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# Medication use during pregnancy, risk of adverse pregnancy outcomes and congenital anomalies: examining mechanisms of systematic bias

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BOSTON UNIVERSITY  
SCHOOL OF PUBLIC HEALTH

Dissertation

**MEDICATION USE DURING PREGNANCY, RISK OF  
ADVERSE PREGNANCY OUTCOMES AND CONGENITAL ANOMALIES:  
EXAMINING MECHANISMS OF SYSTEMATIC BIAS**

by

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*“Petit à petit, l’oiseau fait son nid”*

- Proverbe français

## **DEDICATION**

This dissertation is dedicated to my aunt, Yves Joseph Emeline Jérémie, whose love and support were integral in shaping me. Her absence is felt every day.

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**ABSTRACT**

Observational studies of the effects of medication use during pregnancy are threatened by mechanisms of systematic bias which may impact the interpretation of effect estimates. Importantly, these biases may independently or jointly threaten validity, resulting in observed associations that may be incorrect in both direction and magnitude. Methods of quantitatively assessing and addressing these biases are available, and under the correct assumptions, can provide a more accurate understanding and interpretation of effect measures. The goals of this dissertation were to examine previous studies on associations of commonly used medications during pregnancy, adverse pregnancy and fetal outcomes and apply analytic methods to address validity concerns. We used data from the National Birth Defects Prevention Study (NBDPS) for all three studies, which was the largest, population-based case-control study of congenital anomalies from 1997–2011.

In the first study, we evaluated whether the previously reported increased risk of orofacial clefts associated with ondansetron in NBDPS may be explained

by selection bias arising from differential participation. We used study records available on participants and non-participants to calculate inverse probability of participation weights (IPWs) to adjust for differential participation. The unadjusted odds ratio (OR) for ondansetron use and cleft palate was 1.5 (95% CI 1.0–2.0). After adjusting for age, education, study year and location, and periconceptual folic acid use, the estimate was 1.6 (95% 1.1–2.1) and the participation-weighted OR was 1.4 (95% CI 1.0–2.0). When we adjusted for confounding using the same covariates as the confounding-only model and selection bias, the OR was 1.6 (95% CI 1.3–2.2). Our estimates suggested limited evidence of selection bias from differential participation in the association between ondansetron use in the first trimester and cleft palate reported in NBDPS.

In the second study, we assessed and quantified the presence of immortal time bias in a study on the use of decongestants in late pregnancy and preterm delivery, comparing time-fixed to time-varying analyses. We observed that results from a time-fixed approach (aHR = 0.99, 95% CI 0.75, 1.31) for our time-dependent outcome resulted in downward bias compared to results from the time-varying approach (aHR = 1.09, 95% CI 0.82, 1.44). However, we did not observe the same reductions in risk of preterm delivery associated with use of decongestants in the when using a time-fixed approach as previously reported in the literature. Overall, we found that both time-fixed and time-varying approaches suggested that use of decongestants in second and/or third trimester of pregnancy did not confer a protective effect for preterm delivery.

In the third study, we conducted probabilistic and multidimensional bias analyses to address differential and nondifferential exposure misclassification for the association between periconceptional use of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) and amniotic band syndrome. Under the assumption of differential misclassification, assuming better classification in the cases, the bias-adjusted estimates were compatible with either bias away or towards the null. When we assumed greater specificity in the cases, the bias-adjusted estimates suggested bias away from the null in the unadjusted estimates. If we assumed greater sensitivity in the cases, the adjusted estimates suggested bias away when specificity was high ( $> 0.9$ ) or towards the null as specificity decreased. Results suggested substantial bias towards the null when we assumed nondifferential exposure misclassification, particularly if sensitivity and specificity were low (0.3 and 0.8 respectively).

All three studies highlight the importance of examining and quantifying the effect of proposed mechanisms of systematic bias on associations in observational studies otherwise we may be led astray by intuitions. These analyses also underline the critical importance of explicitly stating assumptions since all results are conditional on assumptions being correct. These methods (and others) can be used to quantitatively assess important, potential sources of systematic error to ultimately improve the rigor of observational studies and our ability to draw conclusions.

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## LIST OF ABBREVIATIONS

ABS.....	Amniotic Band Syndrome
BDS.....	Slone Birth Defects Study
BMI.....	Body Mass Index
CATI.....	Computer-Assisted Telephone Interviews
CDC.....	U.S. Centers for Disease Control and Prevention
CI.....	Confidence Interval
COX.....	Cyclooxygenase
CP.....	Cleft Palate
EDD.....	Estimated Delivery Date
EMR.....	Electronic Medical Records
FDA.....	Food and Drug Administration
GI.....	Gastrointestinal
HR.....	Hazard Ratio
IPW.....	Inverse Probability Weight
IV.....	Intravenous
LMP.....	Last Menstrual Period
NBDPS.....	National Birth Defects Prevention Study
NPV.....	Negative Predictive Value
NSAID.....	Non-Steroidal Anti-Inflammatory Drugs
NVP.....	Nausea and Vomiting of Pregnancy
OFC.....	Orofacial clefts

OR..... Odds Ratio  
OTC..... Over-the-Counter  
PPV..... Positive Predictive Value  
QBA..... Quantitative Bias Analysis  
RFTS..... Right from the Start Study  
SMART..... Safety of Medications and Perception of Teratogenicity Study  
URI..... Upper Respiratory Illness  
U.S..... United States

## INTRODUCTION

Medication use during pregnancy has increased by more than 60% in the last 30 years.<sup>1,2</sup> Between 2006 and 2008, the vast majority (>90%) of pregnant people reported using at least one prescription or over-the-counter (OTC) medication during pregnancy; over 80% reporting use during the first trimester, a critical period in embryonic development.<sup>1</sup> Despite the increasing use, information on the teratogenicity and safety of the majority of medications during pregnancy is sparse. Decisions around treatment are largely based on perceptions of fetal risks and whether the potential benefits to the pregnant person outweigh the risks to the fetus.<sup>3</sup>

Randomized clinical trials often exclude pregnant individuals and evidence on exposure to medications and their effects on pregnancy and fetal outcomes is primarily based on observational studies.<sup>4-10</sup> However, these data are prone to several sources of systematic bias (e.g., selection bias, information bias), resulting in observed associations that can be incorrect in both direction and magnitude. The effects of these mechanisms of bias are important to describe and quantify; yet analyses to address their impact on study results are rare.<sup>11-16</sup>

Pharmacological treatment during pregnancy is complex and nuanced. Often, reported medications are linked to common symptoms or conditions of pregnancy.<sup>17</sup> Such conditions include nausea and vomiting of pregnancy (NVP), upper-respiratory infections or pain. Approximately 70–80% of pregnant people report NVP and nearly a quarter report off label use of ondansetron (a 5-HT<sub>3</sub>

receptor antagonist) as a treatment.<sup>18 20</sup> Decongestants are among the most common OTC treatment for asthma and upper-respiratory infections, and are used by at least 15% of pregnant people.<sup>21</sup> Pain, as the result of physiological changes or non-obstetric causes, is also common during pregnancy.<sup>22</sup> Analgesics are among the class of medications most frequently used by pregnant people. Included in the class of analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs), with prevalence estimates for use during pregnancy ranging between 2% and 15%.<sup>22</sup> <sup>25</sup> With widespread and increasing use of both prescription and OTC medications during pregnancy, critically examining the evidence on associations between these commonly used medications and pregnancy, as well as fetal outcomes is an important endeavor to support improved evidence for pharmacological treatments during pregnancy.

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## **2 FIRST-TRIMESTER USE OF ONDANSETRON AND OROFACIAL CLEFTS: EXAMINING SELECTION BIAS**

### **2.1 INTRODUCTION**

Nausea with or without vomiting is the most commonly reported complaint of pregnancy. Nearly 80% of people experience nausea, and 50% experience vomiting during pregnancy.<sup>1,2</sup> Nausea and vomiting in pregnancy (NVP) typically occurs in the first trimester, a critical period for exposure to teratogens due to organogenesis.<sup>1</sup> NVP is generally associated with reduced risks of adverse pregnancy outcomes such as early pregnancy loss and preterm delivery.<sup>3,4</sup> Studies also suggest that NVP is associated with reduced risks of cardiac and noncardiac birth defects, including cleft lip with or without cleft palate.<sup>5,6</sup>

Although very common, there is a lack of consensus on the best treatment for NVP.<sup>7-10</sup> Symptoms can affect the quality of life of the pregnant person and early treatment is recommended to prevent progression to hyperemesis gravidarum, an indication for hospitalization.<sup>1,11</sup> However, between 1983 and 2013, there were no US Food and Drug Administration (FDA)-approved treatments for NVP.<sup>8,12</sup> Given the lack of recourse, treatment of symptoms generally includes off-label use of herbal/natural products, over-the-counter (OTC) or prescription medications.<sup>9</sup> Ondansetron, a serotonin (5-HT<sub>3</sub>) receptor antagonist, is the most commonly used prescription oral antiemetic during pregnancy in the US, despite not being approved for treatment of NVP.<sup>13</sup> Ondansetron use in pregnancy has been increasing over time.<sup>9,13</sup> According to a 2014 US report, an estimated 22%

of people use ondansetron in their first trimester of pregnancy, up from 1% at the end of the 1990s.<sup>13,14</sup>

