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ADHD Medication Use During Pregnancy and Risk for Selected Birth Defects: National Birth Defects Prevention Study, 1998–2011

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Abstract

Objective—The objective of this study was to examine the prevalence of, and maternal characteristics associated with, ADHD medication use before and during pregnancy, and associations between early pregnancy ADHD medication use and risk for 12 selected birth defects.

Method—We used data from the National Birth Defects Prevention Study (1998–2011), a U.S. population–based case-control study examining risk factors for major structural birth defects.

Results—There was an increase in ADHD medication use from 1998–1999 (0.2%) to 2010–2011 (0.5%; $p < .001$). Early pregnancy ADHD medication use was more commonly reported by mothers of infants/fetuses with gastroschisis (crude odds ratio [cOR]: 2.9, 95% confidence interval [CI] = [1.2, 6.9]), omphalocele (cOR: 4.0, 95% CI = [1.2, 13.6]), and transverse limb deficiency (cOR: 3.3, 95% CI = [1.1, 9.6]).

Conclusion—ADHD medication use before and during pregnancy was rare, but the prevalence of use has increased over time. In this analysis, early pregnancy ADHD medication use was associated with three of 12 selected birth defects.

Keywords

ADHD; birth defects; medication use; pregnancy; stimulants

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Coding of drug information in the National Birth Defects Prevention Study used the Slone Drug Dictionary under license from the Slone Epidemiology Center of Boston University. Findings were presented at the 66th Annual Epidemic Intelligence Service Conference, Atlanta, GA, April 24–27, 2017; 30th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Seattle, WA, June 19–20, 2017; 50th Annual Society for Epidemiologic Research Meeting, Seattle, WA, June 20–23, 2017; 30th Annual Education Meeting for Organization of Teratology Information Specialists Members and MotherToBaby Affiliates, Denver, CO, June 24–27, 2017; and the 33rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada, August 26–30, 2017. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ADHD is a common neurodevelopmental disorder characterized by developmentally inappropriate and impairing impulsivity, hyperactivity, and inattention that affect individuals across the lifespan (Asherson, 2016). Although onset typically occurs in childhood, the estimated prevalence of ADHD among U.S. adults aged 18 to 44 is 4.4% to 5.2% (Fayyad et al., 2007; Kessler et al., 2006), and is expected to rise as the growing number of children diagnosed with, and pharmacologically treated for, ADHD age into adulthood. National U.S. data indicate there was a 42% increase in ADHD diagnoses among 4- to 17-year-old children from 2003 to 2011, with a 28% increase in ADHD medication use from 2007 to 2011 (Visser et al., 2014). Approximately two-thirds of children with ADHD may have symptoms into adulthood that could require ongoing treatment (Faraone, Biederman, & Mick, 2006). The prevalence of adult ADHD may rise as clinicians gain awareness of the unique symptom presentation of adult ADHD (e.g., inattention without hyperactivity; Larsson, Dilshad, Lichtenstein, & Barker, 2011; Montejano, Sasane, Hodgkins, Russo, & Huse, 2011; Willcutt et al., 2012), which may result in diagnosing and treating adult patients more frequently. For adults with ADHD, medication is the first-line treatment and may include prescription of stimulant medications (e.g., combination amphetamine/dextroamphetamine, methylphenidate) or the nonstimulant medication atomoxetine (Asherson, 2016; Mohundro & Wicker, 2010).

With increased frequency of ADHD diagnosis and treatment among adults (Anderson et al., 2018; McCarthy et al., 2012; Montejano et al., 2011), there is greater potential for ADHD medication use among pregnant women. Although data are limited, ADHD medication use during pregnancy appears to be increasing (Haervig, Mortensen, Hansen, & Strandberg-Larsen, 2014; Hanley & Mintzes, 2014; Louik, Kerr, Kelley, & Mitchell, 2015). In a sample of U.S. pregnant women, 0.2% reported ADHD medication use in 1998 relative to 1.3% in 2014 (Louik et al., 2015). Little is known about women who use ADHD medications before and during pregnancy. Data from two European registries (Bro et al., 2015; Haervig et al., 2014; Kallen, Borg, & Reis, 2013; Pottegard et al., 2014) and one analysis of U.S. Medicaid data (Huybrechts et al., 2018) collectively suggest that pregnant women using ADHD medications may be younger, unmarried, less educated, and have a lower income than other pregnant women. These studies also tend to suggest pregnant women using ADHD medications are more commonly nulliparous, smokers, and exposed to other medications for comorbid conditions compared with other pregnant women. To our knowledge, no studies have examined maternal characteristics associated with ADHD medication use among U.S. pregnant women outside of the Medicaid population.

Despite the reported increase in ADHD medication use among pregnant women, there is little information about ADHD medication use during early pregnancy and risks for *specific* birth defects. When considering all combined major congenital malformations or all congenital heart defects, most data from cohort and registry studies have shown no statistically increased risk for all defects after ADHD medication use in early pregnancy (Diav-Citrin et al., 2016; Haervig et al., 2014; Kallen et al., 2013; Pottegard et al., 2014; Wajnberg, Diav-Citrin, Schechtmann, & Ornoy, 2011). A recent analysis of U.S. Medicaid data indicated there may be an increased risk for any major congenital malformation and all congenital heart defects after early pregnancy methylphenidate and amphetamine exposure (Huybrechts et al., 2018). However, Huybrechts and colleagues (2018) suggested that, after

demographic and psychiatric morbidity adjustment, most associations attenuated—but a relationship remained between early pregnancy methylphenidate exposure and risk for any congenital heart defect. While clear defect patterns have rarely been reported, specific birth defects have been observed after exposure to ADHD medication in these aforementioned studies, as well as in case reports (Kopelman, Mccullar, & Heggeness, 1975; Matera, Zabala, & Jimenez, 1968; Milkovich & Van der Berg, 1977).

