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Associations between self-reported maternal marijuana use during the periconceptional period and selected birth defects in the National Birth Defects Prevention Study, 1997-2011

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B.S., The University of Georgia, 2014

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Abstract

Associations between self-reported maternal marijuana use during the periconceptional period and selected birth defects in the National Birth Defects Prevention Study, 1997-2011

By: Samantha Marie Olson

Background: Marijuana is the most widely used recreational drug during pregnancy and use is rapidly changing in the United States. More states have legalized its recreational and medical use, and its sales, acceptance, and access have increased. Further, the delta-9 tetrahydrocannabinol (THC) content has reached an all-time high. **Study Objectives:** To update prevalence estimates for self-reported marijuana use during pregnancy and reassess associations between marijuana use in the periconceptional period (one month prior to pregnancy through the first three months of pregnancy) and selected birth defects. **Methods:** The National Birth Defects Prevention Study is a multi-state, population-based case control study from 1997-2011. Cases in the study had one or more eligible birth defects and were liveborn, stillborn, or electively terminated. Controls were liveborn infants without birth defects who were randomly selected either from birth certificates or birth hospital records. Mothers of cases and controls were interviewed and asked about marijuana use and other potential confounders. Logistic regression models were used to calculate unadjusted and adjusted odds ratios (aOR) and 95% confidence intervals. A total of 72 fully adjusted models were fit that included maternal age at delivery, race, education, smoking and binge drinking in the periconceptional period, pre-pregnancy body mass index, use of folic acid, and other illicit drugs. **Results:** Among 43,267 mothers, 4.4% of mothers of cases and 3.9% of mothers of controls used marijuana during the periconceptional period. Periconceptional marijuana users were more likely than non-users to be younger, have less education, smoke cigarettes, binge drink, use other illicit drug, and have a partner who used marijuana during their pregnancy. After adjusting for potential confounders, gastroschisis (aOR=1.33 (1.06, 1.67)) and anencephaly (aOR= 1.68 (1.10, 2.57)) had an increased odds among periconceptional marijuana users compared to nonusers. For heterotaxia (aOR= 0.44 (0.21, 0.92)) and tetralogy of Fallot (aOR= 0.67 (0.45, 0.98)) there was a protective association among users. **Conclusions:** This analysis found an association between periconceptional marijuana use and two non-heart defects. This included gastroschisis which is increasing in prevalence and a more common outcome among younger mothers. Marijuana use is also increasing and could be contributing to this.

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Chapter 1: Marijuana and Birth Defects Literature Review

Introduction

In the United States, a total of 30 states and the District of Columbia (D.C.) recently legalized the medical use of marijuana, and 9 of these states and D.C. legalized its recreational use (1-3). As marijuana legalization continues across the United States, questions have emerged about the health effects of the formerly illicit drug. Cancer patients have used the drug medicinally as a nausea remedy following chemotherapy (4). This, along with the efficacy and safety in mitigating other health concerns, led the U.S. Federal Food and Drug Administration to approve two drugs containing marijuana (4). Due to this and other medical reports of marijuana's utility, many have questioned whether the drug can be used to alleviate nausea associated with other health problems including morning sickness of varying severity during pregnancy (1, 5).

This idea paired with the growing acceptance and perceived safety of marijuana from many groups including pregnant women, women who are not currently pregnant, and young adults begs the question of what, if any, are the true effects of marijuana during pregnancy (6, 7). There is a heterogeneous literature on association between marijuana use and birth defects; findings are limited and inconclusive. However, as the prevalence of use and legalization increases, this research question is more important and timely than ever.

Birth Defects

Birth defects encompass structural, behavioral, functional, and metabolic disorders that are present at birth (8). Globally, serious birth defects affect 3-6% of

infants born each year, and in the United States, birth defects affect one in every thirty-three babies born (9-11). In addition, birth defects are the leading cause of infant death (accounting for 20% of infant mortality) and remain one of the leading causes of years of potential life lost (8, 9, 12).

These statistics likely underestimate the true burden because many birth defects are difficult to diagnose during pregnancy and during the neonatal period (8, 13). The difficulty in diagnosis lies in most pregnancies relying on 2-D ultrasound because other methods such as amniocentesis and chorionic villus sampling are reserved for high-risk pregnancies due to their additional morbidity and mortality risks (8). Additionally, many birth defects may not be included in these estimates because many pregnancies affected by birth defects end in a miscarriage or stillbirth prior to diagnosis (8, 13). Counts may also be missed because neonatal death shortly after delivery or in the early months of life are common depending on the specific birth defect (8, 13).

Although not all birth defects end in neonatal mortality, many need special healthcare throughout life. The most common birth defect is Trisomy 21, commonly known as Down Syndrome (14). Based on 2004-2006 United States data across 14 states, Down Syndrome has an estimated adjusted prevalence of 14.47 cases per 10,000 live births after adjusting for maternal age, a known risk factor for Down Syndrome (14). The most common structural birth defect is cleft lip with and without a cleft palate with an estimated adjusted prevalence of 10.63 cases per 10,000 live births, after adjusting for maternal race/ ethnicity (14).

In addition to these common defects, some birth defects that may be related to marijuana use during pregnancy including anencephaly, diaphragmatic hernia,

esophageal atresia, gastroschisis, and ventricular septal defects (VSD). These defects have an adjusted prevalence of 2.06/10,000 livebirths for anencephaly, 2.61/10,000 for diaphragmatic hernia, 2.17/10,000 for esophageal atresia, and 4.49/10,000 for gastroschisis, after adjusting for maternal race/ethnicity (14). Ventricular septal defects, the most common type of heart defect, have an estimated prevalence of 41.8/10,000 livebirths (based on Metropolitan Atlanta data from 1998-2005) (15).

These estimates provide insight into the burden of birth defects but do not offer a solution to prevent future cases. Thus, the greatest defense to prevent birth defects is to avoid potential teratogens and non-genetic factors that have been identified through human epidemiologic studies to cause structural birth defects (8, 16). Teratogens typically cause a recognizable pattern of birth defects instead of an isolated single defect (16, 17). To adequately assess these potential teratogens evaluating the timing of exposure during pregnancy is critical (18, 19). Developmentally, the first few weeks of pregnancy are the most critical for several important fetal organs (8, 20). For example the third week of development when gastrulation begins, or the forming of the fetus' gut, a fetus is susceptible to teratogens that affect the gut (8). During this time, not only is the gut being formed, but cells for the eyes, brain, limbs, and genitals can easily be influenced by the presence of a teratogen, such as alcohol (8, 16). Shortly after this time from three to eight weeks, the fetus' organs develop during a period of organogenesis, or the embryonic period. Throughout this time period is when the fetus is most at risk for gross structural birth defects (8). Simultaneously, during these critical periods in the first trimester, a woman may not be aware of her pregnancy, especially given evidence that

almost 50% of pregnancies are unplanned (8, 21). This suggests that the most critical development time is also when a woman may not be following prenatal advice.

Understanding the developmental stages and the timing of the introduction of a teratogenic agent has been the optimal way to deduce exposure associations with a birth defect. However, even with a greater understanding of these stages, it is still difficult to parse out specific or potential causes because of limited available data on birth defects. Some of these defects are very rare, and timing of conception and exposure can be difficult to determine (22). Thus, the periconceptional period, defined as one month prior to conception until the end of the third month of pregnancy, is the typical period to look for potential causes of a birth defect. This period provides the best available window to assess exposures that could be associated with birth defects because most defects develop in the first trimester, and furthermore, it is difficult to predict the exact timing of fertilization and of exposure to medications, illicit drugs, food, and other potential risk factors (8). Additionally, one month prior to conception is included for studies that rely on self-reported exposures because women may be more likely to report an exposure before pregnancy because they do not believe it affects the health of the baby even though exposure likely continued into early pregnancy because the exact timing of conception is not always known (23).

Research into the causes of birth defects has been ongoing since the 1940s with the discovery of both Rubella and Toxoplasmosis as causes of adverse fetal outcomes and continues today with the widespread Zika virus outbreak in 2016 that led to the causal link between the virus and birth defects (16, 24). There are demographic, environmental, and genetic risk factors that have been identified to increase ones risk of birth defects

(16). Examples of demographic, environmental, and genetic risk factors include pre-pregnancy obesity and diabetes, tobacco use, and chromosomal abnormalities, respectively (16). An important teratogen known to cause birth defects is alcohol, and folic acid use during pregnancy is known to reduce birth defect outcomes (16). All of these factors are important potential confounders to consider when assessing new risk factors for birth defects, especially when dual-use of illicit drugs, alcohol, and tobacco is common even during pregnancy (13).

However, assessing causality is challenging in birth defects research for many reasons (17, 22, 24). There are few studies adequate to estimate causal associations because studies typically are restricted to live births or have incomplete data on losses and terminations (22). Additionally, birth defects are not always diagnosed at birth which can add to this challenge (18, 22).

Overall, researching birth defects is essential since only 50% of these abnormalities are associated with a specific cause (12). In addition, some birth defects are now easier to detect through echocardiography such as VSD (15, 25). This may contribute an apparent increased prevalence of VSD, but it is unclear if the increase is only due to better detection technology (25). Other birth defects such as gastroschisis have also recently seen a rise in prevalence both domestically and globally, but it is unknown why this increase has been observed (26-28). Due to these increases and others, there is a need for more research to define potential causes of birth defects to ultimately decrease the serious health implications and the financial burden for families, hospitals, and insurance that a birth defects diagnosis brings (8, 29).