In recent years, evidence from observational studies has highlighted the possibility that use of ondansetron in the first trimester of pregnancy may be linked to congenital anomalies, particularly orofacial clefts. Evidence from a retrospective cohort study using Medicaid records, demonstrated no association with the use of ondansetron and cleft lip with cleft palate (RR = 1.0, 95% CI 0.8–1.4) or cleft lip without palate (RR = 1.0, 95% CI 0.7–1.5), but noted an increase in risk of cleft palate only (RR: 1.2, 95% CI: 1.0–1.5).<sup>15</sup> Results from a nested case-control study in a large administrative database, also demonstrated a similar increase in risk of orofacial clefts, with use of both oral and intravenous (IV) ondansetron (aOR: 1.3, 95% CI: 0.8–2.3). However, specifically for cleft palate, results were mixed based on the definition of exposure. When only considering documentation of medically administered ondansetron in the first trimester, the adjusted estimate suggested a larger increase in risk of cleft palate (aOR = 1.5, 95% CI 0.8–2.7). When the authors also considered prescription records, in addition to medically administered ondansetron, the estimate was attenuated (aOR = 1.1, 95% CI 0.9-1.3). Despite beliefs that IV use may be driving the association between use of ondansetron and congenital anomalies, hinting to a mechanism linked to the severity of NVP; other studies of IV-only ondansetron use has demonstrated no association (RR: 1.0, 95% CI: 0.6–1.4).<sup>16,17</sup> Overall, studies of orofacial clefts and ondansetron have demonstrated no association with cleft lip with or without palate, but documented

modest increases in risk for cleft palate.<sup>15,17 20</sup>

Orofacial clefts, usually classified as either cleft lip with or without cleft palate, or cleft palate only, are among the most common congenital defects.<sup>21,22</sup> Although cleft lip with or without cleft palate can be divided into cleft lip only and cleft lip with cleft palate, the two groups are generally considered etiologically similar and included in one category in epidemiologic studies.<sup>23</sup> Cleft lip alone affects 3.1 per 10,000 live births while cleft lip with cleft palate affects 5.6 per 10,000 births, and cleft palate alone affects 5.9 per 10,000 births.<sup>22</sup> Cleft palate is presumed pathogenetically as well as etiologically different than the previous categories.<sup>24</sup> Prevalence of cleft palate varies in different populations, with a higher prevalence among people of Asian, Northern European, or Native American ancestry and a lower prevalence among Black people/people with African ancestry.<sup>25</sup>

Since specific congenital anomalies are rare and studies of associations with medication use can be underpowered, the National Birth Defects Prevention Study (NBDPS) offer the unique opportunity to examine certain research questions as one of the largest studies on causes and potential risk factors of congenital anomalies. Analyses of data from NBDPS have yielded larger estimates (1997–2004, aOR: 2.4, 95% CI: 1.2–4.8), (2005–2011, aOR: 1.6, 95% CI: 1.1–2.3) and (all years, aOR: 1.7, 95% CI 1.2–2.3) for the association of ondansetron and risk of cleft palate.<sup>5,6,12</sup> In contrast, the adjusted OR from the Birth Defects Study (BDS), a study with a similar design to NBDPS, was 0.5 (95% CI 0.3–1.0).

In most case-control designs, including NBDPS, the outcome and exposure have occurred before invitation to participate in the study. There are differences in certain characteristics in the NBDPS control participants compared to the underlying base population, namely race/ethnicity, entry into prenatal care and education. Compared with selected, but nonparticipant controls, NBDPS participant controls are more likely to report their race as non-Hispanic White, be aged  $\geq 30$  years and have completed more than a high school education.<sup>26</sup> Studies indicate that these demographic characteristics are generally associated with higher likelihood of participation in observational studies.<sup>27,28</sup> These characteristics (White, older, greater educational attainment) are also associated with the use of treatment for NVP in NBDPS.<sup>5,12</sup> Moreover, people who identify as Asian/Pacific Islanders have lower participation rates in certain NBDPS centers, particularly California and New York.<sup>26</sup> Notably, these differences in distribution of demographic characteristics are associated with participation rather than selection to be included in the study.<sup>26</sup>

Certain characteristics that may be associated with participation are also associated with the distribution of the exposure and the outcome. Treatment for NVP using ondansetron in NBDPS is more frequently reported by people with greater education attainment, identify as White and older than 25 years old at delivery.<sup>9</sup> If certain characteristics affect the likelihood of participation as well as the distribution of the exposure and/or the outcome, then the possibility of selection bias may arise.<sup>29,30</sup> In a case-control study, the controls must represent the

distribution of the exposure in the population which gave rise to the cases (“the study base”).<sup>31</sup> If the exposure is associated with participation among the controls, then in theory, the NBDPS controls may fail to represent the exposure distribution in the underlying population. Specifically, selection bias can occur if people who report use of ondansetron are more or less likely to participate in the study. The aim of this study is to explore whether the increased risk of cleft palate associated with ondansetron in NBDPS could be affected by selection bias arising from differential participation.

## **2.2 METHODS**

We used data from the NBDPS, a multistate, collaborative case-control study of select congenital anomalies in the United States from 1997 to 2011. Information on the study methodology has been described extensively elsewhere.<sup>32,33</sup> Cases were identified from active, population-based surveillance systems from study centers in 10 US states. Within the respective catchment areas, staff from sites abstracted and reviewed medical records to identify potentially eligible cases identified through surveillance; records of all identified fetuses (liveborn, stillborn and at select sites, terminations) were reviewed for congenital anomalies. Abstracted data from medical records for all identified cases were reviewed by clinical geneticists to confirm the diagnosis.

Congenital anomalies with known or strongly suspected causes (i.e., single gene or chromosomal disorders) were ineligible for participation. Cases with the

following pregnancy outcomes were eligible for inclusion in the study: livebirth, termination, or a fetal death at  $\geq 20$  weeks of gestation. Spontaneous abortions (pregnancy loss at  $< 20$  weeks of gestation) were ineligible. Control infants were randomly selected among unaffected live births from birth certificates or hospital birth records in the same region, with an estimated delivery date during the same period as study cases.<sup>32,34</sup> All study sites obtained Institutional Review Board approval; individual consent was not required for the collection or analysis of these data under those approvals.

People may have been selected but determined to not eligible to be interviewed if they already participated with a previous pregnancy, could not complete the interview in English or Spanish, were incarcerated, or did not have legal custody of the child at the time of the interview. Others were determined to be non-eligible if they were contacted more than 24 months after delivery. The NBDPS study participants are a subset of selected to be interviewed, determined to be eligible and who consented to be interviewed. Non-participants (subsequently referred to as non-interviewed) are people who were selected for the study, deemed eligible but refused to be interviewed. We used previously abstracted study records to obtain the exact number of cases and controls originally selected for the NBDPS, reasons for non-participation and demographic information on the non-participants (**Appendix 1**). Among those eligible, participation rates were 67.4% for cases and 64.8% for controls overall.<sup>34</sup>

### *2.2.1 Exposure(s)*

Selected and eligible individuals were invited to complete an approximately 60-minutes long interview, between 6 weeks to 24 months after the estimated date of delivery (EDD). The primary exposure of interest was first-trimester treatment use of ondansetron. We ascertained exposure status using information compiled and coded in the Sloane Drug Dictionary.<sup>35</sup> People who reported no use of pharmaceutical treatments in the first trimester for NVP served as the reference group in all analyses.

### *2.2.2 Outcome*

Among the interviewed cases included in NBDPS for the duration of the study, there are 4,089 cases of orofacial clefts. Of those, there are 1,310 cases of cleft palate. Medical records were reviewed by a clinical geneticist to exclude cases possibly caused by genetics or other syndromes. Cases in NBDPS are classified as isolated, multiple, or complex.<sup>33</sup> To be consistent with previous studies, the current study only included isolated cleft palate cases — cases with single major defects (including single major defects accompanied by minor defects in the absence of a defined syndrome) and 1,1 multiple major defects in the same organ system. Isolated cases are also presumed to reduce pathogenetic heterogeneity.

### 2.2.3 Statistical Analyses

We summarized descriptive information available on the non-interviewed as well as comparable information available for the interviewed participants. We calculated unadjusted and confounding-adjusted odds ratios (aORs) and 95% confidence intervals (CIs) using logistic regression for the association of ondansetron use in the first trimester and cleft palate. For consistency with previously reported results, to adjust for confounding, we included the following covariates in the model: age in years (< 20, 20–24, 25–29, 30+), educational attainment (<12 years, ≥12 years, periconceptional folic acid use (yes, no), study year, and study site.

#### *Inverse Probability Weighting*

We used inverse probability of participation weights to adjust selection bias.<sup>29</sup> The inverse probability of participation weights (IPWs) are used to create a pseudo-population in which there is a null association between participation and exposure. The probability of participation in the study is ideally estimated from study records, therefore we used information on people who were selected but were not interviewed in NBDPS. Based on the literature, we assumed that certain demographic characteristics such as race/ethnicity, represented by a vector  $L$  in the directed acyclic graph (DAG), determines participation, meaning that in different strata of these factors, the participation rates differ (**Fig 2.2**). To inform the probability of participation, we used demographic information (maternal age,

racial identity) as well as selected birth characteristics (EDD, pregnancy outcome) for interviewed and non-interviewed cases and controls in NBDPS. We assumed that that if we can predict the correct values for participation rates within levels of these demographic factors, we can reweight the data using the inverse of the participation weights.<sup>36</sup> These proportions indicate whether cases and/or controls within levels of these characteristics are under or overrepresented in the data. This corresponds to inverse probability weighting to correct for unequal sampling fractions.<sup>37</sup>

We can write the probability of participation given the covariates  $L$  as  $\frac{pr[L = l_i | P]}{pr[L = l_i]}$  where the conditional probability  $pr[L = l_i | P]$  represents the sample proportion people with the vector of covariates ( $L = l_i$ ) and marginal probability  $pr[L = l_i]$  represents the overall population proportion of people with the same vector of covariates. This weight is equivalent to  $\frac{pr[P|L = l_i]}{pr[P]}$ , using Bayes theorem. This expression is proportional to the Horowitz-Thompson estimate, and participation weights can be estimated by  $pr[P|L = l_i]$ .