To address these literature gaps and previous study limitations, this analysis aimed to assess the prevalence of, and characteristics associated with, use of the most common ADHD medications before and during pregnancy, and the potential associations between maternal early pregnancy ADHD medication use and *specific* selected birth defects.

Method

Participants

We analyzed data from the National Birth Defects Prevention Study (NBDPS) on pregnancies with an estimated date of delivery (EDD) between January 1, 1998, and December 31, 2011. NBDPS was a multisite, population-based, case-control study of risk factors for more than 30 major structural birth defects (Reefhuis et al., 2015). Ten sites collaborated on NBDPS (Arkansas [AR], California [CA], Georgia [GA], Iowa [IA], Massachusetts [MA], New Jersey [NJ], New York [NY], North Carolina [NC], Texas [TX], and Utah [UT]) and ascertained data on pregnancies affected by selected birth defects using standard case definitions from birth defects surveillance systems. Cases included live births (all sites), stillbirths (all sites except NY before 2000 and NJ), and terminations (all sites except GA before 1999, MA before 2011, NY before 2000, and NJ). NBDPS focused on birth defects with unknown etiologies. Infants with known single-gene disorders or chromosomal abnormalities were excluded. Controls included liveborn infants without major birth defects randomly sampled from the same geographic region and time period as cases using data from vital records or hospital birth logs. The study was approved by institutional review boards at all participating institutions.

Mothers were invited to participate in a computer-assisted telephone interview, conducted in English or Spanish, 6 weeks to 24 months after the mother's EDD. The median time to interview was 11 months for case and 9 months for control mothers. The participation rate during the study period was 67% for case and 64% for control mothers. The interview assessed maternal demographics; health and pregnancy history; behavioral, nutritional, and occupational exposures; and over-the-counter and prescription medication, vitamin, and supplement use. Clinical data for birth defect cases were abstracted from medical records and classified by clinical geneticists and clinicians using procedures described elsewhere (Rasmussen et al., 2003; Reefhuis et al., 2015).

During the interview, mothers were asked to report the start and stop dates, duration, and frequency of medication use during the three months before and during pregnancy using calendar dates or pregnancy months. Pregnancy timing was based on estimated date of conception (2 weeks after the last menstrual period) to delivery, where pregnancy months were consecutive 30-day intervals during the time period immediately preceding and during

pregnancy. Mothers may have reported ADHD medication use (a) when asked about any diseases or illnesses occurring before and during pregnancy, with probing for medications taken to treat the indicated disease or illness and (b) when asked about any medications taken before and during pregnancy. Medications were coded using the Slone Drug Dictionary (licensed from Boston University), which links active drug components or ingredients to corresponding products. ADHD medication exposure in this analysis was defined as maternal report of use of ≥1 product(s) in any dose, duration, or frequency that include any of the following medication components: amphetamine, dextroamphetamine, combination amphetamine/dextroamphetamine, lisdexamfetamine, dexmethylphenidate, methylphenidate, methamphetamine, pemoline, or atomoxetine. The first eight components are stimulant medications, and the last component is a nonstimulant medication. All are commonly prescribed for ADHD.

Statistical Analysis

There were 31,965 cases and 11,724 controls whose mothers had EDDs between January 1, 1998 and December 31, 2011. Mothers were excluded from all analyses if they reported illicit methamphetamine use in the 3 months before conception through the end of pregnancy (207 cases; 57 controls) or had missing data on medication exposure before and during pregnancy (545 cases; 213 controls).

We estimated the prevalence of any ADHD medication exposure for all mothers combined, as well as for case and control mothers separately, during two exposure periods: (a) 3 months before conception through the end of pregnancy and (b) during pregnancy only (including the month before conception to account for imprecision in timing). We examined the time trend for ADHD medication use in 2-year increments, and estimated the prevalence of use for each month before and during pregnancy. To assess factors associated with ADHD medication use before and during pregnancy, we examined percentage distributions and used chi-square tests to compare maternal characteristics among control mothers who reported any ADHD medication use in the 3 months before conception through the end of pregnancy with those who reported no ADHD medication exposure. We considered maternal characteristics with at least a 10-percentage point difference between mothers who reported using or not using ADHD medications as meaningful differences. We examined age, race/ethnicity, education, annual household income, maternal smoking and alcohol use (both defined as any use from the month before conception through the third month of pregnancy), any folic acid use (defined as any use during the month before conception through the first month of pregnancy), pregnancy intention, number of previous births (including live and stillbirths), and prepregnancy body mass index (kg/m^2; National Heart, Lung, and Blood Institute [NHLBI], 2000). Potential differences between study sites were examined but are not reported due to low cell counts that may result in identifiable information.

To assess the association between any early pregnancy ADHD medication exposure and selected birth defects, we used logistic regression to estimate crude odds ratios (cORs) and corresponding 95% confidence intervals (CIs). We defined early pregnancy as the month before conception through the third month of pregnancy. In addition to the previously noted exclusion criteria, we excluded mothers who reported pre-pregnancy type 1 or 2 diabetes

(753 cases; 69 controls) due to its association with a number of birth defects (Correa et al., 2008) and concerns about model instability if included as a covariate. Mothers who reported use of an ADHD medication outside of early pregnancy only (nine cases; three controls) and NBDPS birth defects with fewer than three exposed cases (11,298 cases) were also excluded. Due to low statistical power, we were unable to adjust for potential confounders using multivariable models, with the exception of gastroschisis. For gastroschisis, we adjusted for and stratified by age (<20, ≥20 years) due to its strong association with young maternal age (Gill et al., 2012). We conducted a subanalysis restricting the exposure to *stimulant* ADHD medications only compared with those unexposed to any ADHD medication. Analyses were run in SPSS 22.0.

