Prepregnancy Obesity as a Risk Factor for Structural Birth Defects

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

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

Setting: Eight participating states in the United States.

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

Main Exposure: Maternal obesity.

Main Outcome Measures: Crude and adjusted odds ratios.

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

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

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Methods

Infants in the NBDDS who were born on or after October 1, 1997, and had an estimated date of delivery on or before December 31, 2002, were eligible for the current analyses. Eight states participated in this analysis, and each state interviewed approximately 300 eligible case...
mothers and 100 control mothers annually. Cases had 1 or more of 30 eligible birth defects. Infants recognized or strongly suspected to have single-gene conditions or chromosomal abnormalities were excluded from the NBDPDS. Controls were unmatched and were live-born infants without birth defects randomly selected from birth certificates (Arkansas, Iowa, Massachusetts, New Jersey, and Georgia [2001-2002]) or from birth hospitals (California, Georgia [1997-2000], New York, and Texas) to represent the population from which cases were derived. This study was approved by the institutional review boards of the participating study centers and the Centers for Disease Control and Prevention.

Among the birth defect categories included in the NBDPDS, we selected only those for which 150 or more eligible cases with completed interviews were available, as those categories with fewer eligible cases would not have generated sufficiently precise odds ratios (ORs). A total of 16 birth defect categories met this criterion. After all of the cases were aggregated across states, they were further reviewed by clinical geneticists associated with the NBDPDS and classified based on the nature of accompanying congenital anomalies into 1 of 3 categories: isolated, multiple (infants with ≥2 major unrelated birth defects), complex sequence (infants with ≥2 birth defects believed to be pathogenetically related but for which the underlying defect is not clear), microtia and anotia included dysplastic or absent ear pinna or stenosis or atresia of the external auditory canal. Infants with well-defined major congenital heart defects and eligible for inclusion in the NBDPDS were analyzed in aggregate in this study. Some heart defects were excluded from the NBDPDS because they were very rare, not well ascertained in infancy, preterm-related birth defects (patent ductus arteriosus and patent foramen ovale), minor defects of unclear significance (eg, insufficiency of the tricuspid, mitral, or pulmonary valves), and vascular defects rather than true malformations of the heart (eg, vascular rings and aberrant subclavian artery). Muscular ventricular septal defects were ascertained only in the early years of the study; therefore, we chose to exclude them from this analysis. All of the cases with cardiovascular defects were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. Oral clefts were classified into 2 groups that have been established by previous epidemiologic studies to have different risk factors: cleft lip with or without cleft palate and cleft palate only. Only cases of second- or third-degree hypospadias were included in the NBDPDS because first-degree hypospadias is less likely to be consistently ascertained. Maternal interviews were conducted using a standardized computer-based interview, primarily by telephone, in English or Spanish, no earlier than 6 weeks after the infant’s estimated date of delivery, and no later than 24 months after delivery. During the study period (October 1, 1997, to December 31, 2002), participation rates for the interview were 71.4% among case mothers and 67.9% among control mothers. Interviews were completed within an average of 11 months from the estimated date of delivery for cases and 9 months for controls. A total of 1.1% (122 of 10 655) of cases and 1.2% (49 of 4 143) of controls were excluded because the mothers did not complete the interview. To ensure that any associations we observed between maternal obesity and birth defects were not confounded by preexisting diabetes, we also excluded an additional 2.7% of cases (n = 284) and 0.7% of controls (n = 29) whose mothers reported having diabetes prior to conception or did not answer the question on preexisting diabetes. After these exclusions, 10 249 cases and 4 065 controls remained in our initial analyses (Table 1).

Mothers were asked to report their height and prepregnancy weight using either English or metric units. Case and control mothers with invalid or missing values of BMI (3.7% and 4.0%, respectively) were excluded from the analyses presented in Table 2 and Table 3. We used the BMI analytic categories currently recommended by the National Heart, Lung, and Blood Institute and the World Health Organization (underweight, <18.5; normal [reference], ≥18.5 to <25.0; overweight, ≥25.0 to <30.0; and obese, ≥30.0). As only male infants are at risk for hypospadias, all of the analyses for hypospadias were conducted limiting controls to mothers of male infants. Logistic regression was used to examine crude and adjusted ORs for the association between maternal prepregnancy BMI and the frequency of the 16 different categories of birth defects included in this study. All of the ORs were adjusted for maternal race/ethnicity (white, black, Hispanic, or other), maternal age (<18, 18-24, 25-29, 30-34, or ≥35 years), maternal educational level (<12, 12, 13-15, or ≥16 years), parity (0 or ≥1 previous births), smoking in the month prior to conception (yes or no), and any intake of vitamins containing (REPRINTED) ARCH PEDIATR ADOLESC MED/VOL 161 (NO. 8), AUG 2007 WWW.ARCHPEDIATRICS.COM