We then applied a composite weight for each observation  $i$  as follows:

$$w_i^S = \frac{1}{\prod pr[P|L = l_i]} * \frac{1}{\prod pr[A = a_i | L = l_i]}.$$

Stabilized weights are generally preferred to un-stabilized weights as they avoid the influence of extreme weights, yield narrower 95% confidence intervals (increasing efficiency) and have coverage rates that are closer to 95%.<sup>38,39</sup> To calculate stabilized weights, we divided the calculated marginal probabilities (i.e.,

probability of participation and probability of exposure) by the conditional probabilities (i.e., probability of participation and probability of exposure given a set of covariates).

$$w_i^S = \frac{\prod pr[S | V = v_i]}{\prod pr[S | L = l_i]} * \frac{\prod pr[A = a_i | V = v_i]}{\prod pr[A = a_i | L = l_i]}$$

The numerator represents probabilities of participation and exposure, conditional on a vector of time-invariant confounders ( $V$ ). The denominator represents the probability of participation and exposure, conditional on all confounders (both time-varying and time-invariant).  $V$  are typically a subset of  $L$ . In this study,  $V = L$  as we do not have time-varying confounders.

Using pooled logistic regression, we built model(s) that estimate these probabilities and calculated the IPWs. We included categorical predictors of participation: age, race, study center, birth outcome, as well as continuous predictors: year of delivery and gestational age at delivery. We also included interaction terms between continuous and dichotomous outcomes. We used the concordance (c) statistic to measure model discrimination and chose the models that yielded the highest c-statistic for cases and controls.<sup>40</sup> We estimated the OR and 95% CI in the weighted population using multivariable logistic regression, adjusting for stabilized weights, and comparing to the previously published ORs. We conducted analyses in SAS version 9.4 (Cary, NC).

## 2.3 RESULTS

Demographic characteristics of mothers of cases of cleft palate and controls are included in **Table 2.1**. Mothers of cases and controls did not differ on the demographic characteristics examined; the only noted difference was that mothers of cases were less likely to identify as Black or African-American. After excluding people with missing or implausible information for age (n = 54) or year of delivery (n=38), we had information on 44,089 interviewed (participants) and 25,817 non-interviewed (non-participants) (**Figure 2.1**). We also excluded people interviewed whose birth outcome was categorized as a fetal loss (loss at < 20 weeks, (n = 4)) since they were not eligible for NBDPS.

Across the board, interviewed and non-interviewed were mostly similar based on available data, with a few differences. There were more people who were younger than 25 years old among those who were not interviewed than those who were. Overall, among the non-interviewed, there was a greater proportion of people who identified as Asian/Pacific Islander, Black or Hispanic, and a smaller proportion who identified as White compared to the interviewed (**Table 2.2**).

We noted the same pattern when we compared non-interviewed and interviewed by case-control status. A larger proportion of non-interviewed cases were younger than 25 years old delivery (40.4% vs. 33.9%), identified as Asian (3.6% vs. 1.5%), Black (13.5% vs. 10.7%) or Hispanic (25.8% vs. 21.7%) compared to interviewed cases. A smaller proportion of non-interviewed cases identified as White than interviewed cases (52.1% vs. 62.9%) (**Table 2.3**). We

observed the same distribution patterns when comparing available information on the characteristics of interviewed and non-interviewed controls (**Table 2.4**).

We also examined the percentage of interviewed and non-interviewed by racial category and by age. Fewer than half of the eligible people selected for participation who identified as Asian and/or Pacific Islander were interviewed and therefore included in the study. People who identified as White and were selected for inclusion in the study were more likely to complete the interviews (**Table 2.5**). We noted that a lower percentage of people who were younger than 25 years old who were selected, were interviewed than those older. Among people who were younger than 25 years of age, fewer than 60% were interviewed; compared to greater than 65% among older age groups (**Table 2.6**).

The unadjusted OR for the association of ondansetron use in the first trimester of pregnancy and cleft palate was 1.5 (95% CI 1.0–2.0). After adjusting for age, education, study year, study location, and periconceptional folic acid use, the confounding-adjusted estimate was 1.6 (95% 1.1–2.1). The c-statistic for the models to create participation weights ranged from 0.6 to 0.7. The mean of our stabilized composite weights was 1.3 (standard deviation = 0.6); the composite weights ranged from 0.2 to 20.1. Using our calculated weights, the IPW OR was 1.4 (95% CI 1.0–1.9). When we adjusted for confounding using the same covariates as the confounding-only model and adjusted for selection bias using the participation weights, the OR was 1.6 (95% 1.3–2.2) (**Figure 2.3**).

## 2.4 DISCUSSION

In our analyses, we attempted to use study records to account for potential selection bias in the association of ondansetron use in the first trimester and cleft palate due to differential participation. We compared different demographic factors, namely age and race, associated with participation in observational studies. More non-participants identified as Black/African-American, Asian and/or Pacific Islander or Hispanic than participants. We also noted that there was a larger proportion of non-participants who were younger than 25 years of age at delivery compared to participants. Overall, we found limited evidence of selection bias when comparing the unweighted and weighted-estimates, under our assumptions.

There are several strengths to this study. Cases in NBDPS– a large population-based, case-control study– are reviewed and classified by clinical geneticists to reduce outcome misclassification. Information on NVP and use of ondansetron was captured through a standardized interview. Given the off-label use of the medication for NVP, this information may not be accurately captured by prescription claims databases. Ondansetron is a prescription anti-emetic that is often used as a second-line treatment, if OTC or herbal treatments are ineffective. Use of the medication is likely to be recalled with high accuracy.

It should be noted that these analyses are not without limitations and should be interpreted cautiously. Though NBDPS is one of the largest studies on congenital anomalies, we do note that there was a marked increase in the prevalence of ondansetron use during the study years.<sup>9</sup> Estimates of the

population prevalence of ondansetron use currently range between 20 and 25%, compared to less than 5% in our sample.

Selection bias can be difficult to quantify and may be introduced through various mechanisms. As with any bias analysis, the validity of our results is conditional on making the correct assumptions. Information available on the non-interviewed was limited, therefore the measured variables had limited ability to distinguish between participants and non-participants. We considered several models to estimate the probability of participation and calculate weights. However, our composite weights may not have incorporated relevant factors associated with participation and thus residual bias due to selection may still be present. In our specified DAG, we highlighted one potential mechanism of differential participation due to measured demographic factors (e.g., racial identity) associated with the exposure, outcome, and participation in NBDPS. Other demographic factors such as education level may be better predictors of participation, but information on education was not available for the non-interviewed.

We estimated parameters that were conditional on other variables to provide better adjustment for selection bias. However, due subgroups with small sample sizes, we may have introduced error in the analysis which may cause some participants to carry undue influence. We calculated stabilized weights to counteract the possible influence of extreme weights. Stabilization of weights is not without cost; the IPW estimator becomes a conditional contrast and assumes that there is no effect measure modification within levels of covariates.<sup>36,37</sup> We also

made other simplifying assumptions in our analyses. We assumed neither unmeasured confounding nor misclassification. Methods to incorporate additional complexities and conduct multiple bias corrections may be integrated in future analyses.<sup>41,42</sup>

The conventional unadjusted and confounding-adjusted estimates were mostly consistent with the previously published results from NBDPS, with one exception.<sup>5,6,12</sup> Results from an analysis by Anderka et al. using data from the earlier years of NBPDS suggested a greater than 2-fold (aOR = 2.4, 95% 1.2–4.8) increase in risk of cleft palate associated with use of ondansetron.<sup>12</sup> Results from the previous and current analyses are also consistent with a recent meta-analysis of the literature on ondansetron use and cleft palate.<sup>43</sup> The resulting OR from the main pooled analysis of 6 studies (including results from Parker et al. analyses of both BDS and NBDPS data) was 1.3 (95% CI 0.86–1.88). After excluding results from the BDS analysis due to high heterogeneity, the pooled OR was 1.5 (95% CI 1.2–1.8). These results support the conclusion that ondansetron use in the first trimester is associated with increased risk of cleft palate.