Results

Prevalence and Characteristics Associated With ADHD Medication Use

ADHD medication use in the 3 months before conception through the end of pregnancy was rare: 0.2% (98/42,667) of case and control mothers reported use during this period. The prevalence of ADHD medication use was the same for case (0.2%; 74/31,213) and control mothers (0.2%; 24/11,454). Among all exposed mothers, the most commonly reported ADHD medications contained combination amphetamine/dextroamphetamine (39.8%) or methylphenidate (37.8%). Fewer mothers reported use of other stimulant medication components and the nonstimulant atomoxetine (Figure 1). No mothers reported exposure to more than one ADHD medication component. When restricted to pregnancy only, ADHD medication use prevalence remained at 0.2% overall, as well as for case (66/31,213) and control mothers (21/11,454) specifically.

Although ADHD medication use during the 3 months before conception through the end of pregnancy was rare, there was a statistically significant increase in the prevalence of use across study years from 1998–1999 (0.2%) to 2010–2011 (0.5%; $p < .001$; Figure 2). ADHD medication use varied across the months before and during pregnancy. The prevalence of ADHD medication use was highest in the 3 months before conception and fell sharply in the first trimester of pregnancy (Figure 3).

Among control mothers, ADHD medication use before and during pregnancy was significantly more common among more highly educated women (Table 1). Although not statistically significant, ADHD medication use was more common among women who were older, non-Hispanic White, alcohol users during early pregnancy, nulliparous, or had an unplanned pregnancy.

Early Pregnancy ADHD Medication Exposure and Risk for Selected Birth Defects

There were 64 case and 20 control mothers exposed to any ADHD medication at anytime during the month before conception through the third month of pregnancy. There were 12 specific birth defects with at least three exposed cases (Table 2). ADHD medication use in early pregnancy was more commonly reported by mothers of infants/fetuses with gastroschisis (cOR: 2.9, 95% CI = [1.2, 6.9]), omphalocele (cOR: 4.0, 95% CI = [1.2, 13.6]), and transverse limb deficiency (cOR: 3.3, 95% CI = [1.1, 9.6]). After adjustment for

maternal age, the relationship between early pregnancy ADHD medication use and gastroschisis remained significant (adjusted odds ratio [aOR]: 3.0, 95% CI = [1.2, 7.4]); limiting the analysis to women ≥20 years resulted in a similar odds ratio (cOR: 3.2, 95% CI = [1.2, 8.8]). Due to small cell counts, we could not assess the association specifically among young women. We observed no statistically significant associations between ADHD medication use and the nine other birth defects examined. When only early pregnancy ADHD *stimulant* medication use was considered, results were similar (data not shown).

Discussion

ADHD medication use among women before and during pregnancy was rare (0.2%), but the prevalence of use increased from 1998–1999 to 2010–2011. There was a sharp decline in ADHD medication use in the first trimester, which corresponds to pregnancy recognition for most women (Branum & Ahrens, 2017). Compared with unexposed women, women who used ADHD medications before and during pregnancy were more commonly older (particularly ≥35 years), non-Hispanic White, more highly educated, alcohol users during early pregnancy, nulliparous, and less likely to plan their pregnancies. Although use declined during the first trimester, most women who reported ADHD medication use were exposed during early pregnancy, the period of organogenesis. We observed statistically significant associations between any early pregnancy ADHD medication use and increased risk for gastroschisis, omphalocele, and transverse limb deficiency. These findings persisted when examining any early pregnancy *stimulant* ADHD medication use only.

While prevalence estimates have varied across reports (e.g., 0.02% [1997–2008 Danish registry data; Bro et al., 2015] to 0.6% [2006–2011 U.S. commercial claims data; Hanley & Mintzes, 2014]), our findings are in line with studies indicating that ADHD medication use during pregnancy is becoming more common over time. For example, an analysis using Danish population–based registry data estimated a 100-fold increase in the incidence of ADHD medication use among pregnant women between 2003 (5/100,000 person-years) and 2010 (533/100,000 person-years; Haervig et al., 2014). In the most geographically and methodologically comparable analysis to ours, 0.3% of pregnant women in the Slone Epidemiology Center Birth Defects Study reported ADHD medication use across the entire period from 1998 to 2014, but the prevalence of use increased from 0.2% to 1.3% during the study period (Louik et al., 2015). Variations in prevalence estimates may be due to differences in study design, location, time period, medications included, or period of exposure. Despite variations, studies indicate ADHD medication use is increasing among pregnant women (cf. Hanley & Mintzes, 2014). This trend mirrors increases in ADHD medication use among all women of reproductive age (Anderson et al., 2018; Haervig et al., 2014; McCarthy et al., 2012).

Only a few European studies have examined maternal characteristics associated with ADHD medication use during pregnancy, and, to our knowledge, only one U.S. study has done so. In agreement with previous research (Bro et al., 2015; Diav-Citrin et al., 2016; Haervig et al., 2014), our findings suggest that women who use ADHD medications before and during pregnancy are more likely to be nulliparous than nonusers. Data from our analysis also align with the other U.S. report suggesting that non-Hispanic White women may be more likely to

use ADHD medications (Huybrechts et al., 2018). However, women in our study who used ADHD medications were more commonly older and more highly educated, whereas previous research suggests pregnant women who use ADHD medications are younger and less educated (Bro et al., 2015; Haervig et al., 2014; Huybrechts et al., 2018; Kallen et al., 2013; Pottegard et al., 2014). Although previous reports have indicated that pregnant women who use ADHD medications have lower incomes and are more likely to be smokers, our data also showed no associations with these constructs. It is important to note that while previous reports included relatively comparable study years to ours, other methodological differences in study design and data collection methods may contribute to these discrepant findings. It is possible there are population and cultural differences in who uses ADHD medications before and during pregnancy in the United States and Europe, as well as between U.S.-based Medicaid and general populations.