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Table 2. Adjusted Odds Ratios for the Association Between Maternal Body Mass Index and Selected Birth Defects

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Thin, BMI &lt; 18.5</th>
<th>Overweight, 25.0 ≤ BMI &lt; 30.0</th>
<th>Obese, BMI ≥ 30.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, No.</td>
<td>OR (95% CI)</td>
<td>Cases, No.</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>193</td>
<td>0.82 (0.42-1.59)</td>
<td>42</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>425</td>
<td>0.91 (0.56-1.46)</td>
<td>84</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>156</td>
<td>1.06 (0.54-2.09)</td>
<td>35</td>
</tr>
<tr>
<td>Microtia and anotia</td>
<td>216</td>
<td>0.82 (0.43-1.56)</td>
<td>46</td>
</tr>
<tr>
<td>Heart defects</td>
<td>4128</td>
<td>1.12 (0.93-1.36)</td>
<td>939</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>592</td>
<td>0.92 (0.62-1.36)</td>
<td>125</td>
</tr>
<tr>
<td>Cleft lip and cleft palate</td>
<td>1064</td>
<td>1.35 (1.04-1.76)</td>
<td>215</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>278</td>
<td>1.07 (0.63-1.82)</td>
<td>57</td>
</tr>
<tr>
<td>Small-intestinal atresia</td>
<td>163</td>
<td>1.20 (0.63-2.31)</td>
<td>36</td>
</tr>
<tr>
<td>Anorectal atresia</td>
<td>380</td>
<td>0.81 (0.48-1.36)</td>
<td>90</td>
</tr>
<tr>
<td>Second- or third-degree hypospadias</td>
<td>793</td>
<td>1.04 (0.71-1.52)</td>
<td>188</td>
</tr>
<tr>
<td>Limb reduction defects</td>
<td>509</td>
<td>1.08 (0.73-1.61)</td>
<td>123</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>422</td>
<td>1.07 (0.67-1.70)</td>
<td>105</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>286</td>
<td>0.89 (0.49-1.47)</td>
<td>55</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>177</td>
<td>0.98 (0.48-1.98)</td>
<td>48</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>400</td>
<td>0.85 (0.58-1.33)</td>
<td>68</td>
</tr>
</tbody>
</table>

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

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

† All heart defects.
‡ Cleft lip with or without cleft palate.
§ Includes jejunal, ileal, and multiple small-intestinal atresias.

Table 3. Adjusted Odds Ratios for the Association Between Maternal Body Mass Index and Selected Birth Defects Stratified by Isolated and Multiple Defects

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Isolated, 25.0 ≤ BMI &lt; 30.0</th>
<th>Multiple, 25.0 ≤ BMI &lt; 30.0</th>
<th>Isolated, Obese, BMI ≥ 30.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, No. OC (95% CI)</td>
<td>Cases, No. OC (95% CI)</td>
<td>Cases, No. OC (95% CI)</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>39</td>
<td>0.97 (0.66-1.42)</td>
<td>3</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>73</td>
<td>0.99 (0.74-1.31)</td>
<td>11</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>28</td>
<td>1.33 (0.84-2.11)</td>
<td>7</td>
</tr>
<tr>
<td>Microtia and anotia</td>
<td>38</td>
<td>0.96 (0.64-1.44)</td>
<td>8</td>
</tr>
<tr>
<td>Heart defects</td>
<td>753</td>
<td>1.08 (0.96-1.22)</td>
<td>171</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>98</td>
<td>0.97 (0.76-1.25)</td>
<td>27</td>
</tr>
<tr>
<td>Cleft lip and cleft palate</td>
<td>190</td>
<td>0.95 (0.79-1.14)</td>
<td>25</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>25</td>
<td>1.15 (0.71-1.85)</td>
<td>32</td>
</tr>
<tr>
<td>Small-intestinal atresia</td>
<td>30</td>
<td>0.97 (0.63-1.50)</td>
<td>6</td>
</tr>
<tr>
<td>Anorectal atresia</td>
<td>40</td>
<td>1.20 (0.81-1.77)</td>
<td>49</td>
</tr>
<tr>
<td>Second- or third-degree hypospadias</td>
<td>174</td>
<td>1.24 (1.00-1.54)</td>
<td>14</td>
</tr>
<tr>
<td>Limb reduction defects</td>
<td>96</td>
<td>1.24 (0.96-1.61)</td>
<td>27</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>96</td>
<td>1.33 (1.02-1.72)</td>
<td>9</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>41</td>
<td>0.82 (0.57-1.17)</td>
<td>13</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>24</td>
<td>1.27 (0.78-2.09)</td>
<td>21</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>63</td>
<td>0.69 (0.51-0.94)</td>
<td>5</td>
</tr>
</tbody>
</table>

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

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

† All heart defects.
‡ Cleft lip with or without cleft palate.
§ Includes jejunal, ileal, and multiple small-intestinal atresias.