## 2.5 TABLES AND FIGURES

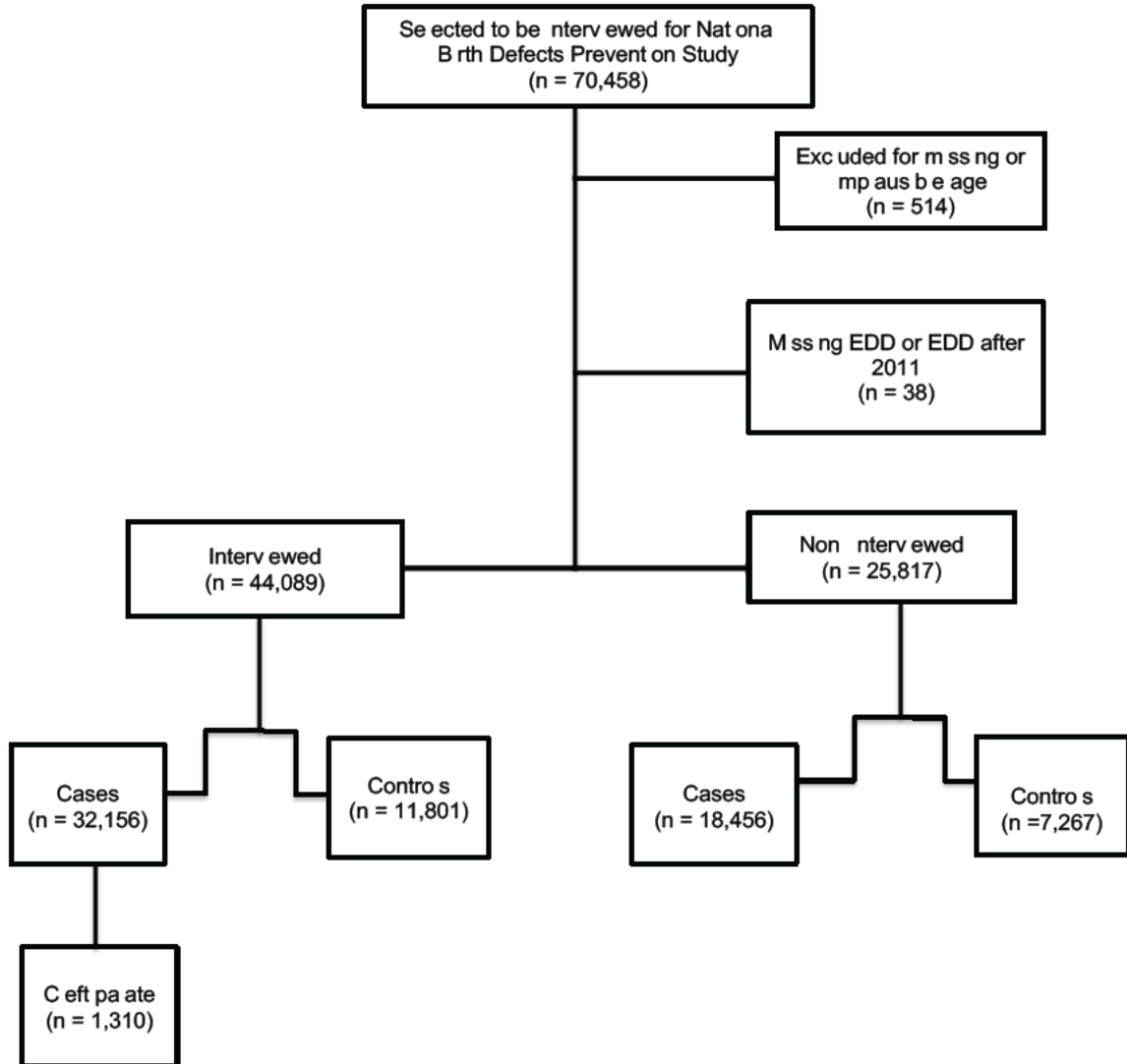
**Table 2.1. Demographic and Reproductive Characteristics of Mothers of Cases with Isolated Cleft Palate and Controls in the National Birth Defects Prevention Study (NBDPS), 1997–2011**

	Isolated Cleft Palate (n = 1,310)		Controls (n = 11,655)	
	No.	%	No.	%
<i>Ondansetron use</i>				
Yes	44	3.4	273	2.3
No	1265	96.6	11,378	97.6
<i>Year of due date</i>				
1997–2001	431	32.9	3,432	29.4
2002–2006	441	33.7	4,133	35.5
2007–2011	438	33.4	4,090	35.1
<i>Study site</i>				
Arkansas	150	11.5	1,471	12.6
California	161	12.3	1,263	10.8
Iowa	128	9.8	1,300	11.2
Massachusetts	210	16	1,402	12.0
New Jersey	61	4.7	576	4.9
New York	122	9.3	989	8.5
Texas	109	8.3	1,413	12.1
CDC/Atlanta	154	11.8	1,267	10.9
North Carolina	110	8.4	1,016	8.7
Utah	105	8	958	8.2
<i>Maternal age, years</i>				
< 20	105	8.0	1,171	10.1
20-24	276	21.1	2,616	22.5
25-29	354	27.0	3,211	27.6
30+	575	43.9	4,657	40.0
<i>Maternal race/ethnicity</i>				
American Indian/Alaska Native	9	0.7	34	0.3
Asian, Pacific Islander	14	1.1	107	0.9
Asian	26	2.0	181	1.6
Black or African-American	89	6.8	1,340	11.5
Hispanic or Latino	206	15.7	2,295	19.7

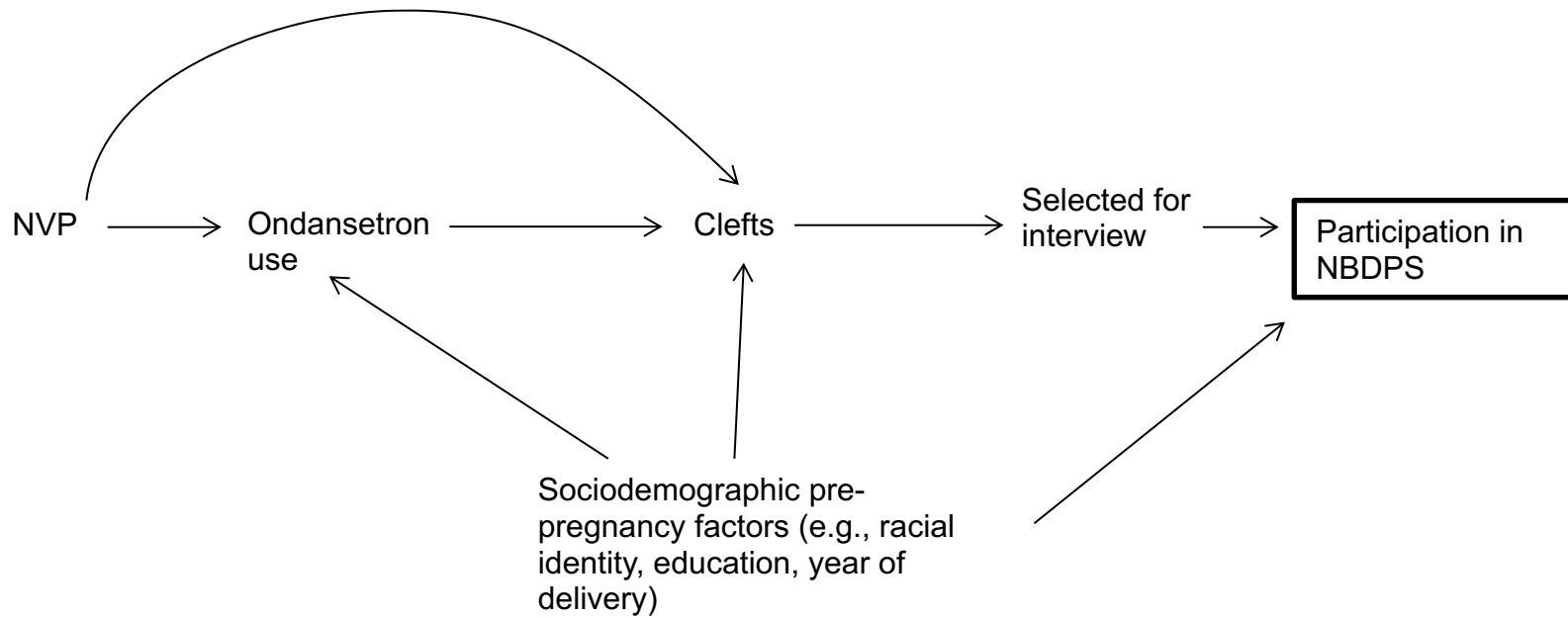
Native Hawaiian/Other Pacific Islander	--	--	15	0.1
White	938	71.6	7,070	60.7
Other	19	1.5	483	4.1
Missing	9	0.7	130	1.1
<i>Birth outcome</i>				
Live birth	1,306	99.7	11,655	100.0
Stillbirth <sup>a</sup>	4	0.3	--	--
<i>Plurality</i>				
Singleton	1,256	95.9	11,267	96.7
Multiples	41	3.1	272	2.3
Not stated/missing	13	0.1	116	1.0

<sup>a</sup> Fetal death  $\geq$  20 weeks

**Figure 2.1.** Flow diagram of selection and participation in the National Birth Defects Prevention Study, 1997–2011



**Figure 2.2** Causal diagram of a potential mechanism that could lead to selection bias of the association between use of ondansetron in the first trimester and orofacial clefts in offspring in the National Birth Defects prevention study.