We examined several maternal characteristics not reported in previous research and found that, relative to unexposed women, women who used ADHD medications before and during pregnancy were more commonly alcohol users during early pregnancy and less likely to plan their pregnancies. Among general population studies, not stratified by sex or medication use, adults with ADHD, compared with those without, are more likely to be alcohol dependent (Bernardi et al., 2012; Kessler et al., 2006). Women with ADHD may also be at increased risk for unplanned pregnancies (Owens, Zalecki, Gillette, & Hinshaw, 2017). In this analysis, we were unable to examine the characteristics associated with ADHD medication use relative to those associated with the underlying condition. This is an important area for future research.

While previous studies have noted no increased risk for all total major malformations or all congenital heart defects combined (Diav-Citrin et al., 2016; Haervig et al., 2014; Wajnberg et al., 2011, with the exception of a noted association between methylphenidate and any congenital heart defect; Huybrechts et al., 2018), this study was among the first to examine the relationship between early pregnancy ADHD medication use and risk for *specific* birth defects. Early pregnancy ADHD medication use was associated with an increased risk for three of the 12 birth defects examined in this analysis: gastroschisis, omphalocele, and transverse limb deficiency. While previous studies have often noted no specific pattern of birth defects, gastrointestinal and limb reduction defects were observed in previous studies among women who used ADHD medications in early pregnancy (Kallen et al., 2013; Kopelman et al., 1975; Nelson & Forfar, 1971). Given limited literature on ADHD medication use in early pregnancy and risk for *specific* birth defects, and the small number of exposed cases for each of the specific birth defects in this analysis, future studies should consider replicating the results of this analysis.

Strengths of this analysis include use of a large, population-based case-control study of major structural birth defects. Clinical geneticists and pediatric cardiologists reviewed all potentially eligible cases in NBDPS to ensure eligibility and provide accurate case classification using detailed, consistent case definitions (Rasmussen et al., 2003; Reefhuis et al., 2015). The case-control design and case confirmation procedures provided an opportunity to examine the association between early pregnancy ADHD medication use and risk for *specific* birth defects, which has not been done previously. Another strength was the

exclusion of women from the analysis who reported illicit methamphetamine use before or during pregnancy, which may be associated with increased risk for some birth defects (Elliott et al., 2009; Plessinger, 1998; Sherman & Sherman, 2003) and has not been adjusted for in previous analyses. Finally, we were able to examine all reported medications used before and during pregnancy, not just medications prescribed, a limitation of previous studies using registry or commercial claims data.

There are limitations to consider. Despite the large sample, there were few women exposed to ADHD medications, resulting in reduced statistical power to examine meaningful differences by ADHD medication exposure. The small number of ADHD medication-exposed cases limited our ability to adjust for possible confounders in multivariable models and also limited our ability to examine associations between individual medication components and specific birth defects. The NBDPS interview did not ask mothers about whether they have ADHD, which limited our ability to examine diagnosis and medication use separately and may have resulted in underreporting of ADHD medication use. Although designed to be population-based, there may be differences in those participating or not participating in NBDPS. There was also a potential for recall bias as ADHD medication use was ascertained via maternal report up to 24 months after the EDD, and exposure was not verified from other sources.

Our findings support monitoring of ADHD medication use among pregnant women; early pregnancy ADHD medication use was associated with an increased risk for three of 12 defects examined: gastroschisis, omphalocele, and transverse limb deficiency. Despite the increased risk in this analysis, the body of literature on early pregnancy ADHD medication use and specific birth defect risks is limited. ADHD medication use among pregnant women in this study was rare, as are the individual birth defects we observed to be at increased risk. This indicates that the absolute risk for having a baby born with each of the specific birth defects noted as at increased risk in this analysis after early pregnancy ADHD medication use is relatively low. Medication may be necessary to manage a woman’s condition, and women along with their clinicians should carefully consider possible consequences of untreated ADHD. It is important for physicians to discuss ADHD medication use with pregnant women and women who could become pregnant to adjust or maintain treatment plans before and during pregnancy.

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Biographies

Kayla N. Anderson, PhD, is an Epidemic Intelligence Service (EIS) officer in the Birth Defects Branch at the National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (CDC). Her primary research interests are in maternal preconception and pregnancy health and its effects on infant and child health outcomes, including birth defects, neurodevelopmental delays, and children's long-term psychosocial health. Her research spans preconception and pregnancy health exposures including fertility treatments, medication exposures, and infectious diseases. During CDC's Level 1 emergency response to the Zika virus epidemic, she served on the

Pregnancy and Birth Defects Task Force, Colombia Team as a senior epidemiologist on the Zika en Embarazadas y Ninos cohort (ZEN) cohort study, a large, prospective cohort study examining the effects of Zika virus infection on children's long-term health and developmental outcomes until age 4. Her general interests also include delineating the effects of prenatal exposures from family environment influences on children's health outcomes. A family and developmental scientist by educational training, she received her PhD and MA from the University of Minnesota–Twin Cities in Family Social Science.

Annelise C. Dutton (née Arth), MPH, is currently a MSN student at Emory University. During CDC's Zika Emergency Response, she served as an epidemiologist with the Pregnancy and Birth Defects Task Force and was an ORISE Fellow with CDC's Division of Congenital and Developmental Disorders. Lead author publications include research related to costs of inpatient hospitalizations related to birth defects, estimation of worldwide folic acid preventable spina bifida and anencephaly cases, and folic acid supplement use among women with previous pregnancies affected by neural tube defects. She was the winner of the 2016–2017 James G. Wilson Publication award for best paper published in the journal Birth Defects Research.

Cheryl S. Broussard, PhD, is an epidemiologist and associate Director for Science in the Division of Congenital and Developmental Disorders of the NCBDDD at the CDC in Atlanta, Georgia. She developed and formerly served as the lead scientist for CDC's Treating for Two: Safer Medication Use in Pregnancy initiative, which has contributed to one of CDC's priorities to strengthen public health–health care collaboration. She recently became a member of the prestigious Teratogen Information System (TERIS) Advisory Board. She led a federal interagency workgroup on medications and pregnancy and has served on expert committees focused on prenatal use of opioid drugs, autoimmune medications, chemotherapeutic agents, and vaccines. In 2016, she was honored at the White House as a recipient of the Presidential Early Career Award for Scientists and Engineers in recognition of her work protecting and promoting the health of pregnant women and babies through innovative research at the frontiers of science and technology. She contributed to CDC's Zika Virus Response as a member of the Pregnancy and Birth Defects Task Force. She joined CDC in 2007 as an EIS officer and, since completing EIS, has served as an advisor to the program. She received her PhD in epidemiology from the University of Texas (UT) School of Public Health at Houston and her MA in health education from UT-Austin. Her first career was as a middle school science teacher, and she has a passion for promoting epidemiology education for secondary school students.

