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# Maternal periconceptional occupational exposure to pesticides and selected musculoskeletal birth defects

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## Abstract

This population-based U.S. study investigated the association between major musculoskeletal malformations and periconceptional maternal occupational pesticide exposure for a wide range of occupations. We conducted a multi-site case–control analysis using data from the National Birth Defects Prevention Study among employed women with due dates from October 1, 1997 through December 31, 2002. Cases included 871 live-born, stillborn, or electively terminated fetuses with isolated craniosynostosis, gastroschisis, diaphragmatic hernia, or transverse limb deficiencies. Controls included 2857 live-born infants without major malformations. Using self-reported maternal occupational information, an industrial hygienist used a job-exposure matrix and expert opinion to evaluate the potential for exposure to insecticides, herbicides or fungicides for each job held during one month pre-conception through three months post-conception. Exposures analyzed included any exposure (yes/no) to pesticides, to insecticides only, to both insecticides and herbicides (I + H) and to insecticides, herbicides and fungicides (I + H + F). We used logistic regression to evaluate the association between exposures and defects, controlling for infant and maternal risk factors. Occupational exposure to I + H + F was associated with gastroschisis among infants of women aged 20 years or older (adjusted odds ratio [aOR] = 1.88; 95% confidence

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interval [CI]: 1.16–3.05), but not for women under age 20 (aOR = 0.48; 95% CI: 0.20–1.16). We found no significant associations for the other defects. Additional research is needed to validate these findings in a separate population.

### Keywords

Pesticides; Maternal occupational exposure; Craniosynostosis; Gastroschisis; Diaphragmatic hernia; Transverse limb deficiencies

## Introduction

Major musculoskeletal birth defects, including craniosynostosis, gastroschisis, diaphragmatic hernia, and transverse limb reduction deficiencies, are an important public health issue of largely unknown etiology with evidence of increased prevalence for gastroschisis. Gastroschisis, a congenital abdominal wall fissure causing herniation of abdominal organs into the amniotic cavity, has increased in prevalence worldwide (Di Tanna et al., 2002) and in the United States (Canfield et al., 2006; Parker et al., 2010). Craniosynostosis, the premature closing of cranial sutures which can result in neurocognitive deficits (Kapp-Simon et al., 2007), occurs in 3–5/10,000 U.S. births (Cohen and MacLean, 2000). Diaphragmatic hernia, in which the abdominal organs enter the chest cavity, constricting the heart and lungs, is a severe defect found in about 2.6/10,000 U.S. births (Parker et al., 2010). Transverse limb deficiencies, the absence of distal limb structures, are the most common type of limb reduction deficiency, occurring in about 4 cases per 10,000 (Stoll et al., 1996).

The role of maternal occupational pesticide exposure in the etiology of these defects is important to assess in light of the prevalence of pesticide use, the large numbers of women in the workforce, and the generally higher exposures encountered in occupational settings. Pesticides may be categorized by their target organism, as insecticides, herbicides, or fungicides. Animal studies have found associations between diaphragmatic hernia and specific herbicides (Costlow and Manson, 1981), limb deficiencies and craniofacial defects and dithiocarbamate fungicides (Larsson et al., 1976; Varnagy et al., 2000), and skeletal abnormalities and organophosphate insecticides (Farag et al., 2003). In epidemiologic studies, various types of limb deficiencies have been investigated primarily in relation to parental agricultural occupation, with mixed results (Engel et al., 2000; Kristensen et al., 1997; Lin et al., 1994; Schwartz et al., 1986; Schwartz and LoGerfo, 1988), and one study of maternal occupations in general did not find associations (Shaw et al., 1999). A study of birth defects and farming found no significant elevations in either gastroschisis or craniosynostosis in farming families compared to non-farming families (Kristensen et al., 1997), a study of craniosynostosis and maternal occupations (Bradley et al., 1995) found no associations, but did not specifically assess pesticide exposure, and no human studies were found for diaphragmatic hernia.

In summary, most previous research focused on agricultural work as a proxy for occupational pesticide exposure, which primarily reflects herbicide exposure, and few epidemiologic studies have examined maternal occupational pesticide exposure in relation to gastroschisis, craniosynostosis or diaphragmatic hernia. Additionally, most studies combined cases of isolated defects with cases having additional defects, and most limb reduction studies combined sub-types, which can have different etiologies. Using self-reported interview data from the National Birth Defects Prevention Study (NBDPS) and expert review by an industrial hygienist, this multi-center population-based study assessed the potential for periconceptional maternal insecticide, herbicide, and fungicide exposure in non-agricultural and agricultural occupations, and examined whether isolated craniosynostosis, gastroschisis, diaphragmatic hernia and transverse limb deficiencies are associated these exposures.