Marijuana

Marijuana, the most commonly used recreational drug in the United States, has recently been legalized both medically and recreationally in many states, but federally, is still classified as a Schedule I drug. The drug's main psychoactive component is delta-9 tetrahydrocannabinol (THC), and the drug is derived from the durable weed, *Cannabis sativa* (30). The plant dates back to 8000 B.C. in Taiwan with early medical uses cited in ancient Chinese texts around 2700 B.C. (30). Initially, the medical uses of the drug, both from a pharmacological and folk medicine perspective, ranged from gout to poor memory to malaria to asthma (30). This was likely due to the lack of other medications and therapies but demonstrates the interest and use of medical marijuana early on and across the globe.

Federally, in the United States, the drug remains illegal for medical or recreational purposes since 1937 through the Marijuana Tax Act (30). Additional legislation like the Boggs Act in 1952 further criminalized the drug, and the Controlled Substance Act of 1970 branded it with the most restrictive category of drug, Schedule I (30). This categorization implies the drug has no valid medical use, and has a high potential for abuse; it shares this classification with both heroin and LSD (30).

However, in recent years marijuana has become a hot topic in news and health studies. Societally and medically, the perspective is shifting back to one of acceptance and medical utility of the drug. Despite the standing federal legislation, surveys have documented the shifting societal approval with many viewing the drug as less harmful than other vices, such as alcohol (7). This view mirrors early Hindu culture where the religion accepted the drug for stress and anxiety relief while outlawing alcohol

consumption (30). For medicine, the original uses may have overstated the drug's pharmacological properties, but recent medical literature still claims that marijuana can provide relief from pain or nausea from cancer, decrease seizures, increase appetite, and act as an antidepressant (1, 20, 30). This has even led to the U.S. Federal Food and Drug Administration approval of two drugs, Dronabinol and Nabilone (a Schedule II synthetic cannabinoid), for alleviating pain associated with chemotherapy (20). And other studies have already suggested the potential utility of these drugs for other diseases such as Huntington's Disease and human immunodeficiency virus (HIV) (1, 20). Additional women's health benefits include a remedy from postpartum depression and to alleviate labor pains, premenstrual symptoms, and menstrual cramps (30, 31). Due to these potential benefits, the use of marijuana during pregnancy has been explored.

Marijuana and Pregnancy

History of Use

Marijuana is the most widely used illicit drug during pregnancy (1, 32, 33). Historic reports state the drug was used over 2,000 years ago to help with childbirth, ease pain, and increase contractions (30). Even historic reports from South East Asia report marijuana tea being used to treat postpartum depression, and this practice could also occur in the United States with the new trend of Californian mothers hosting "tea parties" to offer women a relaxing environment to get high (30, 34).

Although there are several potential medical uses of marijuana during pregnancy, the most common is nausea relief (35, 36). The earliest case report dates back to the nineteenth century when a doctor "saved a patient's life" by prescribing marijuana. There

are also more recent international reports, such as one from Jamaica, describing its assistance in nausea relief (35, 37).

Hyperemesis gravidarum is a severe form of nausea that can cause vomiting, weight loss, and fluctuations in electrolyte levels (1). It is the second most common cause of hospitalization during pregnancy in the United States and affects an estimated 0.3-3.0% of pregnancies (1, 38). Marijuana use has been suggested as a remedy and has gained popularity on online blogs, but clinically, only has case reports and testimonies to support it (5). However, even with modern medicine and technology, no definitive pharmacological or alternative medicines are available for hyperemesis gravidarum leaving room for a myriad of potential remedies including marijuana.

Beyond medical reports, behavioral survey data suggests women's approval of the drug as a morning sickness remedy. Data from the Hawaiian Pregnancy Risk Assessment Monitoring System from 2009 to 2011 showed that women who reported severe nausea during pregnancy were also more likely to report marijuana use (PR= 1.63, 95% CI: 1.08-2.44) (1, 5). Another study in Canada showed that a little over half of women interviewed reported nausea during pregnancy, and among these women a large majority (92%) believed that marijuana helped treat their nausea (35). However, the Canadian report has a small sample size, relies on self-report, and lacks generalizability because the study population was women who were currently using marijuana medicinally (35). However, the combination of these studies offers insight into the reasoning behind use during pregnancy.

Despite the potential nausea relief, the most common time for nausea during pregnancy corresponds to the time when a fetus is at greatest risk for a birth defect.

Although no study has been able to confirm marijuana's effect on pregnancy, there may be biological plausibility to study the association between marijuana use and birth defects. THC is lipid-soluble which allows the drug to cross the placenta, with the highest concentration crossing during early pregnancy (23, 31, 39-41). Studies range from about 10% of marijuana consumed crossing the placenta to animal models showing equivalent concentrations of THC in maternal and fetal plasma, and in some cases, even higher fetal levels if the drug was administered during critical development times (39). These animal studies, specifically mice and rabbit studies, have demonstrated neural tube defects from this exposure (23).

Additionally, it may take up to thirty days for a single exposure to marijuana to be excreted from the body which suggests pre-pregnancy exposure may affect the fetus (40). Beyond THC's effect on the fetus, marijuana components, such as carbon monoxide, are elevated in the bloodstream after use and have been found to be a teratogen in animal models (23, 40). Other potentially harmful effects to the fetus include the increase in maternal heart rate and blood pressure (40).

Despite these findings, little evidence of a negative effect on a fetus has been found in human models, and the argument has been made that these effects are only observed in laboratory models due to the high concentration of the drug administered (39). However, many of these research studies date back to the 1970s and 80s when marijuana overall had a lower concentration of THC, and there is a lack of more recent studies looking at marijuana use in animal models (39, 42).

This is concerning because the THC content in marijuana has increased since then (20, 42). Recent studies show that the average THC in marijuana has increased from

2.8% in 1985 to 5.8-9.8% in 2008 (20). Additionally, hashish samples currently average around 28.2% THC with some as high as 66% THC (20). These dramatic increases come with a variety of products and availability. This includes new blends of synthetic marijuana such as the brand, *Spice*, which can reach more than 500 times the potency of regular THC (20). And it is still unclear if use during pregnancy effects birth outcomes at all or if there is an effect at higher doses (13).

These varying concentrations have been hypothesized to have an effect on the fetal endogenous cannabinoid signaling system which has potential implications to impact all brain and organ systems (43, 44). After crossing the placenta, THC can bind to cannabinoid (CB) receptors of the fetal endogenous cannabinoid signaling system to potentially impair functioning and development, especially in the central nervous system (20, 41, 43, 45). THC could mirror the effects of an endocannabinoid and bind to two characterized cannabinoid receptors (i.e. cannabinoid receptor 1 and cannabinoid receptor 2, that are characterized elsewhere) (43). Additionally, if this exposure alone does not impair a developing fetus, biologists have hypothesized a "second hit" system where both the initial exposure of the mother and second post-natal exposure to the infant could highly impact a developing nervous system contributing to long-term impairment (43). This biologic characterization is based on animal models, but there are animal studies that go beyond hypothesizing the potential pathways and instead show evidence of synthetic cannabinoids, that are found in marijuana blends, impacting a chick's developing brain (20).

Prevalence

The latest National Survey on Drug Use and Health suggests that the prevalence of past month marijuana use among pregnant women has increased by 62% from 2002 to 2014, with the highest prevalence among women aged 18-25 years (1, 46). The adjusted prevalence of marijuana use among these women in 2014 was approximately 3.9% (95% CI 2.9, 5.2%), which was similar to other United States studies and the previous National Birth Defects Prevention Study (NBDPS) analysis of 1997-2005 data that reported approximately 4.0% of pregnant women (4.1% in cases and 3.8% in controls) with self-reported marijuana use during the periconceptional period (39, 46, 47). Although these estimates are similar, the analysis using National Survey on Drug Use and Health only included marijuana use in the previous month and had a small sample size of users. However, the prevalence of marijuana use during pregnancy is likely higher than the self-reported data estimates suggest. Nearly, all prevalence estimates based on toxicology test results yield a slightly higher percentage, and a greater relative rate of increase year to year (48, 49).

Most studies examine data by trimester of use and have found that the majority of pregnant women use marijuana pre-pregnancy or during the first trimester, likely when their pregnancy status is unknown (48). Many of these pregnant users are not frequent marijuana users with use typically occurring less than once a month (50). However, there may be a smaller population that does use marijuana frequently during pre-pregnancy and early pregnancy. One study showed that 29.3% of women pre-pregnancy and 19.9% of pregnant women in the first trimester used ≥ 1 marijuana joint/ day (51). The use seems to decline during the first trimester and throughout the remainder of pregnancy, with only

a small proportion (3/116 users in one study with toxicology data) testing positive at delivery (48, 50, 51). However, since the first few weeks of pregnancy are the most critical for development, if marijuana does effect the fetus, abstinence during later stages of pregnancy may be too late to avoid adverse effects on the fetus.

Population

In addition to studies assessing the prevalence of marijuana use, researchers have characterized users of marijuana during pregnancy. Women who use marijuana during pregnancy have been described as younger, living alone and/or in an urban area, single, of lower education level, and of lower socioeconomic status (36, 50, 52, 53). Since other harmful health characteristics are typically associated with pregnant women using marijuana, it is difficult to determine whether adverse pregnancy outcomes are due to marijuana or other health behaviors that are known to be harmful during pregnancy. Some of these characteristics include poor prenatal care, poor nutrition, history of depression or abuse, and use of other drugs, tobacco, and/or alcohol (23, 32, 48, 50, 54). These harmful health behaviors coincide with the increase in the number of pregnant women using any substance (i.e. other illicit drugs or opioids) and being admitted to substance abuse clinics, which has risen over 50% in the past decade (55, 56). And many (70% of both pregnant and non-pregnant women) believed that there was a slight or no risk at all from marijuana use once or twice a week (6).