Sherry L. Farr, PhD, is a senior epidemiologist in the NCBDDD at the CDC. She began her career at CDC 14 years ago as an EIS officer in the CDC's Division of Reproductive Health. She has published over 60 peer-reviewed papers on reproductive epidemiology and disseminated research findings through scientific reports and national presentations. Her work has been used by state health departments to evaluate policies, national organizations to inform clinical recommendations, and CDC to improve data collection systems and establish priorities. She focuses her current work on the epidemiology of congenital heart defects across the lifespan. Her previous work focused on women's mental health and

substance use, chronic diseases among women of reproductive age, assisted reproductive technology, and mother-to-child transmission of HIV. She has mentored EIS officers, research fellows, MPH students, and ob/gyn residents. She received her master's degree and PhD in epidemiology from the University of North Carolina at Chapel Hill.

Jennifer N. Lind, PharmD, MPH, is a pharmacist and epidemiologist in CDC's Birth Defects Branch and a lieutenant commander in the U.S. Public Health Service. She received her Doctor of Pharmacy degree from Florida A&M University in 2007 and master of public health from Georgia State University in 2012. After receiving her MPH, she completed a fellowship as an EIS officer in CDC's National Center for Chronic Disease Prevention and Health Promotion. She is currently the lead scientist for the Division of Congenital and Developmental Disorders's Treating for Two initiative. Her work focuses on safer medication use during pregnancy and researching the prevention and control of risk factors for birth defects. Her general interests include maternal and child health epidemiologic research and pharmacoepidemiology.

Susanna N. Visser, DrPH, MS, is associate Director for Policy in the Division of Vector-Borne Diseases for the National Center on Emerging and Zoonotic Infectious Diseases. During CDC's 2016–2017 Zika Emergency Response, she served as Partnerships Lead for the Partnerships Team within the Policy and Partnerships Unit. Before her deployment to the Level 1 Emergency Response, she served as lead epidemiologist of CDC's Child Development Studies Team for over a decade in which she specialized in the direction of multisite community-based studies of mental and behavioral disorders of children. She received her doctorate in public health and master of science in epidemiology from the University of Illinois at Chicago. She led an agency initiative to improve the treatment of behavioral disorders in young children, using policy-based and evidence-based intervention methods. She served as the committee epidemiologist for the American Academy of Pediatrics's 2006–2016 ADHD diagnostic and treatment guidelines committee. She has content area expertise in the policy and epidemiology of externalizing disorders and best practices for the diagnosis and treatment of these disorders. Her technical expertise includes the design and analysis of population-based epidemiological studies of neurobehavioral and mental health conditions. Lead author publications include research related to generating population-based estimates of ADHD, rates of medication treatment among youth with ADHD, and factors associated with ADHD medication treatment. She has served as the principal investigator of community-based epidemiologic studies of mental disorders of childhood, a national follow-back survey of children with ADHD and Tourette syndrome, and has participated in several federal, longitudinal research projects investigating developmental outcomes of youth with physical and social risk factors. She received the 2014 Maternal Child Health Epidemiology Young Professionals Achievement Award from the Coalition for Excellence in MCH Epidemiology.

Elizabeth C. Ailes, MPH, PhD, is an epidemiologist in the Birth Defects Branch, Division of Congenital and Developmental Disorders of the NCBDDD at the CDC in Atlanta, Georgia. Much of her research has supported CDC's Treating for Two: Safer Medication Use in Pregnancy initiative, which has contributed to one of CDC's priorities to strengthen

public health–health care collaboration. Her work has focused on medication use among pregnant women and women of reproductive age, risk factors for birth defects, and the diagnosis of and screening for major birth defects. She contributed to CDC's Zika Virus Response as a member of the Pregnancy and Birth Defects Task Force. She joined the Branch in 2011 as an EIS officer. Prior to becoming an EIS officer, her research at CDC focused on the epidemiology of food-borne and waterborne diseases. She received her PhD in epidemiology from Emory University and her MPH in the epidemiology of microbial diseases from Yale University.

Stuart K. Shapira, MD, PhD, is associate Director for Science and Chief Medical Officer in the NCBDDD at the CDC. Prior to this role, he served as a medical officer on the Pediatric Genetics Team in NCBDDD. His research activities included dysmorphology of autism, birth defects epidemiology, and newborn screening. He received his PhD degree in genetics and his MD degree, both from the University of Chicago. He completed a residency in pediatrics and a clinical fellowship in genetics and metabolism at Boston Children's Hospital. He also completed dual research fellowships in genetics and metabolism, and in allergy and immunology at Harvard Medical School. He is board-certified in clinical genetics, biochemical genetics, and molecular genetics. Prior to joining the NCBDDD in 2005, he practiced clinical genetics and metabolic genetics at Baylor College of Medicine in Houston and at the University of Texas Health Science Center in San Antonio. He currently serves as CDC liaison to the Committee on Genetics for the American Academy of Pediatrics, as chairman of the Dysmorphology Workgroup for the Centers for Autism and Developmental Disabilities Research and Epidemiology, and as NCBDDD liaison of the Interagency Collaborative to Advance Research in Epilepsy. He has authored and coauthored more than 100 journal articles, book chapters, and abstracts, and he has been an invited speaker at numerous regional, national, and international scientific conferences.