## Methods

### Study design and participants

We analyzed data from the NBDPS, a U.S. multisite population-based study of risk factors for birth defects (Yoon et al., 2001). The NBDPS collects environmental, clinical, nutritional, behavioral, employment and sociodemographic information via maternal computer-assisted telephone interview. NBDPS cases are live-born infants (all centers), stillborn infants (all centers except New Jersey and New York), or electively terminated fetuses (all centers except New Jersey, New York, and Massachusetts), identified using active surveillance systems, and whose medical record data are abstracted and reviewed by clinical geneticists. Defects classified as part of a known or strongly suspected chromosomal or single gene disorder are excluded. NBDPS controls are live-born infants with no major birth defects identified, randomly selected from birth certificates (Centers for Disease Control and Prevention (CDC)-Atlanta [2001–2002], Iowa, Massachusetts, and New Jersey) or hospital records (Arkansas, California, CDC-Atlanta [1997–2000], New York, Texas).

The current analysis used data from eight NBDPS study sites (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, and CDC-Atlanta) for mothers of case and control infants with due dates or birth dates from October 1, 1997 to December 31, 2002. The study sample was restricted to infants whose mothers were employed at any time during the periconceptional period (1 month prior to conception to 3 months post-conception) to avoid confounding by factors that may be associated with employment, such as maternal health and family structure. All cases of isolated (i.e., no additional major malformations) craniosynostosis, gastroschisis, diaphragmatic hernia, and transverse limb deficiencies ascertained by the NBDPS were included. Transverse limb deficiencies were selected because it was the only limb reduction sub-type with sufficient numbers in our dataset. Due to small numbers, mothers of infants having multiple defects were excluded from the main analysis. A detailed description of these types of defects can be found in Rasmussen et al. (2003).

### Exposure assessment

The telephone interview contained questions about each job held by participating mothers during the periconceptional period, including job title, employer name, employer products and/or services, primary job duties, and substances handled. An industrial hygienist blinded to case or control status reviewed this information and assigned codes based on North

American Industry Classification System (U.S. Census Bureau, 2007) and 2000 Standard Occupational Classification (Bureau of Labor Statistics, 2000). These codes were used together with a literature-based job exposure matrix to assign the potential for exposure for each job (yes/no) to insecticides, herbicides, and fungicides. Also assessed were (1) the probability of exposure associated with each job (0, <1–33%, 34–66%, 67–89%, 90% or greater), and (2) a confidence rating (very low, low, moderate, high) summarizing the hygienist's assessment of the quality of the pesticide exposure assessment, similar to a method used previously by Samanic et al. (2008).

Four exposure measures were identified for each job held during the periconceptional period: (1) exposure to any of the three pesticide types; (2) exposure to insecticides only; (3) exposure to insecticides and herbicides (I + H); and (4) exposure to insecticides, herbicides and fungicides (I + H + F). The comparison group for each measure consisted of those not exposed to any pesticide type. For each of the above measures, mothers reporting more than one job held during the periconceptional period were classified as exposed if at least one job was so classified. Because of extensive overlap between exposure to the three pesticide types, few or no mothers were exposed to herbicides only, fungicides only, insecticides and fungicides only, and herbicides and fungicides only; therefore, these additional exposures could not be assessed in this analysis.