Marijuana use during Pregnancy and Birth Defects

Despite the increase in the prevalence of marijuana use and growing evidence of who is at increased risk of use during pregnancy, the literature is inconclusive on whether

marijuana use is associated with birth defects. An early study indicated a chance that major malformations could be associated with marijuana use during pregnancy (OR= 1.36, 95% CI 0.97, 1.91), but the study was unable to determine which specific defect was most likely to occur (52).

Other studies focused on determining which specific defects could potentially be affected. In previous NBDPS studies, there was an increased adjusted odds of anencephaly (aOR=2.2, 95% CI 1.3, 3.7), gastroschisis (aOR=1.2, 95% CI 0.9, 1.7), esophageal atresia (aOR= 1.4, 95% CI 0.8, 2.4), and diaphragmatic hernia (aOR=1.4, 95% CI 0.9, 2.2) among pregnant marijuana users (47). To control for the likelihood of exposure misclassification in this analysis, four Bayesian analyses were conducted, and all four found gastroschisis and anencephaly to still be associated with periconceptional marijuana use (47). Other studies have also found an increased odds of anencephaly, gastroschisis, and VSD among those who used marijuana during pregnancy (25, 57, 58). For VSD, additional research has explored the potentially greater risk for heavier marijuana use. Researchers found the unadjusted odds greatly increased from 2.20 (95% CI: 1.22, 3.93) to 3.73 (95% CI: 1.56-8.96) when comparing use of two or fewer days per week to three or more days per week (25).

Additionally, a Hawaiian study was able to examine the rate of prenatal use among 50+ birth defect categories compared to all livebirths reported to their health department (13). No cases of diaphragmatic hernia or anencephaly were reported, but an increased rate of VSD and gastroschisis was observed, (RR= 8.83, 95% CI: 4.82-14.87, 23.11, 95% CI: 4.69-69.34, respectively) after removal of cases with other drug use (13). However, these estimates are imprecise with small sample sizes for each birth defect,

especially after excluding other drug use that could have impacted the fetus (13). As a result, out of all defects assessed, the defect that had the most cases was VSD with only 14 exposed cases. Syndactyly had the next highest case count at only 8 (13). Therefore, it is difficult to conclude there is an association with the over 50 other birth defects studied even though several (>20%) defects had an increased rate, including atrial septal defect, cleft palate, cleft lip with and without cleft palate, and other defects (13).

A few other case control studies identified potential increased risks for rare defects but have less evidence to support these associations. One study reported a potential association with limb-body wall complex, based on 11 cases (59). However, many mothers with affected pregnancies also engaged in other harmful activities such as using tobacco and alcohol use or did not take periconceptional folic acid (59). Another study reported the potential association between Ebstein's anomaly and marijuana use, but only identified seven cases and the data date back to the 1980s (60). A non-genetic model that removed cases with first degree relatives that had cardiac or non-cardiac defects showed an increased risk of Ebstein's anomaly among marijuana users (OR=3.6, 95% CI: 1.6, 8.5) (60).

An additional category of adverse birth outcomes related to birth defects and marijuana research is minor physical anomalies. One study reported, that among white pregnant women with any first trimester marijuana use, there was an increased odds of minor physical anomalies (OR=3.2 [95% CI: 1.0-10.2]) (61). These minor anomalies are important to study because they may indicate evidence of a teratogen (67).

In contrast, there were studies that did not find an association between marijuana and birth defects (51, 61). Many of these studies had expected limitations such as a small

sample size, non-differential misclassification of the exposure, or no control for potential confounders. Additionally, many studies included only singleton livebirths which could potentially exclude birth defects that may have caused a miscarriage or stillbirth, resulted in twins, or led to a pregnancy termination decision (40). Also, many studies only report a birth defect determination by a nurse's physical assessment at birth or lack detail into how the birth defect was detected leaving the potential for outcome misclassification (51). Lastly, many of these studies date back several decades and did not focus primarily on birth defects but instead focused on other pregnancy outcomes (40). Additionally, some of these studies found that other known teratogens or risk factors such as tobacco and cocaine did not increase the study population's risk for birth defects (13, 40, 61). Because these are known risk factors, it makes it difficult to draw conclusions based on their assessment of the birth defect and marijuana relationship.

Marijuana use during Pregnancy and Other Adverse Outcomes

Like the literature for birth defects, there are many inconclusive reports regarding marijuana use during pregnancy and health problems during delivery, other pregnancy outcomes, and its long-term impact on infants.

Use of marijuana during pregnancy, or specifically around childbirth, has competing evidence on its effect on infant delivery. As mentioned, marijuana has been used to help childbirth and reported as having no delivery or obstetric complications. However, there is also documentation of the drug being associated with quickened childbirth and increased frequency and intensity of contractions (52, 62). Additionally, after birth, marijuana potentially plays a role in a newborn's hospital stay with many of these infants being placed in a neonatal intensive care unit (NICU) (pOR= 2.02, 95% CI:

1.27-3.21), resulting in expensive healthcare costs (48, 63, 64). However, the studies do not cite a reason for the NICU stay (48, 63, 64).

For other pregnancy outcomes, studies remain as inconclusive as birth defects. Some research shows no difference in birth weights, preterm delivery rates, and mean gestational age at delivery among infants born to mothers who used marijuana during pregnancy (48, 52, 63). However, for low birth weight, there are studies suggesting an effect in opposite directions (40, 48, 52). A study found that low birth weight was the same among marijuana users and non-users, and that very low birth weight was similar between users and non-users after controlling for cigarette smoking (48). In contrast, an Australian study reported that low birth weight had a 2.5% population-attributable risk associated with marijuana use during pregnancy (64). Additionally, a systematic review suggested that when birth weight is classified as a dichotomous or continuous variable an increased association between marijuana use during pregnancy and low birth weight is observed in many studies (63). Preterm birth also has contradicting evidence with some studies reporting increased odds of preterm birth among marijuana users (aOR=2.22, 95% CI: 1.04, 4.74) and others showing no association (50, 64, 65). However, NBDPS study results indicated no association with low birth weight or preterm delivery among pregnant marijuana users and reported narrow confidence intervals for these estimates (aOR=0.7, 95% CI: 0.3-1.6, aOR=1.0, 95% CI: 0.6-1.9, respectively) (66). Additionally, a study conducted with data from a prenatal clinic in Pittsburgh, Pennsylvania, suggested that any use of marijuana during pregnancy led to a reduction in gestational age of 7 days per joint per day after controlling for confounders, and that use during the second

trimester could increase the risk of infants born small for gestational age (SGA) (OR=3.8, 95% CI: 1.2, 14.0) (61).

Other short-term and long-term infant outcomes are not commonly discussed in the marijuana and pregnancy literature. However, Apgar scores do appear in several studies, and no difference has been reported in scores for infants born to mothers who used marijuana during pregnancy compared to those who did not (52, 63). There has been limited research on whether prenatal exposure to marijuana has long-term health effects. There is some evidence of impact later in life such as neurologic impairment that could appear at young ages or during adulthood (68, 69). This includes impairment of productivity levels, impulse control, visual memory, and attention (1, 68).

Overall, marijuana is difficult to study in relation to its potential effects on pregnancy and infant outcomes because many other harmful activities during pregnancy are typically associated with marijuana use. Tobacco is highly associated with marijuana use during pregnancy (aOR= 3.33, 95% CI: 1.89-5.86) (25, 48). Additionally, perhaps due to the increased odds of a marijuana pregnant user also consuming alcohol, there is evidence that marijuana users are five times more likely than non-users to deliver babies that have features similar to those infants with fetal alcohol syndrome (25, 52)

Lastly, postpartum mothers may potentially expose their babies to marijuana if they breast-feed (70). It is estimated that approximately 0.8% of the marijuana ingested by a mother would be ingested subsequently by her infant in one feeding, with the potential of even higher levels in more frequent users (71). There is some evidence that this could inhibit a child's motor development at one year of age (71). This combination of evidence could contribute to the idea of a "second hit" of marijuana that biologists

have suggested could inhibit long-term development preventing an infant from reaching its full potential.

Strengthens of a National Birth Defects Prevention Study (NBDPS) Analysis

Based on the limited and inconclusive studies on marijuana use during pregnancy and how it affects many factors related to pregnancy and infant outcomes, research with more recent data is needed.

For birth defects, although they are common in the United States, many of their causes remain unknown and are difficult to study. To study potential associations, birth defects are often ascertained through medical records from hospital abstractions resulting in many hospital-based case control studies that are isolated to a single geographic location. The National Birth Defects Prevention Study (NBDPS) offers an advantage over this method because the study is population-based and thus more generalizable (66). These medical records are paired with computer-assisted telephone interviews between 6 weeks and 24 months after an infant's estimated date of delivery to assess both the timing and frequency of exposures, such as marijuana use. There are also many potential confounders assessed in the questionnaire including known and unknown risk factors for birth defects, which many other marijuana and birth defect studies have not been able to account for in analysis (19). Other strengths of the study include the collection of buccal cells for genetic laboratory testing studies and the exclusion of cases of known etiology (including single gene conditions and chromosomal abnormalities) (18).