Jennita Reefhuis, PhD, is acting branch chief of the Birth Defects Branch in the NCBDDD at the CDC. She is an epidemiologist with over 20 years of experience in the field of birth defects epidemiology. For the last 16 years, she has worked with the National Birth Defects Prevention Study (NBDPS) at the CDC. Her research interests include the association between birth defects and a variety of different risk factors, including fertility treatments, antidepressants, and occupations. Her publications include topics on exposures such as Zika virus infection, antibiotic use, and selective serotonin reuptake inhibitor (SSRI) use, among others. She received her PhD from the University of Groningen and her MSc from Radboud University, both in the Netherlands.

Sarah C. Tinker, PhD, MPH, is an epidemiologist in the Birth Defects Branch of CDC's NCBDDD. She serves as the principal investigator for the Georgia sites of the NBDPS and the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS). Both NBDPS and BD-STEPS are population-based multisite studies of major structural birth defects. Her research focuses on identifying modifiable risk factors for birth defects, with specialized focus on the prevention of neural tube defects and application of novel epidemiologic methods to birth defects research. She received her PhD in epidemiology and master of public health from Emory University. During CDC's emergency response to the Zika virus

epidemic, she served on the Pregnancy and Birth Defects Task Force and conducted field work in Colombia to establish an enhanced surveillance system to identify pregnant women with Zika infection and to follow their infants to identify the spectrum of adverse outcomes associated with congenital Zika virus infection. She has received awards from CDC and NCBDDD for Excellence in Epidemiology, Excellence in Workforce Wellness, and Excellence in Project Management.

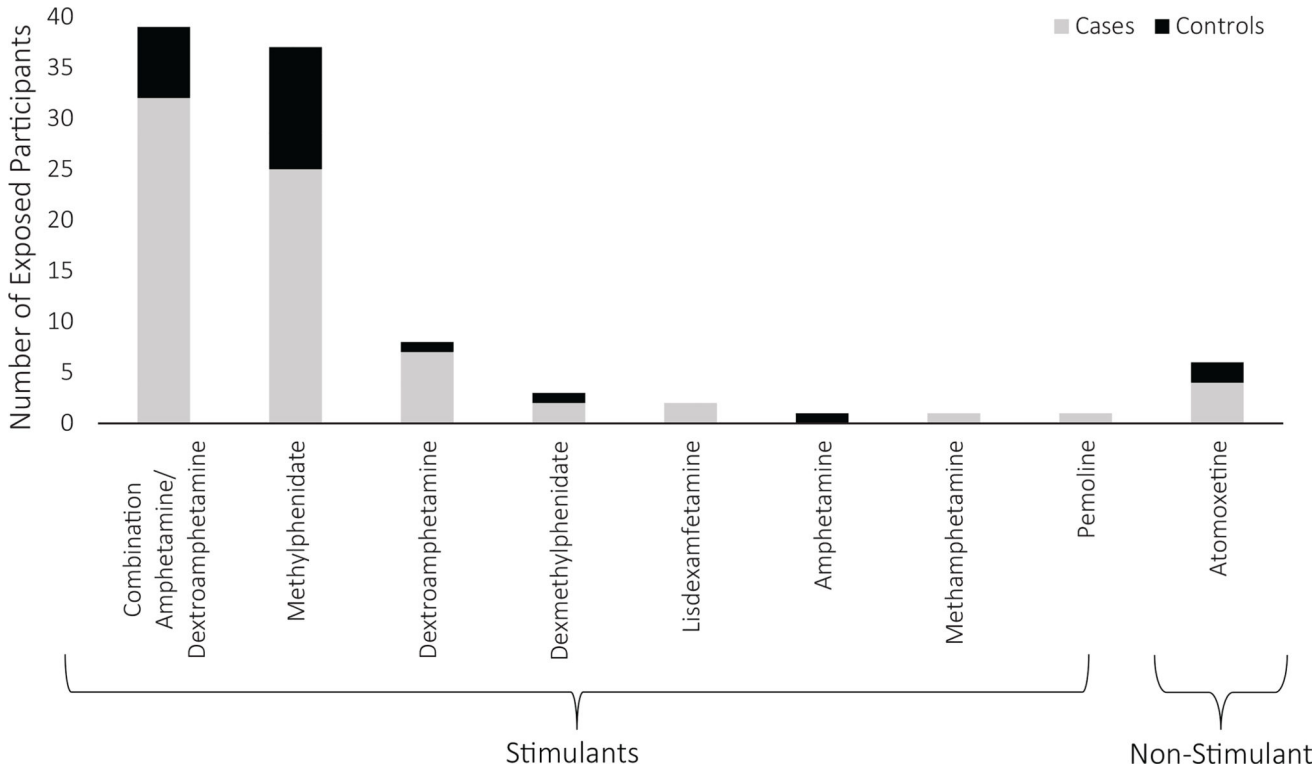

Figure 1.

Distribution of common ADHD medication components reported by exposed case and control mothers in the 3 months before conception through the end of pregnancy, National Birth Defects Prevention Study, 1998–2011.