### Statistical analysis

The most commonly reported jobs classified as having the potential for exposure to one or more pesticides were enumerated using their assigned standard occupational classification (SOC) codes. Distributions of the exposure variables, birth defects, and potential confounders were assessed and bivariable analysis of exposures and outcomes was conducted to compare the prevalence of exposure among the control mothers to that among the case mothers. To assess potential confounding, we examined both the association of the covariables with the exposures among the controls and with the outcomes among the unexposed using chi-square analysis. Covariables assessed as being potential confounders ($p < 0.15$) were incorporated into multivariable models. The following variables were assessed: infant sex; maternal age at delivery (<20 vs 20–34 (ref), ≥35); pre-pregnancy body mass index (≥25 kg/m$^2$ vs <25 kg/m$^2$); gravidity (any prior pregnancies vs nulliparous); singleton vs multiple birth; maternal race/ethnicity (black non-Hispanic vs white non-Hispanic, Hispanic, and other race; Hispanic vs non-Hispanic); maternal education (high school or less vs >high school); folic acid use from one month prior to conception through 1 month post-conception; and maternal smoking and alcohol use from 1 month prior to conception through three months post-conception. For consistency, study site, maternal age and race/ethnicity were included in all models. Unconditional logistic regression analysis was used to assess the association between each exposure variable and birth defect, controlling for all potential confounders. Exposure measures were analyzed in separate models. Because young maternal age is a strong risk factor for gastroschisis (Goldkrand et al., 2004; Hwang and Kousseff, 2004; Salihu et al., 2003; Vu et al., 2008), it was assessed as a potential effect modifier using stratified bivariable analysis, and based on this, multivariable gastroschisis models were stratified on this variable, adjusting for the remaining potential confounders. Next, two sensitivity analyses were conducted: the first to ascertain the impact of removing women reporting a job with a low-confidence exposure score (contradictory or no information) or a job assessed as having a low (<33%) probability of exposure, and the second combining cases with additional defects (multiple cases) with the isolated cases to ascertain possible differences in risk for multiple cases.

## Results

Our study population consisted of 871 case mothers and 2857 control mothers who were employed at any time during the peri-conceptional period. Numbers of isolated cases were as follows: craniosynostosis ($n$ = 273); gastroschisis ($n$ = 258); diaphragmatic hernia ($n$ = 173); and transverse limb deficiencies ($n$ = 167). Of the 1505 jobs classified as possibly involving exposure to one or more pesticides, the most commonly reported were jobs in education or training (20.5%), food preparation and service (20.3%) and sales (15.5%). Table 1 summarizes the pattern and combinations of maternal occupational pesticide exposures and shows considerable overlap by pesticide type. Almost one-third of mothers (32.7%) or (1215/3715) were classified as occupationally exposed to any pesticides; almost all of these 1215 mothers ($n$ = 1212) were classified as exposed to insecticides. Over one-fifth (22.1%) of mothers were classified as exposed to insecticides only, and 8.4% were classified as exposed to all three pesticide types.

Table 2 shows the distribution of infant and maternal characteristics among case and control mothers. Compared to controls, mothers of infants with isolated craniosynostosis, gastroschisis and transverse limb deficiencies were less likely to be non-Hispanic black; gastroschisis and transverse limb deficiency case mothers were more likely to be Hispanic; and craniosynostosis case mothers were more likely to be non-Hispanic white. Craniosynostosis and diaphragmatic hernia cases were more likely to be male. Craniosynostosis case mothers were more likely to be age 35 or older, were less likely to have had a singleton birth and more likely to have taken folic acid supplements. Gastroschisis case mothers were four times more likely than controls to be under age 20. Consistent with their young age, the latter were less likely to have more than a high school education, and less likely to have had previous pregnancies. These mothers were also less likely to be overweight and more likely to be underweight prior to pregnancy, more likely to have smoked and less likely to have taken folic acid supplements during the periconceptional period.

The number and proportion of isolated musculoskeletal cases by exposure status are shown in Table 3. About one-third (32.3%) of control mothers were classified as occupationally exposed to pesticides during the periconceptional period. A higher proportion of gastroschisis case mothers (42.8%) were classified as exposed to pesticides. This difference for gastroschisis was also seen for combined exposure to I + H + F. Exposure proportions for craniosynostosis, diaphragmatic hernia and transverse limb deficiencies were similar to those for the controls across exposure measures.

Table 4 shows crude ORs for the four exposure measures and each isolated musculoskeletal defect, and ORs adjusted for maternal and infant characteristics associated with both exposure and outcomes in the dataset. In crude analysis, positive associations were found for