Another difficulty in studying birth defects is the great complexity and differences in birth defect case classifications including teasing out isolated (only one major defect), multiple (more than one defect not occurring in a sequence), or syndrome (a group of

abnormalities occurring together with a common cause) defects (8, 72). In NBDPS clinical geneticists or dysmorphologists review and classify all cases. For each birth defect case, the clinician reviews their medical data using a step-wise process, standardized case definitions, and the latest clinical literature including embryology and pathogenesis to make a determination of which birth defect category the case should be (18, 72, 73). This includes several defects that rarely occur making NBDPS one of the only ways to study these defects (18, 19, 22).

Although the methodology behind NBDPS offers a beneficial design to explore the relationship between marijuana and birth defects, there are limitations. NBDPS does not offer toxicology tests or another way to capture an objective biomarker of exposure. Thus, self-report of marijuana exposure alone is likely subject to underreporting of the number of pregnant women who used marijuana perhaps because of shame, guilt, a lack of trust in the interviewer, or being uncertain of the timing of use in relation to their pregnancy. In addition, although marijuana use is becoming more prevalent, use of a substance during pregnancy is still considered child abuse in 17 states (74). Research has also shown that this fear and uncertainty of what would happen if others discovered substance use during pregnancy has driven some women to avoid prenatal care visits (74).

Considering the sensitivity of the question and potential for underreporting, ideally, a study would use a combination of multiple questionnaires and toxicology tests throughout different stages of pregnancy; however, even this method has limitations (40, 52, 61). Both the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics approve of drug testing during prenatal care; however, it is hard to

link this test to the exact timing of use which is vital to the link to birth defects (70). A urine test is the most accurate and affordable test; however predicting the timing of use is still difficult (70). Considering these limitations, there is a need to account for the likelihood of underreporting of marijuana use.

Other limitations for birth defect studies include the incomplete ascertainment of cases. Many studies are unable to capture all pregnancy outcomes including livebirths, stillbirths, and pregnancy terminations, which leads to an under-ascertainment of cases where only prevalent cases are considered (22). NBDPS provides a better estimate by including livebirth and stillbirths, but the study is only able to capture birth defects diagnosed prenatally with elected termination from select sites (Arkansas, California, Georgia, Iowa, and Texas) (19).

Thus, this analysis provides advantages over the limited and inconclusive literature because of the number of birth defects considered, of it being population-based and more generalizable, self-reported exposure timing and frequency is available, and detailed interview data are available that include information on important potential confounders.

Conclusion

Further research into marijuana use during pregnancy and its association with birth defects is needed. Studies have already identified a potential increased risk for anencephaly, gastroschisis, and VSD among pregnant marijuana users as compared to non-users. And other studies have identified additional defects, such as diaphragmatic

hernia, esophageal atresia, limb-body wall complex, and Ebstein's anomaly although these results have not been replicated in other studies.

Ultimately, determining if there is an association between birth defects and marijuana is an important public health question as the number of marijuana users steadily increases in the United States. Currently, the United States Federal Food and Drug Administration acknowledges the potential for adverse outcomes if pregnant women use marijuana, but no warnings exist to explain any potential harm marijuana could have on a fetus (1, 75). Thus, as marijuana grows in acceptance, its THC content increases, and medicinal and recreational use becomes legal in more states, marijuana use is likely to become more common during pregnancy. This paired with the perceived relief from nausea during pregnancy, high rates of unplanned pregnancies, and lack of education or awareness on potential marijuana risks during pregnancy indicates that determining whether marijuana is associated with birth defects is a public health question that must be answered.

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Chapter 2: Associations between self-reported maternal marijuana use during the periconceptional period and selected birth defects in the National Birth Defects Prevention Study, 1997-2011.

S. Olson, P. Howards, S. Gilboa, and J. Reefhuis

ABSTRACT:

Background: Marijuana is the most widely used recreational drug during pregnancy and use is rapidly changing in the United States. More states have legalized its recreational and medical use, and its sales, acceptance, and access have increased. Further, the delta-9 tetrahydrocannabinol (THC) content has reached an all-time high. **Study Objectives:** To update prevalence estimates for self-reported marijuana use during pregnancy and reassess associations between marijuana use in the periconceptional period (one month prior to pregnancy through the first three months of pregnancy) and selected birth defects. **Methods:** The National Birth Defects Prevention Study is a multi-state, population-based case control study from 1997-2011. Cases in the study had one or more eligible birth defects and were liveborn, stillborn, or electively terminated. Controls were liveborn infants without birth defects who were randomly selected either from birth certificates or birth hospital records. Mothers of cases and controls were interviewed and asked about marijuana use and other potential confounders. Logistic regression models were used to calculate unadjusted and adjusted odds ratios (aOR) and 95% confidence intervals. A total of 72 fully adjusted models were fit that included maternal age at delivery, race, education, smoking and binge drinking in the periconceptional period, pre-pregnancy body mass index, use of folic acid, and other illicit drugs. **Results:** Among 43,267 mothers, 4.4% of mothers of cases and 3.9% of mothers of controls used marijuana during the

periconceptional period. Periconceptional marijuana users were more likely than non-users to be younger, have less education, smoke cigarettes, binge drink, use other illicit drug, and have a partner who used marijuana during their pregnancy. After adjusting for potential confounders, gastroschisis (aOR=1.33 (1.06, 1.67)) and anencephaly (aOR= 1.68 (1.10, 2.57)) had an increased odds among periconceptional marijuana users compared to nonusers. For heterotaxia (aOR= 0.44 (0.21, 0.92)) and tetralogy of Fallot (aOR= 0.67 (0.45, 0.98)) there was a protective association among users. **Conclusions:** This analysis found an association between periconceptional marijuana use and two non-heart defects. This included gastroschisis which is increasing in prevalence and a more common outcome among younger mothers. Marijuana use is also increasing and could be contributing to this.

Introduction

Marijuana is the most widely used recreational drug during pregnancy (1-3). The National Survey on Drug Use and Health in 2014 reported approximately 3.9% (95% CI 2.9, 5.2%) of pregnant women in the United States used marijuana during their pregnancy (1, 4). This estimate represents a 62% increase in use among pregnant women from 2002 to 2014 (1, 4). Since then, seven more states have fully legalized medical marijuana bringing the total to thirty states and D.C., and four more states have legalized recreational marijuana for a total of nine states overall. The drug has increased in sales, acceptance, and access, and the delta-9 tetrahydrocannabinol (THC) content in marijuana has steadily increased reaching an all-time high in synthetic marijuana compounds (1, 5, 6).

Medical reports, beginning with ancient texts in China around 2700 B.C., have cited marijuana's medicinal uses (7). In the late 1800s, marijuana began being reported to

help with different aspects of pregnancy such as easing pain, increasing contractions, relieving postpartum depression, and most frequently, as a remedy for nausea during pregnancy (7-10). Data from the Hawaiian Pregnancy Risk Assessment Monitoring System from 2009 to 2011 showed that women who reported severe nausea during pregnancy were more likely to report marijuana use during pregnancy (PR= 1.63, 95% CI: 1.08-2.44) (11). Nausea during pregnancy typically occurs during the first trimester; a time when many women are unaware of their pregnancy status and are most likely to use marijuana (12, 13). These first three months are also the time when the fetus is developmentally at greatest risk for developing an exposure-induced birth defect (13).

A previous analysis of 1997-2005 National Birth Defects Prevention Study (NBDPS) data examined the association between marijuana and birth defects and reported an increased adjusted odds of anencephaly (aOR=2.2, 95% CI 1.3, 3.7), gastroschisis (aOR=1.2, 95% CI 0.9, 1.7), esophageal atresia (aOR= 1.4, 95% CI 0.8, 2.4), and diaphragmatic hernia (aOR=1.4, 95% CI 0.9, 2.2) among pregnant marijuana users (14). Gastroschisis has been reported elsewhere as having an increased risk among marijuana users (17, 18, 28). Other studies have suggested an increased risk of ventricular septal defects (VSD), limb-body wall complex, and Ebstein's anomaly (15-17). However, many of these studies had a small sample size and were unable to adjust for potential confounders, such as alcohol, tobacco, or other drug use (15, 18-21).

This analysis aims to address these limitations and add to this body of literature. The main objectives of this analysis are to update prevalence estimates for self-reported marijuana use among all mothers in NBDPS from 1997-2011 and to reassess the associations between self-reported maternal marijuana use during the periconceptional

period and all major birth defects included in NBDPS while adjusting for confounding by other substances including alcohol, tobacco, and other illicit drugs.

Methods

To conduct these analyses, we used the National Birth Defects Prevention Study's (NBDPS) full dataset from 1997-2011. NBDPS is a multi-state, population-based case control study that collected birth defects data from Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah (22). The study population included women who had a liveborn or stillborn infant or a pregnancy termination (in selected sites) with at least one major birth defect diagnosed within the first year of life (cases) and women who had a liveborn infant with no major birth defects (controls) (22). Cases included larger categories of birth defects and subcategories of birth defects for both non-heart and heart defects. Heart defects included several combinations of defects, such as VSD, atrial sepal defect (ASD), and pulmonary stenosis (PS). Birth defects excluded from this study include those of known etiology (including single gene conditions and chromosomal abnormalities) (23). Medical data related to these birth defects were abstracted for standardized case classification by clinical geneticists or dysmorphologists (23-25). For controls, infants were randomly selected from the same geographic area and time period as cases using hospital data or birth records (22).