**Table 2.2. Demographic and Reproductive Characteristics of Interviewed and non-Interviewed in the National Birth Defects Prevention Study (NBDPS), 1997–2011**

	Interviewed (n = 44,089)		Non-interviewed (n = 25,817)	
	No.	%	No.	%
Cases	32,156	72.9	18,456	71.5
Controls	11,801	26.8	7,267	28.2
<i>Year of due date</i>				
1997–2001	12,821	29.1	6,015	23.3
2002–2006	16,007	36.3	9,267	35.9
2007–2011	15,081	34.2	10,115	38.2
<i>Study site</i>				
Arkansas	5,896	13.4	2,601	10.1
California	5,188	11.8	3,199	12.4
Iowa	4,300	9.8	3,120	12.1
Massachusetts	5,360	12.2	3,232	12.5
New Jersey	2,215	5.0	1,036	4.0
New York	3,185	7.2	2,457	9.5
Texas	5,000	11.3	3,473	13.5
CDC/Atlanta	4,892	11.1	3,000	11.6
North Carolina	3,492	7.9	1,705	6.6
Utah	4,561	10.3	1,994	7.7
<i>Maternal age, years</i>				
< 20	4,490	10.2	3,220	13.3
20-24	10,293	23.4	7,037	27.3
25-29	11,967	27.1	6,637	25.7
30-34	10,809	24.5	5,269	20.4
35-39	5,320	12.1	2,794	10.8
40+	1,210	2.7	660	2.6
<i>Maternal race/ethnicity</i>				
American Indian/Alaska Native	150	0.3	149	0.6
Asian, Pacific Islander	358	0.8	372	1.4
Asian	672	1.5	890	3.5
Black or African-American	4,805	10.9	3,532	13.7

Hispanic or Latino	9,286	21.1	6,542	25.3
Native Hawaiian/Other Pacific Islander	72	0.2	102	0.4
White	27,532	62.5	13,414	52.0
Other racial categories	860	2.0	490	1.9
Missing	354	0.8	326	1.3
<i>Birth outcome</i>				
Live birth	42,736	96.9	24,633	95.4
Stillbirth <sup>a</sup>	592	1.3	495	1.9
Induced abortion	692	1.6	580	2.2
Fetal loss < 20 weeks	4	0.0	33	0.1
Not stated	65	0.1	77	0.3
<i>Plurality</i>				
Singleton	41,797	94.8	24,468	94.8
Multiples	1,990	4.5	1,143	4.4
Not stated/missing	302	0.7	206	0.8

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<sup>a</sup> Fetal death  $\geq$  20 weeks

**Table 2.3. Demographic and Reproductive Characteristics of Cases by Interview Status in the National Birth Defects Prevention Study (NBDPS), 1997–2011**

	Interviewed (n = 32,156)		Non-interviewed (n = 18,456)	
	No.	%	No.	%
<i>Year of due date</i>				
1997–2001	9,389	29.2	4,359	23.7
2002–2006	11,725	36.5	6,610	35.8
2007–2011	10,867	33.8	7,101	38.5
<i>Study site</i>				
Arkansas	4,293	13.4	1,736	9.4
California	3,926	12.2	2,430	13.2
Iowa	3,000	9.3	2,177	11.8
Massachusetts	3,960	12.3	2,442	13.2
New Jersey	1,637	5.1	710	3.9
New York	2,207	6.9	1,550	8.4
Texas	3,587	11.2	2,500	13.6
CDC/Atlanta	3,628	11.3	2,197	11.9
North Carolina	2,480	7.7	1,231	6.7
Utah	3,438	10.7	1,483	8.0
<i>Maternal age, years</i>				
< 20	3,302	10.3	2,481	13.4
20–24	7,597	23.6	4,983	27.0
25–29	8,656	26.9	4,651	25.2
30–34	7,743	24.1	3,767	20.4
35–39	3,926	12.2	2,081	11.3
40+	932	2.9	493	2.7
<i>Maternal race/ethnicity</i>				
American Indian/Alaska Native	115	0.4	113	0.6
Asian, Pacific Islander	251	0.8	282	1.5
Asian	488	1.5	656	3.6
Black or African-American	3,437	10.7	2,493	13.5
Hispanic or Latino	6,976	21.7	4,754	25.8
Native Hawaiian/Other Pacific Islander	56	0.2	74	0.4
White	20,218	62.9	9,606	52.1
Other racial categories	376	1.2	253	1.4

Missing	239	0.7	225	1.2
<i>Birth outcome</i>				
Live birth	30,847	95.9	17,306	93.8
Stillbirth <sup>a</sup>	593	1.8	495	2.7
Induced abortion	692	2.2	580	3.1
Fetal loss < 20 weeks	4	0.0	33	0.2
Not stated	21	0.1	42	0.2
<i>Plurality</i>				
Singleton	30,243	94.1	17,326	93.9
Multiples	1,711	5.3	998	5.4
Not stated/missing	202	0.6	132	0.7

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<sup>a</sup> *Fetal death ≥ 20 weeks*

**Table 2.4. Demographic and Reproductive Characteristics of Controls by Interview Status in the National Birth Defects Prevention Study (NBDPS), 1997–2011**

	Interviewed (n = 11,801)		Non-interviewed (n = 7,267)	
	No.	%	No.	%
<i>Year of due date</i>				
1997–2001	3,432	29.1	1,656	22.8
2002–2006	4,271	36.2	2,648	36.4
2007–2011	4,093	34.7	2,931	40.3
<i>Study site</i>				
Arkansas	1,471	12.5	772	10.6
California	1,262	10.7	769	10.6
Iowa	1,300	11.0	943	13.0
Massachusetts	1,400	11.9	789	10.9
New Jersey	578	4.9	326	4.5
New York	978	8.3	907	12.5
Texas	1,413	12.0	973	13.4
CDC/Atlanta	1,264	10.7	803	11.1
North Carolina	1,012	8.6	474	6.5
Utah	1,123	9.5	511	7.0
<i>Maternal age, years</i>				
< 20	1,171	9.9	926	12.7
20–24	2,649	22.5	2,019	27.8
25–29	3,270	27.7	1,962	27.0
30–34	3,047	25.8	1,485	20.4
35–39	1,389	11.8	710	9.8
40+	275	2.3	165	2.3
<i>Maternal race/ethnicity</i>				
American Indian/Alaska Native	35	0.3	237	3.3
Asian, Pacific Islander	107	0.9	90	1.2
Asian	184	1.6	230	3.2
Black or African-American	1,340	11.4	1,017	14.0
Hispanic or Latino	2,307	19.6	1,787	24.6
Native Hawaiian/Other Pacific Islander	16	0.1	26	0.4
White	7,214	61.1	3,745	51.5
Other racial categories	484	4.1	237	3.3

Missing	114	1.0	99	1.4
<i>Birth outcome</i>				
Live birth	11,758	99.6	7,235	99.6
Stillbirth <sup>a</sup>	---	---	---	---
Induced abortion	---	---	---	---
Fetal loss < 20 weeks	---	---	---	---
Not stated	43	0.4	32	0.4
<i>Plurality</i>				
Singleton	11,424	96.8	7,049	97.0
Multiples	277	2.3	144	2.0
Not stated/missing	100	0.8	74	1.0

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<sup>a</sup> *Fetal death ≥ 20 weeks*

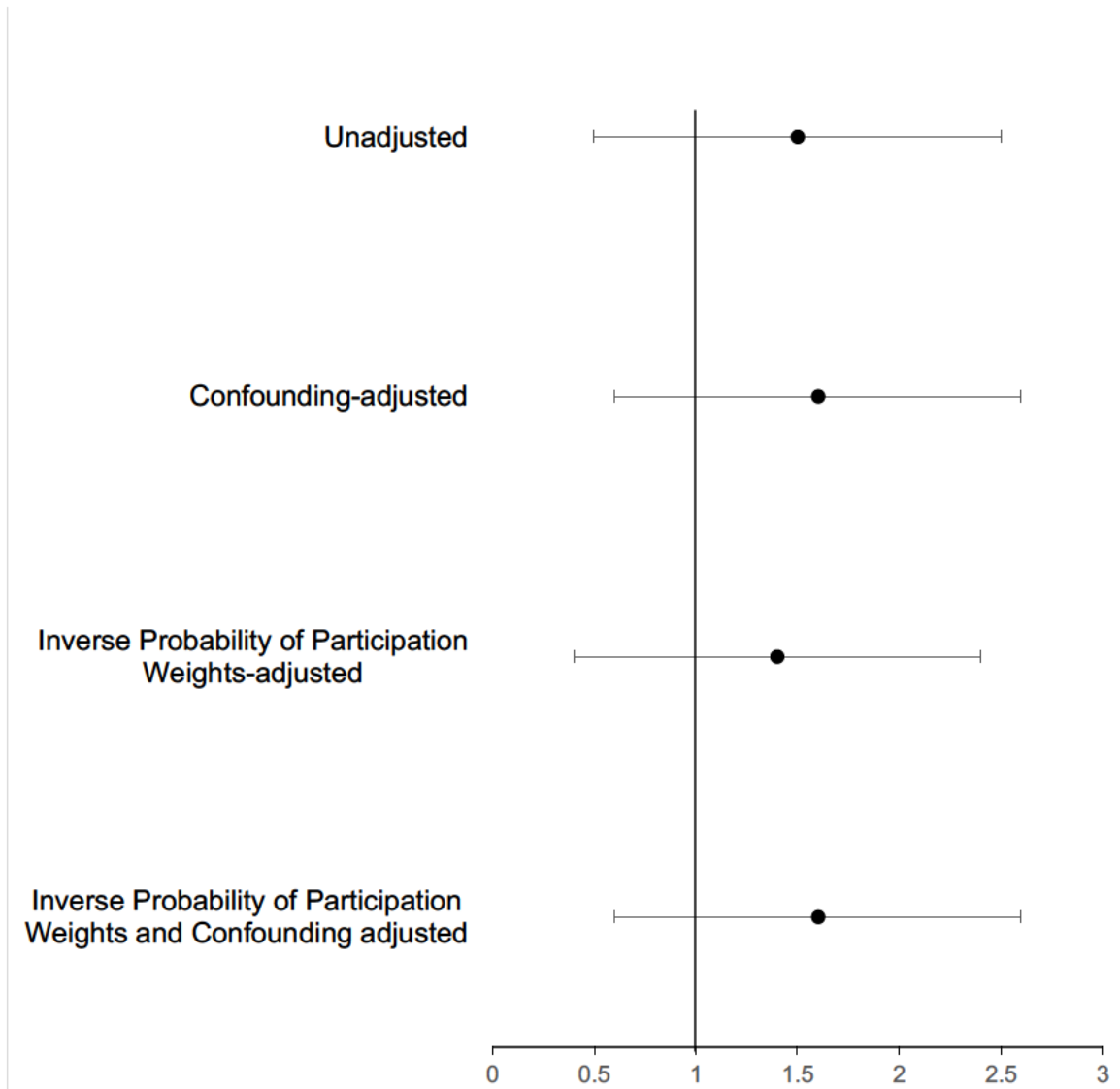
**Table 2.5. Interview Status by Race in the National Birth Defects Prevention Study (NBDPS), 1997–2011**