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gastroschisis and exposure to any pesticide (OR = 1.57; 95% CI: 1.21–2.03) and exposure to I + H + F (OR = 2.35; 95% CI: 1.61–3.42). These associations were attenuated in the multivariate analysis (OR = 1.08; 95% CI: 0.81–1.44 for exposure to any pesticide; and OR = 1.36; 95% CI: 0.89–2.08 for exposure to I + H + F). For craniosynostosis, crude and adjusted ORs were near null. For diaphragmatic hernia, near-null ORs were found for exposure to insecticides and herbicides only; for the other exposure measures, associations were negative but not statistically significant. For transverse limb deficiencies, the ORs were near null, except for exposure to insecticides and herbicides only, where the adjusted OR was elevated but not statistically significant. Because crude ORs for any pesticide exposure and gastroschisis were elevated in mothers age 20 and older (OR = 1.43; 95% CI: 1.04–1.95; exposed cases = 68) versus in mothers under age 20 (OR = 0.86; 95% CI: 0.51–1.44; exposed cases = 42), the multivariate gastroschisis models were stratified on maternal age, (age < 20 vs 20), adjusting for potential confounders. Adjusted ORs for these models are shown in Table 5. For exposure to I + H + F, a positive association with gastroschisis is seen in women age 20 and older (OR = 1.88; 95% CI: 1.16–3.05) while for women under age 20 the point estimate, was in the opposite direction (OR = 0.48; 95% CI: 0.20–1.16). We observed no statistically significant point estimates for the other three exposure measures by age group.

These analyses were repeated excluding 899 women reporting jobs assessed as having low-confidence exposure information or low probability of exposure. The case–control composition of these exclusions was similar to that of the dataset as a whole. Multivariate results for gastroschisis and exposure to I + H + F among women age 20 and older were similar to that of the main analysis (OR = 1.77; 95% CI: 1.04–3.02). For exposure to any pesticide, point estimates for women age 20 and older increased from 1.18 (95% CI: 0.84–1.64) in the main analysis to OR = 1.68 (95% CI: 1.05–2.69) in this sensitivity analysis. A second sensitivity analysis combining cases having multiple defects ($N$ = 110) with cases having a single defect for each of the four defects also found a statistically significant elevation in risk for gastroschisis among women age 20 and older classified as exposed to I + H + F (OR = 1.80; 95% CI: 1.12–2.89), consistent with our original finding (please refer to online supplementary Tables 5a and 5b for details). In both sensitivity analyses, patterns of associations for the unstratified gastroschisis, craniosynostosis, diaphragmatic hernia and transverse limb deficiency models were similar to those of the main analysis (please refer to online supplementary Tables 4a and 4b for details).

## Discussion

This study examined potential occupational exposure to insecticides, herbicides and fungicides based on job descriptions and expert industrial hygienist ratings to estimate the risk for selected major musculoskeletal defects associated with these exposures. About one-third of mothers were potentially exposed to one or more of these pesticide types, and insecticide exposure accounted for most of these exposures. No literature is available to be compared with these findings. The jobs most commonly observed in this study as having potential pesticide exposure include those in education or training, food preparation and service, and retail sales. There is little or no information from other studies on the potential for pesticide exposure in these occupational groups.

After controlling for maternal characteristics relevant to both exposure and outcome, we found an elevated risk of having an infant with isolated gastroschisis among mothers age 20 and older who were categorized as occupationally exposed to all three pesticide types (I + H + F) (OR = 1.88; 95% CI: 1.16–3.05), but not among mothers under age 20 who were similarly exposed. Thus, although very young maternal age is itself a risk factor for gastroschisis, our age-stratified analysis found exposure to I + H + F to be a risk factor for this birth defect only among mothers age 20 or older. Similar results for this exposure measure were found in the two sensitivity analyses we conducted: excluding women reporting jobs assessed as having low confidence/probability of exposure, and adding cases with additional defects. Our finding of statistically non-significant negative associations for infants of women under age 20 is difficult to interpret, and might be elucidated in additional research using a separate population.

The above findings for mothers age 20 and older are consistent with those of previous studies which have found similar age-dependent patterns for gastroschisis and other types of maternal periconceptional exposures. Lupo et al. (2012) found an association between occupational exposure to polycyclic aromatic hydrocarbons and gastroschisis among mothers aged 20 and over, but not among those under age 20. Feldkamp et al. (2008) found a similar pattern of results for maternal smoking. Werler et al. (2009) found an increased risk for gastroschisis among infants of mothers age 25 and older who smoked or used non-aspirin NSAIDS or bronchodilators, but not among infants of younger mothers reporting these behaviors. Werler et al. hypothesized that uterine vascular damage from chronic exposures to these agents may be a mechanism for gastroschisis in older women. Similarly, it is possible that our gastroschisis results for women age 20 and older may be explained, at least in part, by some sort of pesticide-related cumulative effect over time as they age because these women, who were exposed to all three pesticides, had the highest risk in our study, and represented the only statistically significant increased risk found. However, no literature regarding specific mechanisms of pesticides with respect to gastroschisis have yet been identified for comparison, and chemical structures of various pesticides differ. The only other study that examined gastroschisis in relation to occupation (Kristensen et al., 1997) looked at farm families vs non-farm families and found no association, but this study focused on agricultural occupation only and cases likely included those with additional defects. Therefore, additional research examining women in a variety of occupations is needed to confirm our findings.