Mothers of cases and controls were invited to participate in a computer-assisted telephone interview that had to be completed within 6 weeks to 24 months from their estimated date of delivery (22). This yielded a high response rate to the interview of 67% among cases and 65% among controls (23).

The full NBDPS dataset was analyzed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). Similar to previous analyses of NBDPS illicit drug data, the exposure period was defined as one month prior to conception through the end of the third month of pregnancy (13). This time period provides the best available window to assess exposures that could be associated with birth defects because most defects develop in the first trimester, and furthermore, it is difficult to predict the exact timing of fertilization and of exposure to medications, illicit drugs, food, and other potential risk factors (13). One month prior to conception is included for studies that rely on self-reported exposures because women may be more likely to report an exposure before pregnancy because they do not believe it affected the health of their baby, although for some exposures, they likely continued into early pregnancy, especially because the exact timing of conception is not always known (26).

Marijuana exposure was assessed in several ways. The majority of exposure data was ascertained from the maternal drug use interview section (n=1,843 for periconceptional exposure, n=2,292 for any marijuana exposure, including 14 mothers with no information about the specific timing of use during the three months before their pregnancy through the end of their pregnancy). Medication data related to marijuana, hash, THC, and cannabis were also examined. This assessment did not identify any exposed mothers who were not previously ascertained from the maternal drug section (n=4 for periconceptional exposure, n=5 for any marijuana exposure). Lastly, comments from interviewers related to marijuana use were reviewed resulting in the identification of three additional marijuana users of which one used periconceptionally; these users were not previously identified through maternal drug use or medication data.

Data on demographics and potential confounders were collected from the interview. Similar, to the previous NBDPS analysis, we considered maternal age at delivery, race/ ethnicity, level of education, smoking or binge drinking (>= 4 drinks per episode) in the periconceptional period, pre-pregnancy body mass index (BMI), and use of folic acid or multi-vitamins containing folic acid (during the month before or first month of pregnancy) as confounders in our analysis and reviewed their distribution (14). We also considered other illicit drug use to be a confounder. We examined nausea or vomiting during the first three months of pregnancy and marijuana use by a partner because of literature suggesting an association between these covariates and the exposure (11). However, nausea and partner's use of marijuana were not considered confounders in our analysis.

We fit logistic regression models to calculate unadjusted and adjusted odds ratios (OR, aOR, respectively) and 95% confidence intervals (CI) for individual birth defect categories. Only unadjusted results are reported for birth defect categories with fewer than five exposed cases. For all adjusted models, we added age at delivery and pre-pregnancy BMI to the model as continuous variables; all other confounders were assessed categorically. Covariates with an unknown or refused response were coded as missing, and observations with missing values were dropped from the adjusted model.

Results

The NBDPS full dataset included 44,029 mothers (32,200 mothers of cases and 11,829 mothers of controls). Among these mothers, 762 were excluded who were missing a response to all marijuana interview questions. Among the remaining mothers with an exposure response, 5.4% of cases and 5.0% of controls reported using marijuana at least

once during the three months before their pregnancy to the end of their pregnancy. Among these 43,267 mothers, 4.4% of cases and 3.9% of controls reported marijuana use at least once during the periconceptional period of one month before pregnancy through the first three months of pregnancy (Figure 1). There is a slight increase in marijuana use in the periconceptional period by the estimated year of the date of delivery among case mothers versus controls (Figure 1).

Factors associated with periconceptional marijuana use in NBDPS included mothers who were more likely to be younger (<25 years vs 25- 34 years) (OR=3.42, 95% CI: 3.08, 3.79), have less education (≤ 12 years) (OR=2.70, 95% CI: 2.45, 2.98), smoked cigarettes in the periconceptional period (OR=11.00, 95% CI: 9.93, 12.19), binge drank in the periconceptional period (OR=7.04, 95% CI: 6.38, 7.75), and used other illicit drugs (OR=27.96, 95% CI: 24.00, 32.57) than mothers who did not use marijuana periconceptionally (Table 1). Mothers who used marijuana periconceptionally were also much more likely to have a male partner who also used marijuana at least once in the three months before their pregnancy to the end of their pregnancy (OR=38.58, 95% CI: 34.38, 43.31) (Table 1). A similar percentage of marijuana users reported nausea during the first three months of pregnancy (4.3%) and did not report nausea (4.2%) as compared to non-users. Among non-Hispanic black mothers, marijuana use was more common than among Non-Hispanic white mothers (7.3% vs 4.2%). The opposite was found for Hispanic mothers as compared with Non-Hispanic white mothers (2.8% vs 4.2%). Marijuana users were less likely than non-users to have a BMI ≥30 (OR=0.87, 95% CI: 0.77, 0.98) and less likely to use folic acid in the month prior to pregnancy through the first month of pregnancy (OR= 0.49, 95% CI: 0.45, 0.54).

Among mothers who used marijuana during the periconceptional period, there was an increased odds of several defect categories including amniotic band syndrome and limb body wall complex (ABS-LBWC) (OR=1.90, 95% CI: 1.24, 2.91), bilateral renal agenesis or hypoplasia (OR=1.80, 95% CI: 1.02, 3.19), and gastroschisis (OR=3.43, 95% CI: 2.85, 4.12) compared to non-users (Table 2). Within ABS-LBWC marijuana use had the strongest association with limb abnormalities (OR=2.29, 95% CI: 1.40, 3.74). Marijuana use was not associated with any individual major categories of heart defects, but it was associated with subcategories and one combination of major categories including atrial sepal defect (ASD) not otherwise specified (NOS) (OR=1.46, 95% CI: 1.03, 2.09), ASD ostium secundum (OS) (OR=9.20, 95% CI: 2.43, 34.79), and the combination of VSD, ASD, and pulmonary stenosis (PS) (OR=2.97, 95% CI: 1.05, 8.43).

After adjusting for potential confounders, many of the aforementioned associations moved towards the null. However, gastroschisis still remained associated with periconceptional marijuana use (aOR= 1.34, 95% CI: 1.06, 1.68) (Figure 2a). Anencephaly/ craniorachischisis had a stronger association after adjusting for these covariates (aOR= 1.68, 95% CI: 1.10, 2.56). For heart defects, Ebstein's anomaly had an increased odds (aOR=1.44, 95% CI: 0.66, 3.12), and lastly, for both, heterotaxia with congenital heart disease (CHD) (aOR=0.44, 95% CI: 0.21, 0.92) and tetralogy of Fallot (aOR=0.66, 95% CI: 0.45, 0.98), there was a protective association when comparing users to non-users (Figure 2b).

Discussion

The prevalence of periconceptional marijuana use among mothers in NBDPS is 4.4% of cases and 3.9% of controls. Our study was similar to the 3.9% of pregnant

women who used marijuana that was reported based on the National Survey on Drug Use and Health in 2014 (1, 4). However, the national survey did not include specific information on which month of pregnancy that the woman was using marijuana (4). Additionally, our study adds that a large percentage of these pregnant women used marijuana during the periconceptional period, which other studies have suggested (21, 27). Our analysis does not show a strong increase in marijuana use over time. However, it also does not include the period when legalization of recreational marijuana use started, which began in 2012 in Colorado and Washington (states that were not included in NBDPS).

For our second objective, we were able to fit 72 adjusted models for each of the different birth defects. Our analyses suggested that there may be an association between periconceptional marijuana use and gastroschisis and anencephaly/craniorachischisis after adjusting for covariates. Both of these defects also had increased adjusted odds ratios in the previous NBDPS analysis from 1997-2005 (14). Additionally, gastroschisis has been reported to be associated with marijuana use during pregnancy in other studies (17, 18, 28).

For heart defects, Ebstein's anomaly had an elevated odds ratio, and there is another study that suggested a similar association after adjusting for covariates (20). However, our analyses had an imprecise estimate with only 8 exposed cases. To our knowledge, this is the first study to show a potential protective effect of periconceptional marijuana use for heterotaxia with CHD and tetralogy of Fallot after adjusting for covariates. Although the estimate for heterotaxia with CHD is strong, it is not precise. Tetralogy of Fallot had a more precise estimate but a weaker association.

Our unadjusted analyses identified several other, relatively rare defects that were more prevalent among marijuana users compared with non-users, including bilateral renal agenesis or hypoplasia, ABS-LBWC, ASD NOS, ASD OS, and the combination of VSD, ASD, and PS. Some of these defects have been seen in other studies with similar unadjusted findings; however, in our analysis after adjusting, these findings did not hold (15, 18, 19).

Our findings on the demographics of pregnant women using marijuana were similar to those previously reported. Although other studies have reported an association between maternal and paternal marijuana use, this is the first to suggest such a strong association. Additionally, the analysis suggests that pregnant women who use marijuana in the periconceptional period are more likely to use other illicit drugs, smoke cigarettes, and binge drink. Although other studies have estimates to suggest these associations, our results are more precise estimates (15, 21). Our analysis did not find that the population of pregnant women using marijuana reported nausea more frequently than non-users. However, our data did not have information on the severity of the nausea which may be important because only women who experience severe nausea may choose to use marijuana to relieve their nausea. Further, the use of marijuana to relieve nausea may be more common now in states where use is legal than it was at the time of NBDPS.