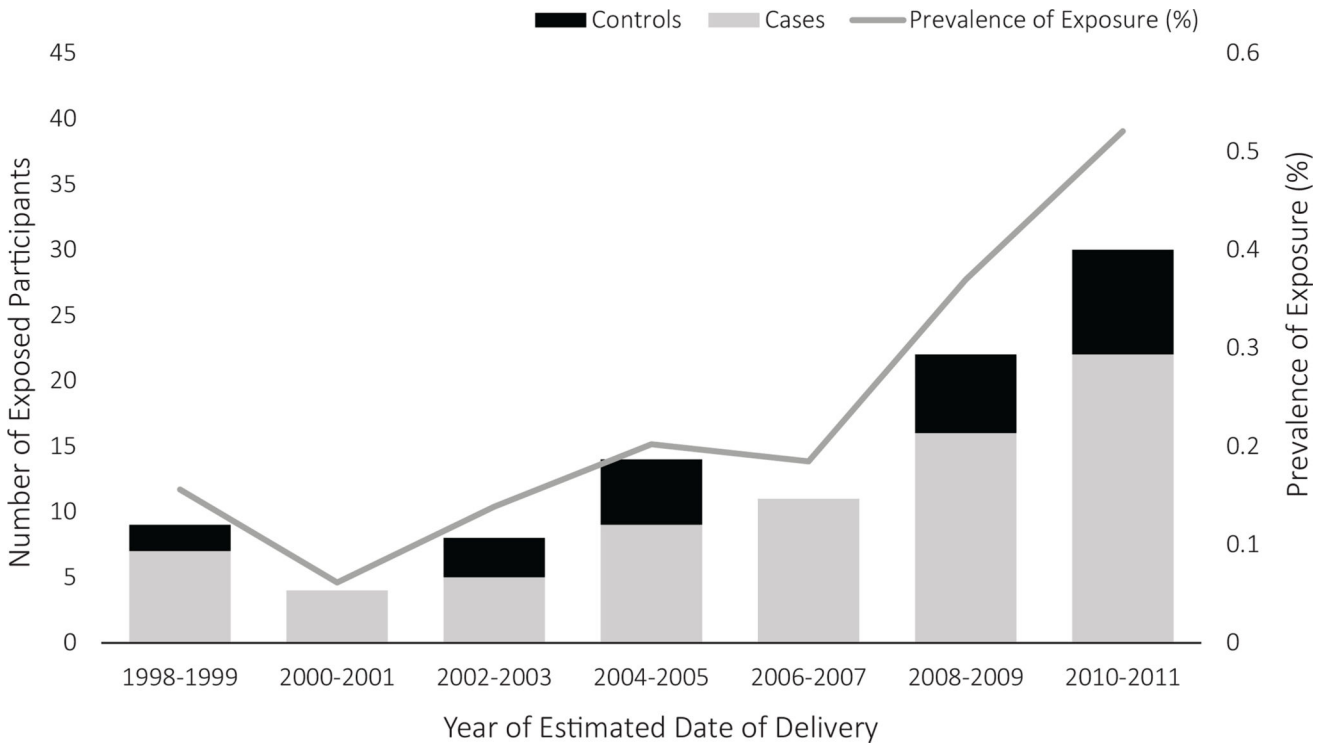

Figure 2.

Distributions of any ADHD medication use in the 3 months before conception through the end of pregnancy by the year of their estimated date of delivery, National Birth Defects Prevention Study, 1998–2011.

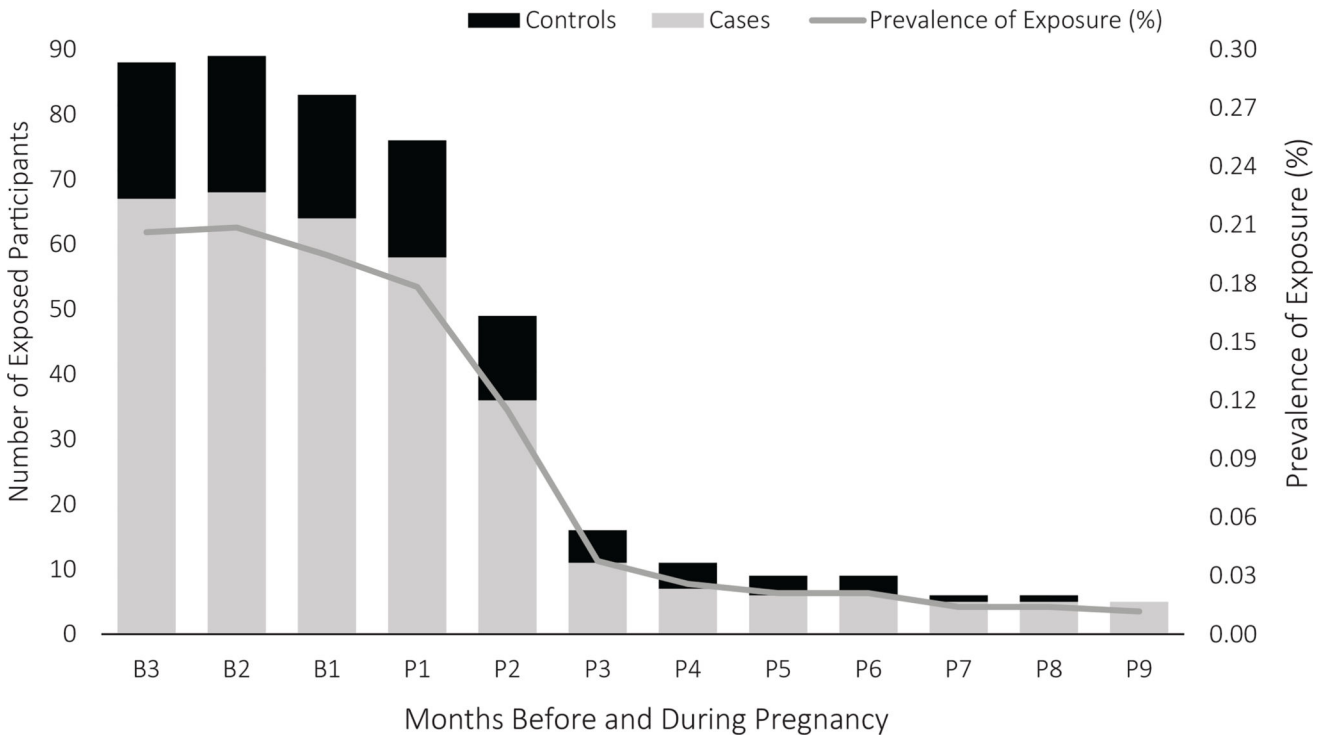

Figure 3.

Distributions of any ADHD medication use in the 3 months before conception through the end of pregnancy, National Birth Defects Prevention Study, 1998–2011.