Our findings for gastroschisis are important in light of the increases in prevalence worldwide from 0.29/10,000 births in 1974 to 1.66/10,000 births in 1998 (Di Tanna et al., 2002), and in the U.S. from 3.73/10,000 births (1999–2001) to 4.49/10,000 births (2004–2006) (Canfield et al., 2006; Parker et al., 2010). These increases over time appear to be independent of the strongest risk factor: young maternal age (Loane et al., 2007; Vu et al., 2008), suggesting changes in environmental exposures could potentially be a factor.

The current study found no statistically significant associations with any occupational pesticide exposure measure and craniosynostosis. These findings are consistent with previous research, though it is difficult to compare due to differences in study design. Bradley et al. (1995) compared occupations with potential exposure to toxic agents to a reference group of professional, managerial, technical, and administrative support occupations and found no associations for maternal occupation, but this study did not assess exposure to pesticides specifically. Kristensen et al. (1997) found no significant differences in craniosynostosis prevalence between farm and non-farm families in Norway, but this study was limited to farming-related occupations only. No significant associations between maternal occupational pesticide exposure and diaphragmatic hernia were found in the current study. No other human studies have been conducted to date, although one animal study found associations with exposure to the chlorophenoxy herbicide 2,4-dichloro-phenyl-p-nitrophenyl ether (nitrofen) in rats (Costlow and Manson, 1981), so additional research is needed. We also did not find significant associations with respect to transverse limb deficiencies. Similar to our findings, Shaw et al. (1999) did not find an association between longitudinal, transverse and amniotic band limb deficiencies in relation to maternal occupational pesticide exposure in a variety of occupations, and Lin et al. (1994) did not find associations for isolated limb reduction deficiencies in relation to potential parental occupational exposure. Among studies that focused specifically on agricultural occupations, results were mixed. Schwartz et al. (1986) found a higher prevalence of limb reduction deficiencies if either parent worked in agriculture, Kristensen et al. (1997) found a higher prevalence in these birth defects in grain farmers combined with pesticide purchase, and Engel et al. (2000) found an elevated risk of limb defects (syndactyly, polydactyly syndactyly and “other limb reductions”) among infants of mothers engaged in agricultural occupations. On the other hand, no significant associations were found for isolated limb reduction deficiencies in relation to parental agricultural occupation (Lin et al., 1994; Schwartz and LoGerfo, 1988), although these latter two studies, in contrast to our analysis, found elevated risks for limb reduction deficiencies having additional defects. These studies investigating occupational pesticide exposure in relation to limb reduction defects are difficult to compare with the current study because most focused on agricultural occupations, and we did not have the statistical power in this study to assess limb defects in relation to these occupations. Comparability was also limited by the fact that some studies combined paternal and maternal occupational exposure, and most examined all limb reduction deficiencies combined or those not specifically including transverse limb deficiencies, and did not separate isolated from multiple defects.

### Strengths and limitations

This analysis was based on a multi-center population-based case control study, which provided sufficient numbers of musculoskeletal defect cases and sub-groups of these cases for a robust analysis of most exposure measures. This study also employed a detailed survey instrument that in additional to occupation, asked about demographics, lifestyle and medical history, thereby enabling many potential confounders to be assessed and controlled for. Case medical records were abstracted and reviewed by clinical geneticists using rigorous standards for inclusion in the study. Using a literature-based job-exposure matrix and subject-specific evaluation by an experienced industrial hygienist blinded to case–control status, this study systematically examined maternal occupational exposure to the major types of pesticides, including insecticides, herbicides and fungicides, and the risk for selected musculoskeletal defects, using information from a wide range of occupations. Few other studies have evaluated occupational exposure to pesticides using expert raters, and evidence exists suggesting that this type of exposure information has higher validity than information based on self-report or job exposure matrices alone (Teschke et al., 2002). Additionally, most previous studies combined multiple and isolated defects, which can have different etiologies, while we were able to restrict our analysis to isolated defects due to large numbers of cases.