	Interviewed		Non-interviewed	
	No.	%	No.	%
<i>Maternal race/ethnicity</i>				
American Indian/Alaska Native	150	50.2	149	49.8
Asian, Pacific Islander	358	49.0	372	51.0
Asian	672	43.0	890	57.0
Black or African-American	4,805	57.6	3,532	42.4
Hispanic or Latino	9,286	58.7	6,542	41.3
Native Hawaiian/Other Pacific Islander	72	41.4	102	58.6
White	27,532	67.2	13,414	32.8
Other	860	63.7	490	36.3
Missing	354	52.1	326	47.9

**Table 2.6. Interview Status by Age in the National Birth Defects Prevention Study (NBDPS), 1997–2011**

	Interviewed		Non-interviewed	
	No.	%	No.	%
<i>Maternal age, years</i>				
< 20	4,490	56.8	3,420	43.2
20-24	10,293	59.4	7,037	40.6
25-29	11,967	64.3	6,637	35.7
30-34	10,809	67.2	5,269	32.8
35-39	5,320	65.6	2,794	34.4
40+	1,210	64.7	660	35.3

**Figure 2.3. Unadjusted, Confounding-adjusted, and Selection-bias Adjusted Associations Between Ondansetron Use in the First Trimester and Cleft Palate, National Birth Defects Prevention Study, 1997–2011**



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### **3 DECONGESTANT USE IN LATE PREGNANCY AND PRETERM DELIVERY: EXAMINING IMMORTAL-TIME BIAS**

#### **3.1 INTRODUCTION**

Chronic rhinitis, which consists of a set of symptoms typically including a runny nose, itchy nose, or postnasal drip, is a common condition of pregnancy that may have significant adverse effects on quality of life or coexisting asthma, if uncontrolled.<sup>1</sup> Pregnancy rhinitis is an inflammation of the mucous membranes in the nasal cavity, typically manifesting in the first trimester and again in late pregnancy, without other signs of respiratory tract infections, no known allergic cause, and disappearing completely within 2 weeks of delivery.<sup>2,3</sup> The pathogenesis is unclear but increased circulating blood volume, possibly enhanced by a vasodilating effect of progesterone, has been suggested as being responsible for pregnancy-induced nasal congestion.<sup>4</sup> Placental growth hormone may also play a role in causing rhinitis by stimulating the growth of the mucosa, including the nasal mucosa, in turn causing nasal congestion.<sup>1,3</sup> Incidence figures of rhinitis during pregnancy are likely underestimates. Approximately 20–40% of women of reproductive age report rhinitis, and 10–30% experience worsening symptoms during pregnancy.<sup>3,5</sup>

Oral decongestants are among medically indicated treatments of rhinitis, particularly severe pregnancy rhinitis; although decongestants should be avoided in the first trimester and in pregnant people with hypertension.<sup>1,5</sup> After the first

trimester, pseudoephedrine is the recommended oral decongestant for treatment of rhinitis.<sup>6</sup> Decongestants, such as pseudoephedrine, are among the most common over-the-counter (OTC) treatment for asthma and upper-respiratory infections, and are used by at least 15% of pregnant people.<sup>7</sup> Approximately 1 in 6 participants in the National Birth Defects Prevention Study (NBDPS) and the Slone Birth Defects Study (BDS) reported use of decongestants during pregnancy, with increasing use during the second trimester.<sup>7</sup> Epidemiologic studies have identified elevated risks of defects of the heart, eyes and ears, gut, abdominal wall, and limbs associated with first-trimester use of decongestants.<sup>8 13</sup> However, evidence on safety of fetal exposure to decongestants in later pregnancy or its association with other adverse pregnancy outcomes, such as preterm birth, is sparse.

Prematurity remains the leading cause of death in children younger than 5 years of age worldwide. Nearly 1 million children die yearly from complications of preterm birth and surviving infants may face disabilities or impairments.<sup>14,15</sup> Preterm birth is a live birth occurring before 37 weeks of completed gestation.<sup>16</sup> Preterm birth can be further categorized as extremely preterm (<28 weeks), very preterm (28 to <32 weeks), and moderate to late preterm (32 to <37 weeks).<sup>16</sup> Preterm birth may be the result of spontaneous preterm labor or intervention by a provider through induction of labor or caesarean delivery. Estimates of the prevalence of preterm birth suggest that globally, nearly 15 million live births, or approximately 11%, are preterm.<sup>14,15</sup> The majority of preterm births occur at 32–

36 weeks' gestation (>84%).

Studies examining the association between preterm delivery and use of decongestants have suggested an inverse relationship.<sup>13,17</sup> In a population-based study of pregnancies in Sweden, Källén and Olausson observed an odds ratio of 0.68 (95% CI: 0.52–0.88) for preterm birth among people who took oral decongestants in the second or third trimester compared to those who did not.<sup>13</sup> The authors hypothesized that pregnancy rhinitis may be a marker of a well-functioning placenta and that people using decongestants during pregnancy may have more severe rhinitis and presumably better pregnancy outcomes.<sup>13</sup> If correct, the observed protective effects would be an example of confounding by indication. Subsequently, Hernandez et al, in an analysis of control participants in BDS reported that exposure to decongestants in the second and/or third trimester may decrease the risk of preterm delivery by up to 58% (aHR 0.42, 95% CI 0.21–0.84), compared to no exposure.<sup>17</sup> The results from the Hernandez et al study were similar to the previous findings from Källén and Olausson despite the fact that prescription phenylpropanolamine was the predominant decongestant exposure in the latter study, compared to OTC pseudoephedrine in the former.

However, a later study from Matok et al. argued that these reductions in risk of preterm delivery were instead the result of immortal time bias due to misclassified person-time.<sup>18</sup> Immortal time refers to “a period of follow-up during which, by design, the study outcome cannot occur”.<sup>19 21</sup> The span of time between the start of follow-up time but before a participant initiates a particular treatment or

exposure coincides with immortal time. This bias can also be conceptualized as misclassification resulting from the assignment of participants to the exposed category, during the follow-up period considered immortal.<sup>22</sup> The authors argued that the time between the start of a trimester until the initiation of medication use was misclassified as exposed in the time fixed analyses. Pregnancies need to continue until the initiation of treatment to be classified as exposed.<sup>18 20</sup> after using a time-varying analysis, Matok et al. demonstrated that the “protective” effects of the previous studies disappeared (aHR 0.93, 95% CI 0.42–2.06).

In this study, we examined the association between use of decongestants in the second and/or third trimester of pregnancy, and preterm delivery. We replicated a time-fixed approach and compared the results to time-varying analyses to assess for the presence and quantify the magnitude of potential immortal time bias using data from NBDPS.

## **3.2 METHODS**

### *3.2.1 Study design and study population*

The NBDPS was a population-based case-control study in the United States aimed to identify risk factors for major structural congenital anomalies. An overview of the design and methodology of NBDPS has been published elsewhere.<sup>23,24</sup> Cases were selected from active, population-based surveillance systems in 10 study centers (Arkansas, California, Georgia/Centers for Disease Control and Prevention (CDC), Iowa, Massachusetts, New Jersey, New York, North Carolina,

Texas and Utah) and congenital anomalies confirmed by clinical geneticists. Controls, i.e., infants without congenital anomalies, were randomly selected annually from birth certificates or hospital records from the same ascertainment area and time period as cases. Although cases included live births, stillbirths (fetal deaths >20 weeks' gestation) or terminations, all control infants were liveborn.

Within six weeks to twenty-four months of the estimated delivery date, eligible participants were contacted by telephone and interviewed via computer-assisted telephone interviews (CATI) on various factors related to demographics, reproductive factors, pregnancy history, health behaviors, lifestyle characteristics, pre-pregnancy diet, supplement use, and medications (including both prescription and OTC medications). Interviews were conducted between 1997 and 2013 for infants with estimated due dates (EDD) between 1997 and 2011. Participation rates were 67% among case mothers and 64% among control mothers. Informed consent was obtained from all participants and the Centers for Disease Control and Prevention Institutional Review Board (IRB) and the IRB(s) of the individual NBDPS study centers approved study materials and interview content.

### *3.2.2 Outcome*

The primary outcome was preterm birth, regardless of whether preterm birth was medically indicated or spontaneous, defined as delivery at gestational age less than 37 completed weeks. Full-term pregnancies were censored at 37 weeks. Because the risk of preterm birth is higher among pregnancies with congenital anomalies, we restricted our analysis to the NBDPS controls. This group of 11,829

participants, whose pregnancies resulted in a live-born, non-malformed infant between 1997 and 2011, constitute a retrospective cohort study. We excluded participants who had missing information on birth outcome (n = 37); multifetal gestations (n = 377); reported missing or implausible gestational ages (<24 weeks or >42 weeks, n = 6), and missing EDD or date of conception (n = 31) (Figure 3.1).

### 3.2.3 *Exposure(s)*

Participants were asked a series of questions on medication use, start and stop dates from 3 months prior to conception until delivery. Information on all reported medications was compiled and coded using the Slone Drug Dictionary, which links drug products to their active ingredients (licensed by the NBDPS from Boston University's Slone Epidemiology Center).<sup>25</sup> Participants were considered exposed if they reported use of both oral and/or nasal preparations of prescription and/or OTC decongestants (alpha-adrenergic antagonists including ephedrine, phenylephrine, pseudoephedrine), for any indication and in any dose. Among the exposed, we removed participants who reported use of a decongestant on an as needed basis over a span of more than 90 days during the follow-up period (n = 121). In order to account for calendar and gestational time, recommendations for studies of preterm births are that follow-up time should only begin after the lower gestational age limit for birth registration.<sup>26</sup> Since we restricted to livebirths and by definition, a preterm livebirth cannot occur before the 20<sup>th</sup> week of pregnancy or after the 37<sup>th</sup> week of pregnancy, we categorized exposure as use during the second and/or third trimester of pregnancy (from week 20 to week 37 of gestation)

and 2) use of decongestants during the third trimester only (week 27 to week 37 of gestation). The reference category consisted of participants reporting no use of decongestants in neither the second nor the third trimester of pregnancy.