Underreporting is a limitation of our analysis. Many illicit drug studies indicate a likelihood of underreporting of self-reported marijuana use due to the stigma associated with it, fear of incarceration, or fear of potential loss of infant custody (15, 30). Ideally, toxicology testing in addition to self-reported questionnaires at several time points before and during pregnancy could address for these limitations (31-33). However, there are

limitations to toxicology testing as well and conducting such a study would be costly and logistically challenging (31-33).

Overall, these data do not address recent changes in marijuana use in the United States. With the recent legalization of both medical and recreational marijuana, the access to the drug has greatly increased since 1997-2011. The THC content of marijuana has also increased over the years, so even if the prevalence of exposure is the same, the exposure to THC is likely higher among users than is represented by these data (5). Although the change in concentration from 1997 to 2018 may not be as drastic as the change from the 1980s, synthetic blends like, *Spice*, that mirror a high-potency marijuana and some hashish samples can average around 28.2% THC but reach as high as 66% THC (5). Thus, data from more recent years would provide further insight into the current and changing landscape of marijuana use in the United States and could show different results if prior exposure levels were below the threshold that affects development.

Conclusion

This is the largest study to assess the adjusted associations between self-reported maternal marijuana use during the periconceptional period and 72 different birth defects, including some defects that have not previously been studied in relation to marijuana use during pregnancy. The findings suggest an association for two non-heart defects, gastroschisis and anencephaly/ craniorachischisis, among periconceptional marijuana users. Gastroschisis has been increasing in prevalence and is most common among younger women, but little is known about why. Marijuana use is also increasing and could be contributing to this increase.

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Tables

Table 1: Description of NBDPS mothers stratified by periconceptional marijuana users and non-users, NBDPS, 1997-2011.

	Periconceptional Marijuana Users (n =1,844)		***Non-Periconceptional Marijuana Users (Reference) (n =41,421)***		
	n	*Row %*	*n*	*Row %*	***OR 95% CI***
Age at Delivery					
<25 years	1,162	8.1%	13,261	91.9%	3.42 (3.08, 3.79)
25-34 years (reference)	560	2.5%	21,853	97.5%	
≥35 years	122	1.9%	6,309	98.1%	0.75 (0.62, 0.92)
Race/ Ethnicity					
Non-Hispanic White (reference)	1,069	4.2%	24,295	95.8%	
Non-Hispanic Black	321	7.3%	4,106	92.8%	1.78 (1.56, 2.02)
Hispanic	298	2.8%	10,283	97.2%	0.66 (0.58, 0.75)
Other Race or Ethnicity	156	5.4%	2,726	94.6%	1.30 (1.09, 1.55)
Education (years)					
≤12	1,207	6.6%	16,971	93.4%	2.70 (2.45, 2.98)
>12 (reference)	632	2.6%	23,983	97.4%	
Periconceptional Cigarette Smoking[a]					
Yes	1,285	15.3%	7,124	84.7%	11.00 (9.93, 12.19)
No (reference)	557	1.6%	33,964	98.4%	
Periconceptional Binge Drinking (>=4 drinks)[a]					
Yes	857	15.7%	4,611	84.3%	7.04 (6.38, 7.75)
No (reference)	955	2.6%	36,151	97.4%	
Pre-Pregnancy BMI					
<30 (reference)	1,502	4.5%	31,635	95.5%	0.87 (0.77, 0.98)
≥30	328	4.0%	7,981	96.1%	
Folic Acid Use[b]					
Yes	663	2.9%	22,047	97.1%	0.49 (0.45, 0.54)
No (reference)	1,180	5.7%	19,375	94.3%	

Other Illicit Drug Use					
Yes	375	50.2%	372	49.8%	27.96 (24.00, 32.57)
No (reference)	1,468	3.5%	40,713	96.5%	
Nausea[c]					
Yes	1,253	4.3%	28,000	95.7%	1.02 (0.92, 1.13)
No (reference)	585	4.2%	13,359	95.8%	
Father's Use of Marijuana					
Yes	1,343	30.5%	3,063	69.5%	38.58 (34.38, 43.31)
No (reference)	422	1.1%	37,136	98.9%	

[a]Use at least once during the periconceptional period (one month before pregnancy through the first three months of pregnancy).

[b]Use at least once during the month before pregnancy through the first month of pregnancy.
[c]Use at least once during the first three months of pregnancy.

Table 2: Unadjusted and adjusted odds ratios for self-reported maternal periconceptional marijuana use and all NBDPS birth defects, 1997-2011.

NBDPS 1997-2011			
Birth Defect Categories[a]	**Exposed cases/ Total number of cases**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)[b]**
Non-Heart Birth Defects			
Amniotic band syndrome and limb body wall complex [ABS-LBWC]	24/334	1.90 (1.24, 2.91)	1.04 (0.63, 1.71)
ABS-LBWC: Limb anomalies only	18/211	2.29 (1.40, 3.74)	1.06 (0.59, 1.90)
ABS-LBWC: Craniofacial disruptions +/- limb anomalies	3/65	1.19 (0.37, 3.80)	
ABS-LBWC: BWC +/- Limb anomalies and +/- craniofacial disruptions	3/58	1.34 (0.42, 4.29)	
Neural tube defects	89/2150	1.06 (0.84, 1.34)	1.14 (0.88, 1.48)
Anencephaly and craniorachischisis	34/647	1.36 (0.95, 1.95)	1.68 (1.10, 2.56)
Spina bifida	44/1277	0.88 (0.64, 1.20)	0.89 (0.63, 1.26)
Encephalocele	11/226	1.26 (0.68, 2.32)	1.33 (0.68, 2.60)
Hydrocephaly	24/511	1.21 (0.79, 1.84)	1.05 (0.65, 1.69)
Dandy-Walker malformation	11/185	1.55 (0.84, 2.87)	1.41 (0.70, 2.82)
Cerebellar hypoplasia	1/62	0.40 (0.06, 2.91)	
Holoprosencephaly	7/172	1.04 (0.49, 2.23)	0.70 (0.28, 1.74)
Cataracts[c]	11/355	0.79 (0.43, 1.46)	0.66 (0.34, 1.28)
Anophthalmos/microphthalmos	11/232	1.22 (0.66, 2.25)	1.04 (0.52, 2.07)
Glaucoma/anterior chamber defects[c]	7/182	0.99 (0.46, 2.13)	1.28 (0.55, 2.97)
Anotia/microtia	25/692	0.92 (0.61, 1.39)	0.96 (0.60, 1.53)
Choanal atresia	3/166	0.45 (0.14, 1.42)	
Oral clefts[c]	201/4723	1.08 (0.91, 1.28)	0.91 (0.75, 1.10)
Cleft palate[c]	59/1603	0.93 (0.71, 1.23)	0.78 (0.57, 1.06)
Cleft lip w/wo cleft palate[c]	142/3120	1.16 (0.96, 1.41)	0.98 (0.79, 1.21)
Cleft lip with cleft palate[c]	92/2022	1.16 (0.92, 1.46)	0.95 (0.74, 1.23)
Cleft lip without cleft palate[c]	50/1098	1.16 (0.86, 1.57)	1.03 (0.74, 1.45)
Esophageal atresia	29/756	0.98 (0.67, 1.43)	1.07 (0.70, 1.63)
Intestinal atresia/stenosis	21/477	1.13 (0.72, 1.77)	0.93 (0.56, 1.54)
Duodenal atresia/stenosis	9/237	0.97 (0.49, 1.90)	0.97 (0.47, 1.98)
Colonic atresia/stenosis	5/56	2.40 (0.96, 6.05)	0.96 (0.33, 2.82)
Anorectal atresia/stenosis - All	39/1077	0.92 (0.66, 1.29)	0.86 (0.60, 1.23)