Due to the relatively large numbers of statistical comparisions we conducted in this study, it is possible that our findings of an association between gastroschisis and exposure to all three pesticide types among women age 20 and older were due to chance. Several issues related to exposure assessment also exist. We were not able to assess the impact of specific pesticides or chemical classes of pesticides such as organophosphates, organochlorines, or chlorophenoxy herbicides because this information was not available. Secondly, because we did not have the same level of exposure assessment for paternal occupational exposures, we did not incorporate it into our analysis. However the effects of paternal pesticide exposures are currently being evaluated by other researchers of the NBDPS because previous research suggests that paternal occupations with the potential for pesticide exposure are associated with birth defects (Bradley et al., 1995; Garcia, 1998; Garry et al., 1996; Shi and Chia, 2001). Additionally, this analysis did not have the data to assess non-occupational sources of pesticide exposure, such as residence in an agricultural area, which have been linked to gastroschisis (Mattix et al., 2007; Waller et al., 2010), and limb deficiencies (Schwartz and LoGerfo, 1988; Shaw et al., 1999). However, occupational exposures are generally higher than environmental exposures, and absence of environmental source information is not expected to result in systematic bias in our results. Finally, because some jobs in this study were assessed as having a low probability of exposure or low confidence in the measures used to assess exposure, the potential for exposure misclassification existed. We addressed this concern by running a sensitivity analysis excluding women whose jobs were assessed as having either low confidence or low probability of exposure. This yielded results similar to those of the main analysis, with stronger associations for our main finding, increasing our confidence in these results.

## Conclusion

This population-based case control study found statistically significant associations for gastroschisis and periconceptional maternal occupational exposure to combined insecticides, herbicides and fungicides in infants of mothers age 20 and older, but not in mothers under age 20. This is important in light of the increased prevalence of gastroschisis in recent years. Additional research is needed to validate these results in a separate population. Future research using the current population will focus on the role of other periconceptional pesticide exposure metrics in the risk for major musculoskeletal defects, including exposure frequency, intensity and cumulative exposure.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijheh.2013.06.003.

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## Table 1

Pattern of maternal occupational pesticide exposures (*N* = 3715), National Birth Defects Prevention Study, 1997–2002.

| **Exposure type** | ***N*** | **%** |
|---|---|---|
| **Any pesticide** | **1215** | **32.71** |
| Any insecticides[a] | 1212 | 32.62 |
| Any herbicides[a] | 387 | 10.42 |
| Any fungicides[a] | 319 | 8.59 |
| Insecticides only | 821 | 22.10 |
| Herbicides only | 3 | 0.08 |
| Fungicides only | 0 | 0.00 |
| Insecticides and herbicides only | 72 | 1.94 |
| Insecticides and fungicides only | 7 | 0.19 |
| Herbicides and fungicides only | 0 | 0.00 |
| Insecticides, herbicides and fungicides only | 312 | 8.40 |
| **No exposure** | **2500** | **67.29** |
| **Total** | **3715** | |

13 participants had missing exposure information.

[a]Includes exposure to the other two pesticide types.

## Table 2

Selected infant and maternal characteristics for controls and cases with selected isolated musculoskeletal defects, National Birth Defects Prevention Study, 1997–2002.