### 3.2.4 Covariate(s)

We summarized descriptive characteristics of exposed and unexposed participants examined as potential confounders. These characteristics included: 1) demographic factors: age (< 20, 20–24, 25–29, ≥ 30 years), educational attainment in years (< 12, 12, 13–15, ≥ 16), self-reported race/ethnicity (non-Hispanic Black, non-Hispanic white, Hispanic, Asian, Native American, and other), study site, and year of delivery. 2) Behavioral factors such as smoking (yes/no) and alcohol consumption (yes/no) during pregnancy, pregnancy planning (wanted to be pregnant, wanted to wait, did not want to be pregnant, did not care). 3) Medical and anthropomorphic characteristics and factors such as pre-pregnancy body mass index (BMI) (< 18.5, 18.5–< 25, 25–< 30, ≥ 30 kg/m<sup>2</sup> according to the National Institutes of Health categories), parity, pre-existing and gestational diabetes (yes/no), pre-pregnancy high blood pressure diagnosis, and preeclampsia (yes/no).

### 3.2.5 Statistical Analyses

We used Cox proportional hazards models to estimate unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the relationship between timing of decongestant use and preterm delivery.<sup>27,28</sup> In the first analysis,

we replicated a time-fixed approach which classified exposure to decongestants as a fixed dichotomous variable (yes/no) and indicating use any time during the second and/or third trimester. We also modeled exposure to decongestants as a time-varying exposure, to take into consideration the greater opportunity for exposure with longer gestations.<sup>18,29</sup> We characterized use of decongestants as time-varying, allowing exposure status to switch between exposed and unexposed. As an example, a participant reported decongestant use from week 23 to week 24. From the start of follow-up to week 23, in our time-varying analyses, the participant contributed unexposed person-time, exposed person time for a week (7 days) of follow-up between weeks 23 to 24 of gestation, and then unexposed again until censored at week 37 (Figure 3.2).

We compared our time-fixed exposure Cox regression to our time-varying exposure hazard ratio. Gestational age, in weeks, was the time-scale; we also conducted analyses using gestational days as the time-scale for comparison. We tested the proportional hazard assumption graphically using a plot of the log cumulative hazard where the logarithm of time is plotted against the estimated log cumulative hazard calculated as  $\ln[-\ln(S(t))]$ . None of the covariates considered as potential confounders changed the estimate by more than 10%. Therefore, we included age, smoking and drinking status, diabetes, preeclampsia, and parity in our multivariable modeling, keeping in line with the previous analyses by Matok et al. We also include a multivariable model that omits preeclampsia since the analyses from Hernandez et al noted that the large reductions in risk of preterm

delivery were only observed in people without pre-eclampsia. We conducted all analyses in SAS version 9.4 (Cary, NC).

### **3.3 RESULTS**

For our analytical cohort, we applied the previously mentioned exclusion criteria, resulting in an analytic sample of 11,263 participants (Figure 3.1). Approximately 7.7% (n = 863) of our analytic sample reported use of decongestants in the second and/or third trimester of pregnancy, 3.6% reported use of decongestants in the third trimester of pregnancy only. The prevalence of preterm birth was the same among decongestant users (8.0%) and non-users (8.0%). Decongestant use decreased during the study years; of the participants reporting decongestant use, 36.7% reported due dates from 1997–2001, compared to 24.8% with estimated due dates between 2007 and 2011. Decongestants use was more prevalent among participants who reported their race as white, higher educational attainment, were older, likely to report alcohol consumption during pregnancy, and multiparous. Use of decongestants was least common in young (< 20 years of age), Hispanic participants (Table 3.1). Among people who reported use of decongestants, the prevalence decreased over the follow-up time 32.0% reported use at the beginning of follow-up (20 weeks) to 18.0% at the end (37 weeks) (Figure 3.2). Among people who reported timing and number of days, the majority reported decongestant use for 7 days or less. Nearly 20% of decongestant users reported use for 2, 3 or 7 days (Figure 3.3).

Among eligible births, 8.0% were classified as preterm (7.6% of preterm births were among those reporting use of decongestants in second and/or third trimester, and 2.8% were among those reporting use only in the third trimester). The vast majority of preterm births (87.9%,  $n = 794$ ) were moderate to late preterm, 8.5% ( $n = 77$ ) were very preterm and 3.5% ( $n = 32$ ) were extremely preterm. There was no discernible geographic distribution to reported preterm delivery. Preterm deliveries were slightly more frequent in Arkansas (16.6% vs. 12.1%) and Texas (14.8% vs. 11.8%) and were less frequent in California, Iowa, Massachusetts, New York, and Utah. Characteristics of participants with preterm and term deliveries were largely similar, with two exceptions. Those with preterm delivery were more likely to report their race as Black (15.5% preterm vs. 10.7% term), report a diagnosis of pre-pregnancy high blood pressure (24.3% preterm vs. 12.4% term) and preeclampsia (18.2% preterm vs. 8.0% term). Those with preterm delivery were also more likely to report both gestational (8.2%) and non-gestational (2.4%) diabetes compared to term births (6.7% and 0.6% respectively) (Table 3.2).

Sixty-nine participants reporting preterm births also reported decongestant use during the second and/or third trimester of pregnancy; of those, 24 preterm births were exposed only during the third trimester. Overall, results from the time-varying and time-fixed approaches suggest a null association between use of decongestants in late pregnancy and preterm delivery (**Table 3.3**). Generally, results for the time-fixed analyses were downwardly biased compared to the time-varying analyses. The unadjusted time-fixed HR was 0.96 (95% CI 0.73–1.26) for

the association between use of decongestants in the second and/or third trimester of pregnancy and preterm delivery. Our results were nearly identical whether we adjusted for preeclampsia (aHR = 0.96, 95% CI 0.73–1.27) or not (aHR = 0.99, 95% CI 0.75–1.31). Decongestant use in the third trimester suggested a slightly protective effect in the time-fixed analyses (aHR = 0.75, 95% CI 0.50–1.12).

For the time-varying analyses, the unadjusted time-varying hazard ratio was 1.04 (95% CI 0.79–1.38) for the association between use of decongestants in the second and/or third trimester of pregnancy and preterm delivery. The adjusted HR for the model that includes preeclampsia was 1.07 (95% CI 0.79–1.44), and 1.09 (95% CI 0.82–1.44) for the model that excludes preeclampsia. The unadjusted time-varying HR was 0.87 (95% CI 0.59–1.30) and adjusted estimate was 0.89, 95% CI 0.59–1.34) for use of decongestants in the third trimester only. When we used gestational days as the time-scale instead of weeks, the adjusted estimate were nearly the same (data not shown). We attempted to investigate the association of decongestant use and preterm delivery, stratified by preeclampsia diagnosis. However, due to small sample size, associations could not be estimated.

### **3.4 DISCUSSION**

We used a large population-based study to account for potential time bias when assessing the association between a time-varying exposure and time-dependent outcome. Results from our analysis concluded that decongestant use

in late pregnancy did not confer a protective effect for preterm delivery. This contrasts from results from Källén and Olausson, as well as Hernandez et al, but is in line with results from Matok et al.<sup>13,17,18</sup> We observed a null association using both time-fixed and time-varying approaches. Results from the time-fixed analyses suggested downward bias compared to results from the time-varying analyses. These discrepancies may suggest the potential for immortal-time bias in NBDPS analyses of a time-dependent outcome, using a time-fixed approach for exposure to medications. Perhaps more notably for medications that are used episodically and OTC such as decongestants.

We did note that the point estimates for exposure in the third trimester only were indicative of a slightly protective effect; a reduction in risk of nearly 10% in the time-varying analysis and 25% in the time-fixed analysis. However, both estimates were imprecise, with confidence intervals also including estimates compatible with protective, null, or harmful effects. Furthermore, evidence of immortal time bias would be more evident time-fixed analysis examining the association of third trimester use only and preterm delivery since use of decongestants declines with increasing gestation. The prevalence of use of decongestants in the second and/or third trimester was lower in our data than in the analysis of the Birth Defects Study by Hernandez et al (~8% vs 19%).<sup>17</sup> Similar to the Hernandez et al study, participants who reported use of decongestants were more likely to report their race as white, be older, have more years of education, and other markers of higher socioeconomic status.

Though the premise of these analyses were to examine evidence of immortal time bias, we do consider whether there is an elucidated biologic mechanism by which decongestants were to in fact confer a protective effect against preterm delivery. While it is difficult to disentangle the potential effects of the medications from the effects of the underlying ailment, Källén and Hernandez discussed the role of confounding by indication, suggesting decongestants are indicated treatments for pregnancy rhinitis; a marker of a well-functioning placenta and thus an indicator of a healthy pregnancy.<sup>13,17</sup> It would stand to reason that people reporting use of decongestants may have more severe rhinitis and presumably healthier pregnancies. If accurate, this would present a potential mechanism for the protective findings of the earlier studies. We could not identify the specific indication for use of a decongestant in the NBDPS and address confounding by indication. Few people are likely be familiar with the term, “pregnancy rhinitis,” and report its occurrence.