Note. B3 to B1 correspond to the third, second, and first months before conception, P1 to P9 correspond to the first to ninth month of pregnancy.

Table 1

Characteristics of Control Mothers Exposed and Unexposed to ADHD Medications[a] From 3 Months Before Conception Through the End of Pregnancy, National Birth Defects Prevention Study, 1998–2011.

	Exposed to ADHD medications before or anytime during pregnancy (*n* = 24)	Unexposed to ADHD medications before or anytime during pregnancy (*n* = 11,430)	*p*[b]
Age (years)			.25
<20	3 (12.5%)	1,105 (9.7%)	
20–34	15 (62.5%)	8,705 (76.2%)	
≥35	6 (25.0%)	1,620 (14.2%)	
Race/ethnicity			.05
Non-Hispanic White	18 (78.3%)	6,635 (58.1%)	
Not non-Hispanic White	5 (21.7%)	4,790 (41.9%)	
Education (years)			.03
≤12	4 (17.4%)	4,537 (40.1%)	
>12	19 (82.6%)	6,764 (59.9%)	
Income			.49
<US$40,000	10 (47.6%)	5,770 (55.1%)	
≥US$40,000	11 (52.4%)	4,707 (44.9%)	
Any early pregnancy smoking[c]			.56
Yes	3 (13.0%)	2,011 (17.7%)	
No	20 (87.0%)	9,330 (82.3%)	
Any early pregnancy alcohol use[c]			.13
Yes	12 (52.2%)	4,178 (37.0%)	
No	11 (47.8%)	7,127 (63.0%)	
Any early pregnancy folic acid use[d]			.91
Yes	13 (54.2%)	6,055 (53.0%)	
No	11 (45.8%)	5,375 (47.0%)	
Pregnancy intention			.12
Wanted to be pregnant then	8 (42.1%)	5,532 (59.5%)	
Wanted to wait until later	3 (15.8%)	1,885 (20.3%)	
Did not want to be pregnant at all	4 (21.1%)	1,063 (11.4%)	
Did not care	4 (21.1%)	822 (8.8%)	
Number of previous births[e]			.13
0	13 (54.2%)	4,476 (39.2%)	
≥1	11 (45.8%)	6,950 (60.8%)	
Prepregnancy body mass index (kg/m^2)			.82
<30	20 (83.3%)	8,932 (81.6%)	
≥30	4 (16.7%)	2,020 (18.4%)	

Note. Column counts and percentages may not equal expected *N* due to missing data on maternal characteristics for case and control mothers.

[a] ADHD medication components include amphetamine, dextroamphetamine, combination amphetamine/dextroamphetamine, lisdexamfetamine, dexmethylphenidate, methylphenidate, methamphetamine, pemoline, or atomoxetine.

[b] Estimated *p* values are based on chi-square tests performed for each maternal characteristic and ADHD medication use.

[c] From the month before conception through the third month of pregnancy.

[d] From the month before conception through the first month of pregnancy.

[e] Includes previous live births and stillbirths.

Table 2

Associations Between ADHD Medication[a] Use From One Month Before Conception Through the Third Month of Pregnancy and Selected Birth Defects, National Birth Defects Prevention Study, 1998–2011.

Defect	ADHD medication exposed[b] (*N*)	ADHD medication unexposed[c] (*N*)	cOR (95% CI)	aOR[d] (95% CI)
Controls[e]	20	11,362		
Tetralogy of Fallot	3	1,157	1.5 [0.4, 5.0]	
Coarctation of the aorta	4	1,120	2.0 [0.7, 6.0]	
Pulmonary valve stenosis	3	1,506	1.1 [0.3, 3.7]	
Atrial septal defect (secundum or NOS)	6	2,915	1.2 [0.5, 2.9]	
Neural tube defects[f]	3	2,084	0.8 [0.2, 2.8]	
Craniosynostosis	3	1,574	1.1 [0.3, 3.7]	
Cleft palate	4	1,536	1.5 [0.5, 4.3]	
Cleft lip with or without cleft palate	3	3,012	0.6 [0.2, 1.9]	
Gastroschisis	7	1,374	2.9 [1.2, 6.9]*	3.0 [1.2, 7.4]*
Omphalocele	3	424	4.0 [1.2, 13.6]*	
Hypospadias, 2nd/3rd degree	5	2,505	1.3 [0.4, 3.8]	
Transverse limb deficiency	4	695	3.3 [1.1, 9.6]*	

Note.

Data marked with an * are significant at $p < .05$.

This table includes birth defects with ≥ 3 exposed cases. The total sample of eligible cases (19,153) does not sum to Table 2 individual defects reported as cases may have ≥ 1 eligible defect. cOR = crude (unadjusted) odds ratio; CI = confidence interval; aOR = adjusted odds ratio; NOS = not otherwise specified.

[a]ADHD medication components include amphetamine, dextroamphetamine, combination amphetamine/dextroamphetamine, lisdexamfetamine, dexmethylphenidate, methylphenidate, methamphetamine, pemoline, or atomoxetine.

[b]Mothers exposed to ADHD medications in early pregnancy (one month before conception through the third month of pregnancy).

[c]Mothers unexposed to ADHD medications (in the 3 months before conception through the end of pregnancy).

[d]Adjusted for maternal age (<20, ≥ 20 years).

[e]As pulmonary valve stenosis, cleft palate, and cleft lip with or without cleft palate were only ascertained by a subset of the study sites in certain years, and hypospadias only affects male infants, controls for these analyses were similarly restricted. For pulmonary valve stenosis, there were 10,944 controls, of whom 20 reported ADHD medication exposure in early pregnancy. For cleft palate and cleft lip with or without cleft palate, there were 11,250 controls, of whom 20 reported ADHD medication exposure in early pregnancy. For hypospadias, there were 5,803 controls of whom nine reported ADHD medication exposure in early pregnancy.

[f]Includes anencephaly, encephalocele, and spina bifida.