| | **Controls (*N* = 2857) *N* (%)** | **Craniosynostosis (*N* = 273) *N* (%)** | **Gastroschisis (*N* = 258) *N* (%)** | **Diaphragmatic hernia (*N* = 173) *N* (%)** | **Transverse limb deficiency (*N* = 167) *N* (%)** |
|---|---|---|---|---|---|
| *Infant characteristics* | | | | | |
| Sex | | | | | |
| Male | 1417 (49.6) | 193 (70.7)* | 122 (47.3) | 106 (61.3)* | 85 (50.9) |
| Female | 1438 (50.4) | 80 (29.3) | 136 (52.7) | 67 (38.7) | 82 (49.1) |
| Singleton birth | | | | | |
| Yes | 2763 (96.7) | 255 (93.4)* | 254 (98.5) | 164 (94.8) | 158 (94.6) |
| No | 94 (3.3) | 18 (6.6) | 4 (1.6) | 9 (5.2) | 9 (5.4) |
| *Maternal characteristics* | | | | | |
| Age at delivery | | | | | |
| <20 | 208 (7.3) | 13 (4.8)* | 81 (31.4)* | 15 (8.7) | 17 (10.2) |
| 20–34 | 2213 (77.5) | 194 (71.1) | 173 (67.1) | 137 (79.2) | 129 (77.3) |
| ≥35 | 436 (15.3) | 66 (24.2) | 4 (1.6) | 21 (12.1) | 21 (12.6) |
| Race/ethnicity | | | | | |
| Non-Hispanic White | 1885 (66.2) | 215 (78.8)* | 153 (59.5)* | 118 (68.2) | 110 (65.9)* |
| Non-Hispanic Black | 359 (12.6) | 8 (2.9) | 18 (7.0) | 14 (8.1) | 10 (6.0) |
| Hispanic | 477 (16.7) | 37 (13.6) | 67 (26.1) | 34 (19.7) | 41 (24.6) |
| Other | 128 (4.5) | 13 (4.8) | 19 (7.4) | 7 (4.1) | 6 (3.6) |
| Education | | | | | |
| <High school | 266 (9.3) | 17 (6.3) | 46 (18.0)* | 18 (10.4) | 16 (9.6) |
| High school | 690 (24.2) | 64 (23.5) | 110 (43.1) | 42 (24.3) | 45 (27.0) |
| >High school | 1895 (66.5) | 191 (70.2) | 99 (38.8) | 113 (65.3) | 106 (63.5) |
| Prior pregnancies | | | | | |
| Yes | 1993 (69.8) | 192 (70.3) | 132 (51.2)* | 115 (66.5) | 106 (63.5) |
| No | 863 (30.2) | 81 (29.7) | 126 (48.8) | 58 (33.5) | 61 (36.5) |
| BMI ($kg/m^2$)[a] | | | | | |

| | Controls ($N$ = 2857) $N$ (%) | Craniosynostosis ($N$ = 273) $N$ (%) | Gastroschisis ($N$ = 258) $N$ (%) | Diaphragmatic hernia ($N$ = 173) $N$ (%) | Transverse limb deficiency ($N$ = 167) $N$ (%) |
|---|---|---|---|---|---|
| <18.5 | 144 (5.1) | 14 (5.2) | 21 (8.2)* | 7 (4.2) | 6 (3.7) |
| 18.5–<25 | 1606 (57.3) | 144 (53.1) | 183 (71.8) | 105 (62.5) | 86 (52.4) |
| 25–<30 | 626 (22.3) | 65 (24.0) | 46 (18.0) | 35 (20.8) | 43 (26.2) |
| ≥30 | 428 (15.3) | 48 (17.7) | 5 (2.0) | 21 (12.5) | 29 (17.7) |
| Folic acid use[b] | | | | | |
| Yes | 1537 (53.8) | 171 (62.6)* | 104 (40.3)* | 90 (52.0) | 87 (52.1) |
| No | 1320 (46.2) | 102 (37.4) | 154 (59.7) | 83 (48.0) | 80 (47.9) |
| Smoking[c] | | | | | |
| Yes | 576 (20.2) | 62 (22.7) | 95 (36.8)* | 39 (22.5) | 27 (16.2) |
| No | 2281 (79.8) | 211 (77.3) | 163 (63.2) | 134 (77.5) | 140 (83.8) |
| Alcohol use[c] | | | | | |
| Yes | 1265 (44.5) | 126 (46.2) | 122 (47.5) | 71 (41.0) | 77 (46.1) |
| No | 1581 (55.6) | 147 (53.9) | 135 (52.5) | 102 (59.0) | 90 (53.9) |

Percentages may not add up to 100% due to rounding.

[a]BMI refers to body mass index prior to pregnancy.

[b]From one month prior to conception through first month of pregnancy.

[c]From one month prior to conception through third month of pregnancy.

*Variable proportions different from controls at $p < 0.05$.

## Table 3

Periconceptional maternal occupational pesticides exposures among controls and isolated cases, National Birth Defects Prevention Study, 1997–2002.

| | **Controls ($N$ = 2847)[a] $N$ (%)** | **Craniosynostosis ($N$ = 273) $N$ (%)** | **Gastroschisis ($N$ = 257)[a] $N$ (%)** | **Diaphragmatic hernia ($N$ = 171)[a] $N$ (%)** | **Transverse limb deficiency ($N$ = 167) $N$ (%)** |
|---|---|---|---|---|---|
| Any pesticide | 920 (32.3) | 84 (30.8) | 110 (42.8) | 47 (27.5) | 54 (32.3) |
| Insecticides only | 634 (22.3) | 56 (20.5) | 65 (25.3) | 31 (18.1) | 35 (21.0) |
| Insecticides and herbicides only | 54 (1.9) | 5 (1.8) | 5 (1.9) | 4 (2.3) | 4 (2.4) |
| All three types | 223 (7.8) | 23 (8.4) | 40 (15.6) | 11 (6.4) | 15 (9.0) |

[a]Missing exposures for controls ($N$ = 10), gastroschisis ($N$ = 1), diaphragmatic hernia ($N$ = 2).