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

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

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

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

In Table 3, adjusted ORs are presented for the association between maternal BMI and the 16 birth defect categories, stratified by isolated and multiple birth defects. For most of the categories of birth defects, the percentages of cases with multiple birth defects were less than 25%, except for esophageal atresia (59.7%), anorectal atresia (54.7%), and omphalocele (42.9%) (Table 3). Although there was some loss of precision owing to this stratification, the same pattern as described earlier was observed among infants with isolated birth defects, ie, a positive association between maternal obesity and the 7 categories of birth defects described earlier and a strong inverse association between maternal obesity and gastrochisis. Based on differences in the ORs of 25% or more, 8 of the 16 birth defect categories had higher ORs for obesity among the subgroup with multiple birth defects, 5 had higher ORs among the subgroup with isolated birth defects, and 3 had no meaningful difference in the magnitude of the ORs across these subgroups.

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

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

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

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

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

Other potential limitations of this study include the use of self-reported height and prepregnancy weight and the possibility of recall bias for these variables. Studies that have compared self-reported height and weight with measurements of height and weight among US adults are consistent in observing small differences. For example, Nieto-Garcia et al31 observed that women of childbearing age underestimate their weight by 0.6% to 0.83% and overestimate their height by 0.40% to 0.42% and that obese women underestimate their weight by a larger amount, ie, 1.5%. In our study, women were asked to recall their weight prior to becoming pregnant, about 18 to 20 months before their interview. To the extent that errors in reporting are similar among case mothers and control mothers, nondifferential misclassification may have been introduced into our estimates, resulting in a bias toward the null. Differential misclassification of BMI probably did not occur, as case mothers would be unlikely to overestimate or underestimate their prepregnancy weight compared with control mothers.

A total of 3.7% of cases and 4.0% of controls were missing values for BMI. Seventy-one percent of these missing values were the result of mothers reporting weight but not height. Of those women who did not report height, 87.7% were non-US-born Hispanic women. Very few women failed to report their prepregnancy weight (1.2% of cases and 1.1% of controls), again suggesting that differential reporting of weight is probably not an important concern in this study. Also, the fact that large prospective studies, which are not susceptible to recall bias, observed associations of very similar magnitude to ours for maternal obesity and all of the birth defects in aggregate,38 spina bifida,32,33 heart defects,39 and oral clefts40 suggests that the associations we observed for these birth defects are not explained by recall bias.

Our findings for gastroschisis remained the same after adjustment for maternal age, a known risk factor for gastroschisis.41 The fact that both younger maternal age and lower BMI are strong risk factors for gastroschisis suggests that the etiology of gastroschisis may differ substantially from the etiology of birth defects that are positively associated with maternal obesity.

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

This study and previous studies adjusted findings for supplementation with vitamins containing folic acid. Thus, differences between obese and nonobese women in daily multivitamin use prior to conception do not explain the effects observed for obesity. Two recent studies have linked other health behaviors with an increased risk for neural tube defects. Carmichael et al37 observed that physically active women had a 30% to 50% lower risk for neural tube defect–affected pregnancies independent of maternal obesity. In a subsequent study, Carmichael et al38 observed that when present during the first trimester of pregnancy, diets to lose weight, fasting diets, and eating disorders were associated with an increased risk of delivering offspring affected by neural tube defects independent of maternal obesity. They suggested that food restriction might increase the risk of neural tube defects via decreased availability of micronutrients or via ketosis, which accompanies reduced food intake and fasting.

Our study supports previous evidence as well as provides new evidence for the associations between mater-
nal obesity and particular categories of birth defects. Future inquiries are needed to unravel the underlying reasons for these associations.

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Author Contributions: Dr Waller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Waller, Shaw, Rasmussen, Hobbs, Canfield, Siega-Riz, and Correa. Analysis and interpretation of data: Waller, Shaw, Rasmussen, Hobbs, Canfield, Siega-Riz, and Correa. Drafting of the manuscript: Waller, Shaw, Hobbs, Canfield, Siega-Riz, and Correa. Critical revision of the manuscript for important intellectual content: Waller, Shaw, Rasmussen, Hobbs, Canfield, Siega-Riz, and Correa. Statistical analysis: Waller, Shaw, Canfield, Gallaway, and Correa. Obtained funding: Shaw, Hobbs, and Canfield. Administrative, technical, and material support: Canfield and Gallaway. Study supervision: Waller.

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Additional Contributions: Suzanne Gilboa, PhD, and Lilah M. Besser, MSPH, of the Centers for Disease Control and Prevention assisted with replicating the analysis of these data.

REFERENCES