Non-complex sequences anorectal atresia/stenosis	30/895	0.85 (0.58, 1.24)	0.83 (0.55, 1.25)
High anorectal atresia/stenosis non-complex sequences	8/212	0.96 (0.47, 1.96)	1.05 (0.48, 2.27)
Low anorectal atresia/stenosis non-complex sequences	16/475	0.86 (0.51, 1.42)	0.86 (0.50, 1.49)
Cloacal exstrophy	5/100	1.29 (0.52, 3.19)	0.97 (0.35, 2.70)
Biliary atresia	7/199	0.89 (0.42, 1.91)	0.94 (0.41, 2.15)
Hypospadias second/third degree[c]	81/2562	0.77 (0.59, 0.99)	0.88 (0.66, 1.16)
Bladder exstrophy	2/74	0.68 (0.17, 2.79)	
Bilateral renal agenesis or hypoplasia	13/190	1.80 (1.02, 3.19)	1.40 (0.74, 2.68)
Limb deficiency	58/1254	1.19 (0.90, 1.57)	1.02 (0.74, 1.39)
Longitudinal limb deficiency	23/480	1.23 (0.80, 1.90)	1.00 (0.61, 1.64)
Longitudinal preaxial limb deficiency	12/280	1.10 (0.61, 1.97)	0.93 (0.49, 1.78)
Transverse limb deficiency	33/721	1.18 (0.82, 1.69)	1.06 (0.70, 1.59)
Intercalary limb deficiency	4/67	1.56 (0.56, 4.30)	
NOS limb deficiency	0/24		
Craniosynostosis	49/1559	0.78 (0.57, 1.05)	0.94 (0.67, 1.32)
Diaphragmatic hernia	40/874	1.18 (0.85, 1.64)	1.11 (0.76, 1.61)
Omphalocele	24/439	1.42 (0.93, 2.16)	1.20 (0.75, 1.92)
Gastroschisis	173/1412	3.43 (2.85, 4.12)	1.34 (1.06, 1.68)
Sacral agenesis or caudal dysplasia	7/110	1.67 (0.77, 3.60)	1.64 (0.70, 3.84)
Heart Birth Defects			
Any heart defect	495/12364	1.02 (0.90, 1.16)	0.92 (0.80, 1.07)
Heterotaxia with Congenital Heart Disease (CHD)	9/346	0.66 (0.34, 1.28)	0.44 (0.21, 0.92)
Heterotaxia without CHD	3/78	0.98 (0.31, 3.12)	
Conotruncal defects	101/2621	0.98 (0.79, 1.22)	0.88 (0.69, 1.13)
Truncus arteriosus	4/138	0.73 (0.27, 1.99)	
Interrupted aortic arch, type B	4/50	2.13 (0.76, 5.95)	
Interrupted aortic arch, NOS	1/8	3.51 (0.43, 28.54)	
Tetralogy of Fallot	39/1211	0.82 (0.59, 1.14)	0.66 (0.45, 0.98)
D-Transposition of the great arteries (TGA)	32/771	1.06 (0.74, 1.53)	1.10 (0.73, 1.64)
Double outlet right ventricle-(TGA)	9/192	1.21 (0.61, 2.37)	0.80 (0.36, 1.79)
Double outlet right ventricle-Other	5/123	1.04 (0.42, 2.56)	1.00 (0.38, 2.62)
Ventricular septal defect-conoventricular	8/146	1.42 (0.69, 2.92)	1.29 (0.56, 2.97)
Atrioventricular septal defect	19/373	1.32 (0.82, 2.11)	1.06 (0.63, 1.79)
Anomalous pulmonary venous return (APVR)	14/382	0.93 (0.54, 1.60)	0.79 (0.42, 1.48)
Total APVR	12/303	1.01 (0.56, 1.82)	0.83 (0.41, 1.67)

Partial APVR	2/79	0.64 (0.16, 2.60)	
Left-ventricular outflow tract obstruction defects	82/2245	0.93 (0.73, 1.18)	1.08 (0.83, 1.41)
Hypoplastic left heart syndrome	28/661	1.08 (0.73, 1.60)	1.21 (0.79, 1.85)
Interrupted aortic arch type A	2/22	2.45 (0.57, 10.53)	
Coarctation of the aorta	39/1174	0.84 (0.60, 1.18)	1.04 (0.72, 1.50)
Aortic stenosis	15/513	0.74 (0.44, 1.25)	0.85 (0.48, 1.49)
Right ventricular outflow tract (RVOT) defects	98/2112	1.19 (0.95, 1.49)	1.05 (0.82, 1.36)
Right ventricular outflow tract defects - excluding Ebstein cases	90/1962	1.18 (0.94, 1.49)	1.02 (0.78, 1.32)
Pulmonary atresia	13/265	1.27 (0.72, 2.23)	1.06 (0.53, 2.12)
Pulmonary valve stenosis[c]	73/1559	1.21 (0.94, 1.56)	1.04 (0.78, 1.38)
Ebstein anomaly	8/180	1.14 (0.56, 2.33)	1.44 (0.66, 3.12)
Tricuspid atresia	8/179	1.15 (0.56, 2.35)	1.02 (0.46, 2.29)
Septal defects	204/4745	1.10 (0.93, 1.30)	0.93 (0.77, 1.12)
Ventricular septal defect perimembranous	70/1669	1.07 (0.83, 1.39)	0.92 (0.69, 1.23)
Ventricular septal defect muscular (simple) [c]	6/161	1.13 (0.45, 2.80)	1.25 (0.43, 3.60)
Ventricular septal defect muscular (not simple)	25/670	0.95 (0.63, 1.43)	1.21 (0.77, 1.90)
Ventricular septal defect not otherwise specified (NOS) (simple)[c]	0/17		
Ventricular septal defect NOS (not simple)	3/56	1.39 (0.43, 4.46)	
Ventricular septal defect ostium secundum (OS)	1/20	1.29 (0.17, 9.66)	
Multiple ventricular septal defects	2/69	0.73 (0.18, 3.00)	
Atrial septal defect (ASD) secundum or ASD NOS	136/3080	1.13 (0.93, 1.38)	0.93 (0.75, 1.15)
Atrial septal defect secundum	100/2458	1.04 (0.83, 1.30)	0.84 (0.66, 1.07)
Atrial septal defect NOS	35/621	1.46 (1.03, 2.09)	1.31 (0.88, 1.96)
ASD OS	3/11	9.20 (2.43, 34.79)	
Single ventricle/complex	12/332	0.92 (0.51, 1.65)	0.87 (0.46, 1.67)
Association: Aortic stenosis (AS) + Coarctation of the aorta (COA)	2/125	0.40 (0.10, 1.62)	
Association: COA + VSD	15/308	1.26 (0.74, 2.13)	1.35 (0.73, 2.49)
Association: VSD + ASD	35/768	1.17 (0.82, 1.67)	1.15 (0.78, 1.71)
Association: VSD + ASD + COA	2/95	0.53 (0.13, 2.15)	

Association: Pulmonary valve stenosis (PVS) + ASD	15/261	1.50 (0.88, 2.54)	0.90 (0.48, 1.66)
Association: PVS + VSD	8/150	1.38 (0.67, 2.83)	1.04 (0.46, 2.39)
Association: VSD + ASD + Pulmonary stenosis (PS)	4/37	2.97 (1.05, 8.43)	
Association: VSD + ASD + AS	0/9		

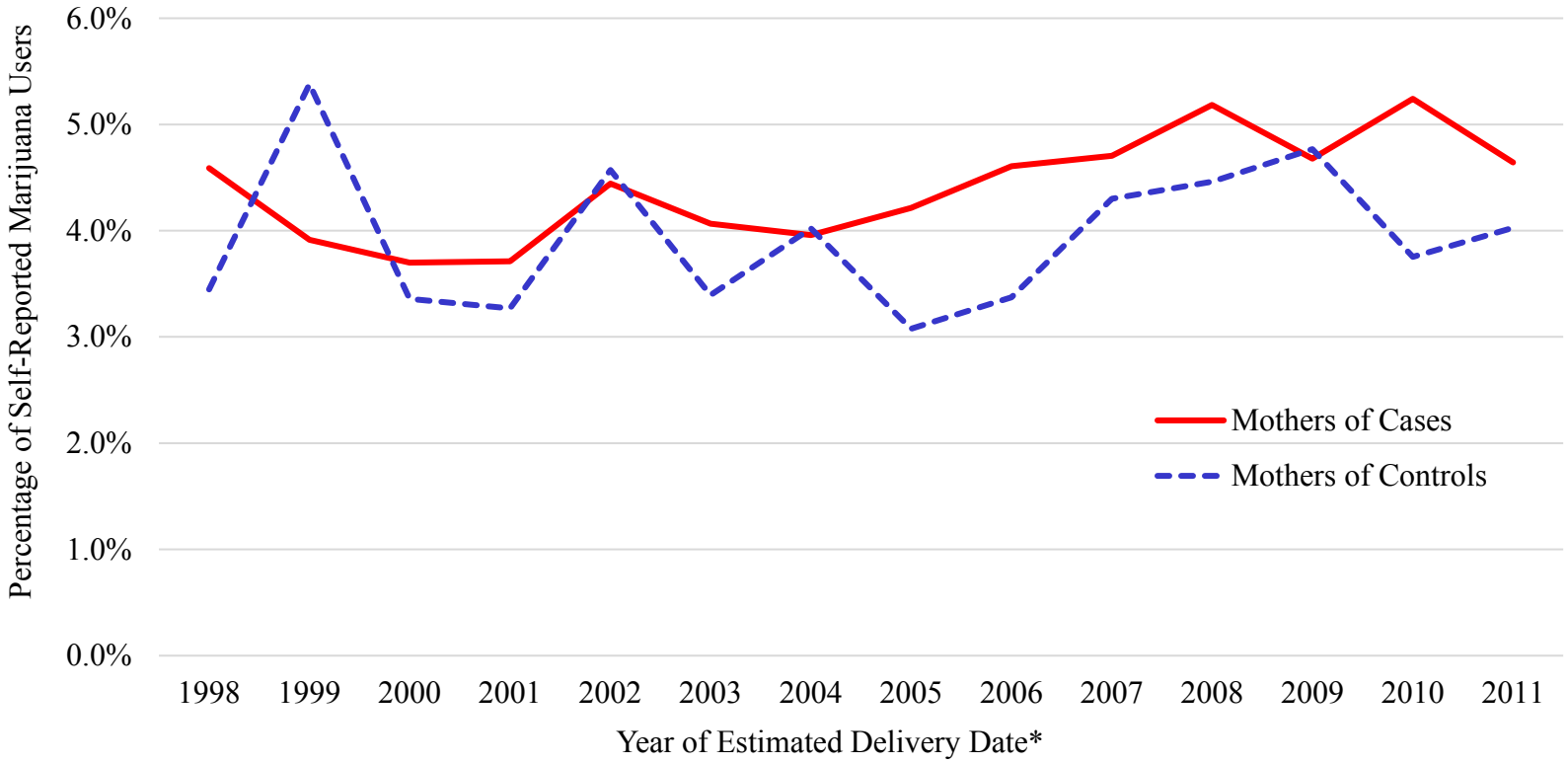
[a]Bolded categories represent birth defect categories that have additional sub-levels (italics) with more specific classification.

