – 2.35	<0.001
Morbid obesity	3.8	2.70	1.89 – 3.86	<0.001
Any of the above	1.8	1.30	1.09 – 1.55	0.004
No obesity diagnosis	1.4	1.00		Reference

<sup>a</sup>Includes any diagnosis given during any hospitalization in the 12 months prior to the birth hospitalization.

<sup>b</sup>Includes any diagnosis given during the birth hospitalization.

<sup>c</sup>Includes any diagnosis given during any hospitalization in the 12 months prior to and including the birth hospitalization.

**TABLE 3**

Risk of CP associated with a pre- or perinatal hospital diagnosis of maternal morbid obesity, adjusted for sociodemographic factors in a multivariate logistic regression model.<sup>a</sup>

	Odds Ratio	95% CI	P value
Morbid obesity	2.56	1.79 – 3.66	<0.001
Maternal race			
White	1.00		Reference
Black	1.25	1.16 – 1.36	<0.001
Hispanic	0.96	0.91 – 1.02	0.20
Asian	0.79	0.73 – 0.86	<0.001
Other	0.98	0.81 – 1.19	0.85
Maternal age ≥ 35 years	1.39	1.31 – 1.47	<0.001
Maternal education, years			
Primary school or none (0–5 y)	1.32	1.17 – 1.49	<0.001
Secondary school (6–11 y)	1.24	1.14 – 1.34	<0.001
High school graduate (12 y)	1.20	1.11 – 1.29	<0.001
Some college (13–15 y)	1.14	1.06 – 1.22	0.001
College graduate (> 16 y)	1.00		Reference
No prenatal care	2.25	1.95 – 2.59	<0.001
Low insurance status <sup>b</sup>	1.03	0.98 – 1.08	0.32
Male infant	1.31	1.26 – 1.37	<0.001

<sup>a</sup>Logistic regression model includes all the variables listed in the table.

<sup>b</sup>Medicare/Medicaid/Self-Insured

TABLE 4

Association of maternal and perinatal complications with pre- or perinatal hospital diagnosis of morbid obesity and with CP.

Potential Mediator	Morbid obesity	Cerebral palsy
	RR <sup>a</sup> (95% CI)	RR <sup>b</sup> (95% CI)
Maternal conditions		
Hypertension	24.9 (22.9 – 27.1)	2.82 (2.22 – 3.58)
Hypertension of pregnancy	5.92 (5.72 – 6.13)	1.89 (1.75 – 2.03)
Pregestational diabetes	10.27 (9.46 – 11.16)	2.10 (1.76 – 2.52)
Gestational diabetes	5.31 (5.05 – 5.57)	1.35 (1.22 – 1.50)
Any diabetes	5.91 (5.67 – 6.16)	1.45 (1.33 – 1.59)
Eclampsia	5.57 (4.07 – 7.62)	3.31 (2.26 – 4.86)
Preeclampsia	4.77 (4.50 – 5.05)	2.16 (1.98 – 2.37)
Delivery complications		
Uterine rupture	3.61 (2.27 – 5.73)	10.6 (8.24 – 13.7)
Cord prolapse	1.91 (1.41 – 2.59)	5.24 (4.40 – 6.24)
Obstructed labor	1.91 (1.80 – 2.03)	1.22 (1.13 – 1.32)
Any perinatal infection	1.88 (1.74 – 2.03)	3.02 (2.83 – 3.22)
Chorioamnionitis	1.77 (1.56 – 1.97)	4.06 (3.76 – 4.39)
Preterm delivery	1.45 (1.37 – 1.53)	5.08 (4.86 – 5.31)
Placental abruption	1.42 (1.17 – 1.72)	6.34 (5.79 – 6.95)
Infant conditions		
Birth defects	1.51 (1.41 – 1.62)	7.14 (6.83 – 7.47)

<sup>a</sup>Risk of maternal or perinatal complication in women with a pre- or perinatal diagnosis of morbid obesity compared to women with no obesity diagnosis.

<sup>b</sup>Risk of having a child with CP among women with maternal or perinatal complication compared to women without maternal or perinatal complication.