### Table 4

Multivariable analysis of periconceptional maternal occupational pesticide exposure and selected isolated musculoskeletal defects in their infants, National Birth Defects Prevention Study, 1997–2002.

| | **Craniosynostosis (*N* = 273) OR (95% CI)** | **Gastroschisis (*N* = 257) OR (95% CI)** | **Diaphragmatic hernia (*N* = 171) OR (95% CI)** | **Transverse limb deficiencies (*N* = 167) OR (95% CI)** |
|---|---|---|---|---|
| *Any pesticide* | | | | |
| Crude OR | 0.93 (0.71–1.22) | 1.57 (1.21–2.03) | 0.79 (0.56–1.12) | 1.00 (0.72–1.40) |
| Adjusted OR[a] | 0.96 (0.72–1.26) | 1.08 (0.81–1.44) | 0.76 (0.54–1.09) | 0.97 (0.69–1.38) |
| *Insecticides only* | | | | |
| Crude OR | 0.90 (0.66–1.23) | 1.34 (0.99–1.82) | 0.76 (0.51–1.14) | 0.94 (0.64–1.39) |
| Adjusted OR[a] | 0.90 (0.66–1.24) | 0.98 (0.70–1.37) | 0.76 (0.51–1.14) | 0.90 (0.60–1.34) |
| *Insecticides and herbicides only* | | | | |
| Crude OR | 0.94 (0.37–2.39) | 1.21 (0.48–3.08) | 1.15 (0.41–3.23) | 1.26 (0.45–3.55) |
| Adjusted OR[a] | 1.25 (0.48–3.25) | 0.60 (0.20–1.80) | 1.09 (0.39–3.10) | 1.69 (0.59–4.85) |
| *All three types* | | | | |
| Crude OR | 1.05 (0.67–1.66) | 2.35 (1.61–3.42) | 0.77 (0.41–1.44) | 1.15 (0.66–2.00) |
| Adjusted OR[a] | 1.13 (0.69–1.84) | 1.36 (0.89–2.08) | 0.69 (0.36–1.34) | 1.06 (0.59–1.92) |

[a]Odds ratios adjusted for the following maternal variables: craniosynostosis (Black vs rest; Hispanic vs non-Hispanic; age <20; singleton vs multiple birth; high BMI; folic acid use during B1-P1; study site); gastroschisis (Black vs rest; Hispanic vs non-Hispanic; age < 20; gravidity; education high school or less; high BMI; smoking during B1-P3; folic acid use during B1-P1; study site); diaphragmatic hernia (Black vs rest; Hispanic vs non-Hispanic; age < 20; study site); transverse limb deficiency (Black vs rest; Hispanic vs non-Hispanic; age < 20; high BMI; study site).

## Table 5

Multivariable analysis of periconceptional maternal occupational pesticide exposure and isolated gastroschisis in their infants, stratified on maternal age, National Birth Defects Prevention Study, 1997–2002.

| Exposure type | Maternal age < 20 | | | Maternal age ≥ 20 | | |
|---|---|---|---|---|---|---|
| | **Cases** | **Controls** | **OR[a] (95% CI)** | **Cases** | **Controls** | **OR[a] (95% CI)** |
| Any pesticide | 41 | 113 | 0.81 (0.47–1.41) | 66 | 778 | 1.18 (0.84–1.64) |
| Insecticides only | 31 | 68 | 1.10 (0.60–2.04) | 33 | 556 | 0.95 (0.63–1.44) |
| Insecticides and herbicides only | 1 | 5 | 0.88 (0.07–11.11) | 3 | 44 | 0.68 (0.20–2.34) |
| All three types | 9 | 40 | 0.48 (0.20–1.16) | 30 | 169 | **1.88 (1.16–3.05)** |

*Note:* N/s represent numbers of infants born to exposed mothers, and are smaller than that of the whole study group due to adjustment for covariates, some of which have missing values.

[a]Odds ratios adjusted for Hispanic vs non-Hispanic ethnicity, gravidity, maternal education high school or less, high maternal BMI, maternal smoking, maternal folic acid use, and study site. Black vs rest not controlled for due to sparse numbers in mothers under age 20.