[b]Adjusted for age at delivery (continuous), race/ethnicity, education, periconceptional cigarette smoking, periconceptional binge drinking (≥4 drinks), pre-pregnancy BMI (continuous), folic acid use (one month before pregnancy through the first month of pregnancy), and other illicit drug use.

[c]The exposed controls/ total number of controls was 455/11615 except for these defects: cataracts and glaucoma/anterior chamber defects (383/9893), oral clefts (including cleft palate, cleft lip w/wo cleft palate, cleft lip with cleft palate, cleft lip without cleft palate) (453/11481), hypospadias second/third degree (242/5913), pulmonary valve stenosis (435/11615), and ventricular septal defect muscular (simple) (24/723).

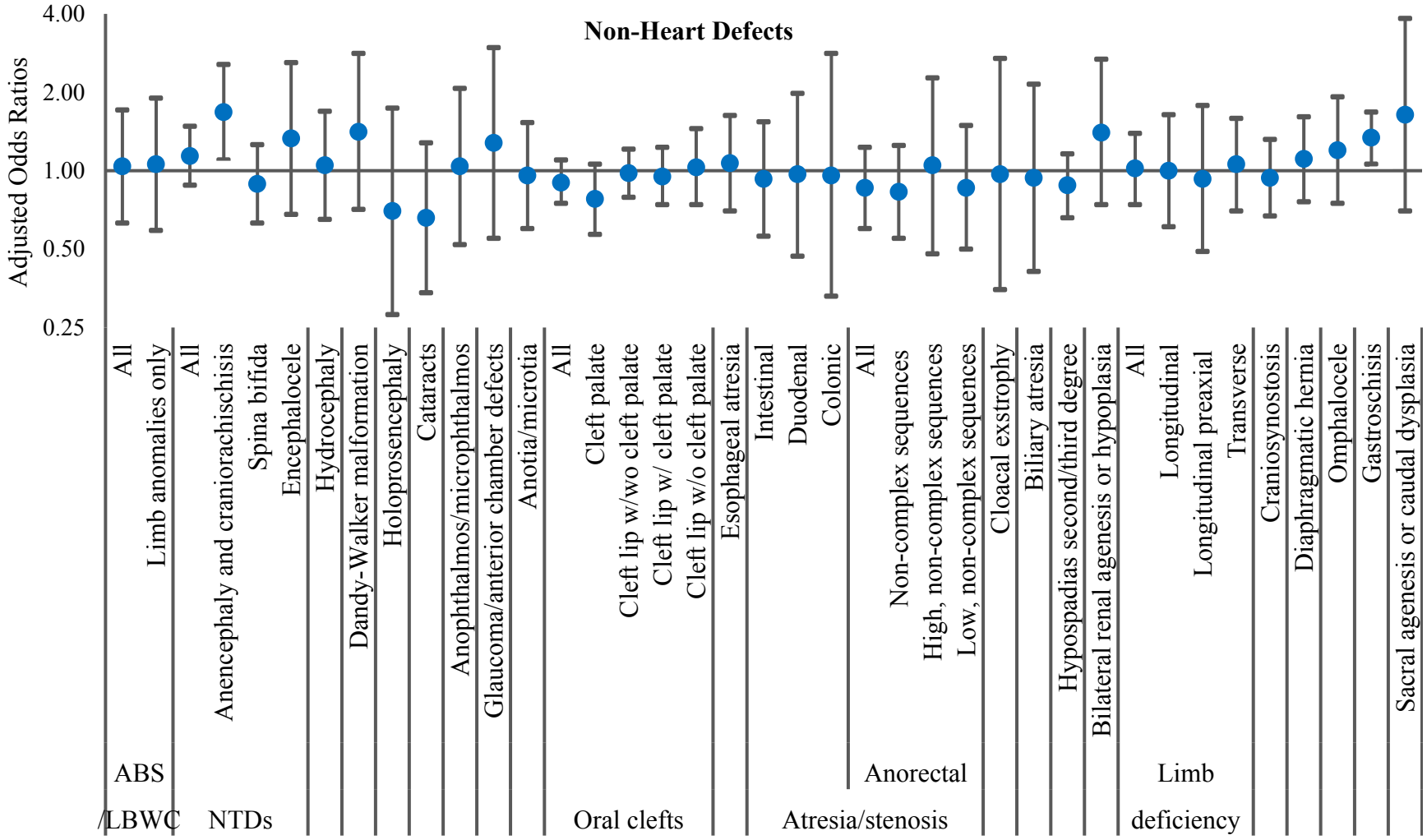
Figures/ Figure Legends

Figure 1. Self-reported maternal marijuana use during the periconceptional period among case and control mothers by year of their delivery date, NBDPS, 1998-2011.



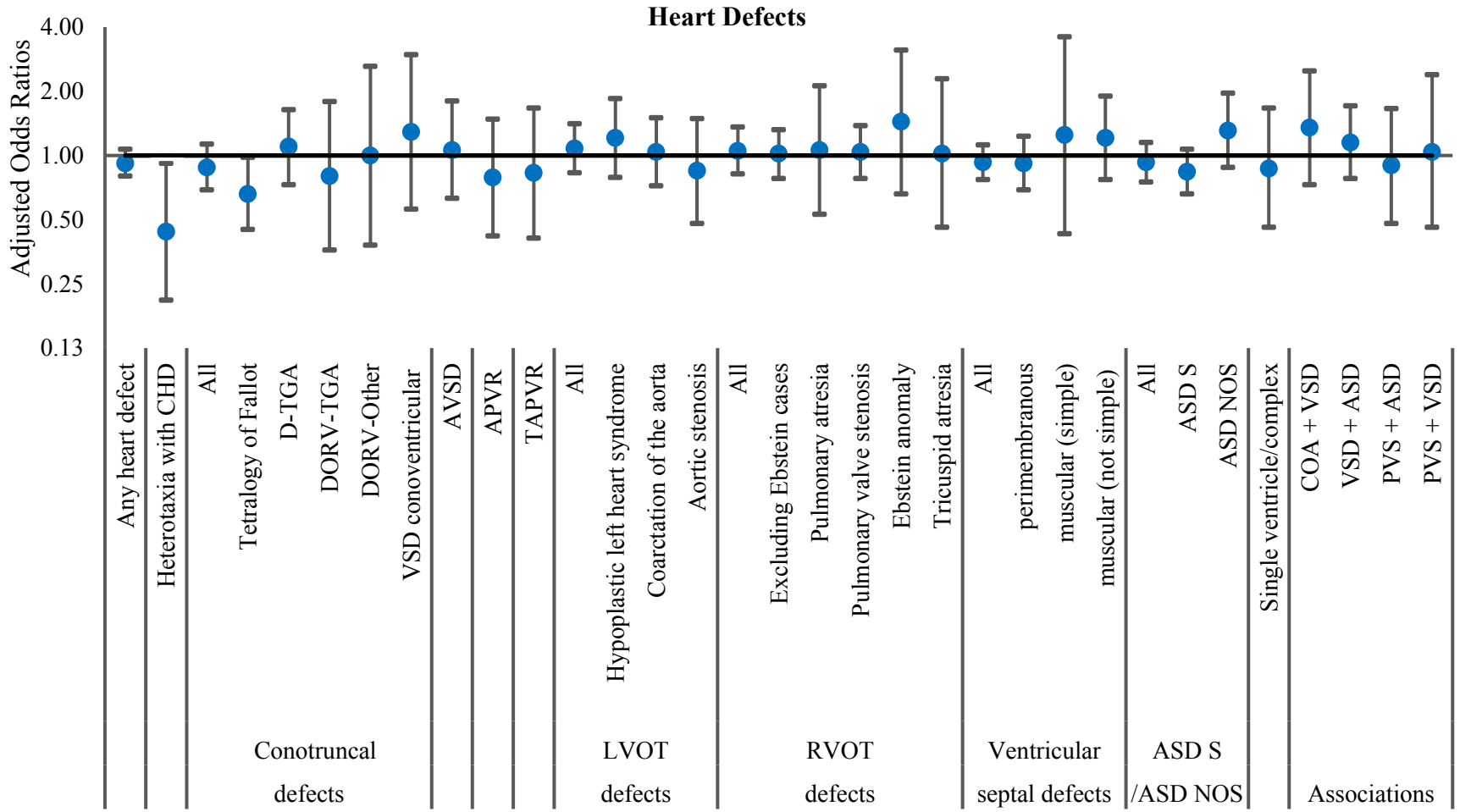
*One case did not have an estimated delivery date and was excluded from this figure.

Figure 2a. Adjusted odds ratios for non-heart defects among self-reported maternal periconceptional marijuana users, NBDPS, 1997-2011.



*ABS/LBWC: Amniotic band syndrome and limb body wall complex, NTDs: Neural tube defects.

Figure 2b. Adjusted odds ratios for heart defects among self-reported maternal periconceptional marijuana users, NBDPS, 1997-2011.



*CHD: Congenital heart disease, TGA: Transposition of the great arteries, DORV: Double outlet right ventricle, VSD: Ventricular septal defect, AVSD: Atrioventricular septal defect, APVR: Anomalous pulmonary venous return, APVR: Anomalous pulmonary venous return: T: Total, P: Partial, ASD: Atrial septal defect, S: Secundum, NOS: Not otherwise specified, COA: Coarctation of the Aorta, PVS: Pulmonary valve stenosis.