Other limitations should be considered when interpreting our results. Information on frequency and duration of exposure was retrospectively collected, through self-report. Reporting information on retrospective exposures in adequate detail may be difficult, therefore recall of medications taken episodically may be subject to misclassification. If our study under-ascertained unexposed preterm deliveries, our findings would likely be biased towards no effect.

While immortal time bias is most severe in studies when the outcome is death or is related to death since participants must survive long enough to receive

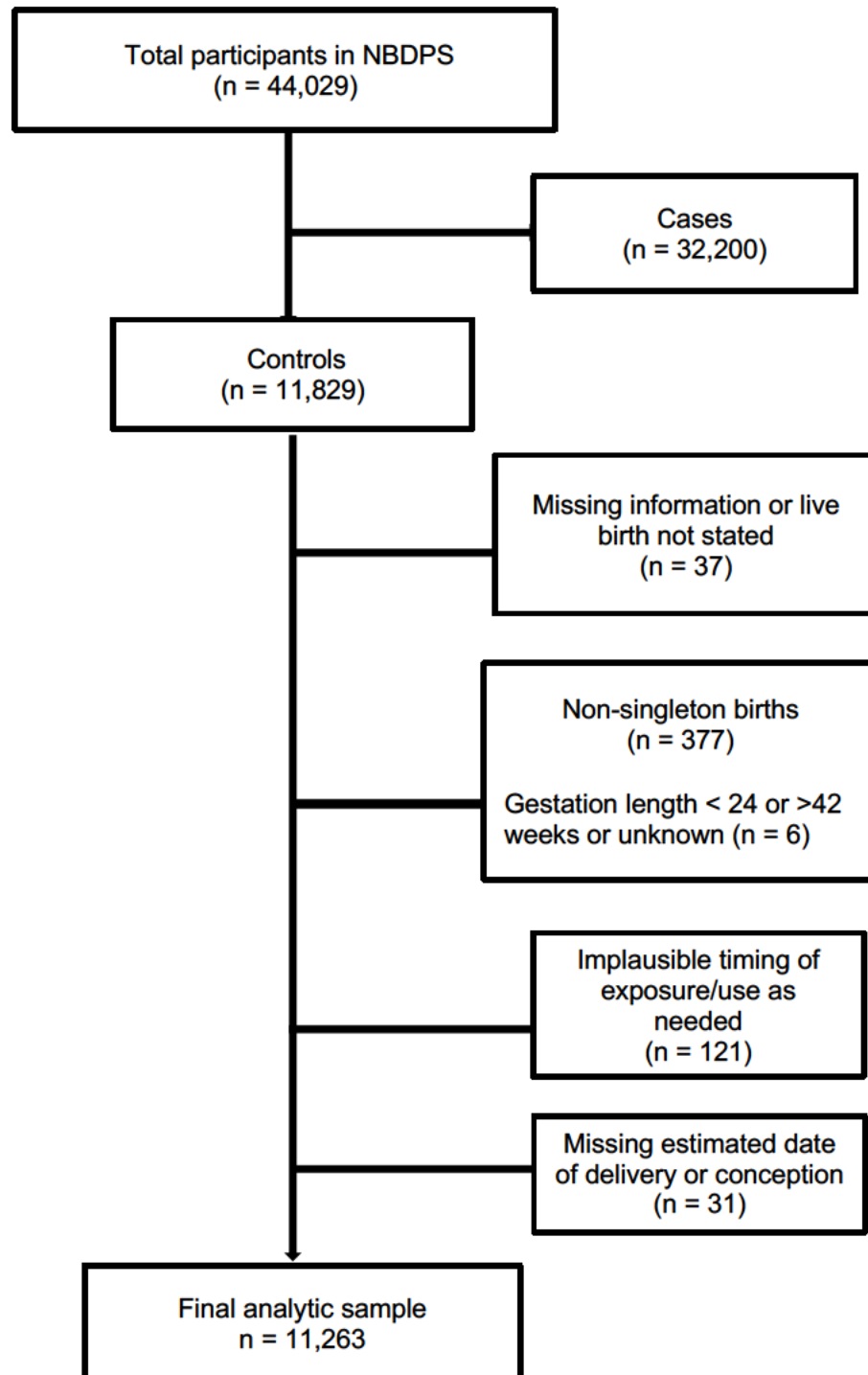
the treatment, bias can also occur with non-fatal outcomes.<sup>19,35</sup> In studies where the outcome is never fatal, misclassifying immortal time in the exposed may not result in bias if the incidence rate in the exposed is comparable to the rate in the unexposed, though it may affect precision.<sup>35</sup> In cases where the study outcome is nonfatal but is associated with death, the bias is a function of the number of events of interest occurring in the immortal time relative to the person-time in the reference group.<sup>30</sup> Immortal time bias is particularly relevant in drug safety in pregnancy studies. Information on drug safety and teratogenicity during pregnancy is primarily studied through non-experimental observational studies given ethical concerns.

Improperly accounting for the exposure period in the analyses will bias the effect estimate differently depending on the analytical methods. Simulation studies of time-to-event analyses have illustrated the magnitude and direction of bias resulting from inappropriately addressing immortal time, under various assumptions.<sup>31,32</sup> When using a standard Cox model, the bias is greatest with decreasing hazards and the least with increasing hazards.<sup>33</sup> With increasing hazards, there are few events occurring before the exposure while with decreasing hazards, more events occur at an earlier time point increasing the likelihood that an event would precede the expected treatment. Thus, employing the proper methodologic tools to obtain unbiased results is crucial. Immortal time bias may be present in studies when the period between the start of a trimester and the treatment initiation is misclassified as exposed, while being truly immortal or when follow-up is differential for exposed and unexposed and a time-fixed analysis is

employed.<sup>18</sup> In pregnancy studies, this can occur when fetuses do not survive sufficient time and therefore have a reduced chance of being classified as exposed. The chances of being exposed increase as gestational age increases.<sup>18,34</sup> This can result in spurious associations.<sup>13,17,34</sup>

### 3.5 TABLES AND FIGURES

**Figure 3.1.** Study population and exclusions, National Birth Defects Prevention Study, 1997–2011



**Table 3.1.** Characteristics of U.S., Singleton, Live Births by Decongestant Use in the National Birth Defects Prevention Study (NBDPS), 1997–2011

	Eligible births (n=11,263)		Decongestant use 2/3rd trimester (n=863)		Decongestant use 3rd trimester only (n=400)		No decongestant use (n=10,400)	
	No.	%	No.	%	No.	%	No.	%
<i>Preterm birth<sup>a</sup></i>								
Yes	903	8.0	69	8.0	25	6.0	834	8.0
<i>Year of due date</i>								
1997–2001	3,254	28.9	317	36.7	154	38.5	2,937	28.2
2002–2006	4,071	36.1	332	38.5	156	39.0	3,739	36.0
2007–2001	3,938	35.0	214	24.8	90	22.5	3,724	35.8
<i>Study site</i>								
Arkansas	1,408	12.5	130	15.1	66	16.5	1,278	12.3
California	1,227	10.9	81	9.4	40	10.0	1,146	11.0
Iowa	1,234	11.0	104	12.1	49	12.3	1,130	10.9
Massachusetts	1,322	11.7	104	12.1	54	13.5	1,218	11.7
New Jersey	531	4.7	27	3.1	9	2.3	504	4.9
New York	955	8.5	64	7.4	32	8.0	891	8.6
Texas	1,358	12.1	90	10.4	40	10.0	1,268	12.2
CDC/Atlanta	1,203	10.7	111	12.9	46	11.5	1,092	10.5
North Carolina	970	8.6	70	8.1	30	7.5	900	8.7
Utah	1,055	9.4	82	9.5	34	8.5	973	9.4
<i>Maternal age, years</i>								
< 20	1,135	10.1	41	4.8	19	4.8	1,094	10.5
20-24	2,572	22.8	144	16.7	64	16.0	2,428	23.4
25-29	3,132	27.8	282	32.7	123	30.8	2,850	27.4
30-34	2,882	25.5	276	32.0	130	32.5	2,606	25.1
35-39	1,288	11.4	109	12.6	56	14.0	1,179	11.3
40+	254	2.3	11	1.3	8	2.0	243	2.3
<i>Maternal education</i>								
< 12 years	1,817	16.1	67	7.8	27	6.8	1,750	16.8
12 years	2,623	23.3	153	17.7	70	17.5	2,470	23.8
13 - 15 years	2,943	26.1	280	32.4	128	32.0	2,663	25.6
≥ 16 years	3,564	31.6	352	40.8	168	42.0	3,212	30.9
Missing	316	2.8	11	1.3	7	1.8	305	2.9
<i>Maternal race/ethnicity</i>								
Black	1,245	11.1	64	7.4	30	7.5	1,181	11.4
Hispanic	2,805	24.9	114	13.2	51	12.8	2,691	25.9
White	6,470	57.4	628	72.8	289	72.3	5,842	56.2

Other racial categories	736	6.5	57	6.6	30	7.5	679	6.5
Missing	7	0.1	0	--	0	--	7	0.1
<i>Maternal BMI, kg/m<sup>2</sup></i>								
Underweight (<18.5)	572	5.1	26	3.0	13	3.3	546	5.3
Normal weight (18.5 – <25)	5,775	51.3	469	54.4	216	54.0	5,303	51.0
Overweight (25 – <30)	2,439	21.7	192	22.3	88	22.0	2,247	21.6
Obese (30+)	1,970	17.5	162	18.8	73	18.3	1,808	17.4
Out of range/Missing	507	4.5	14	1.6	10	2.5	493	4.7
<i>Smoking during pregnancy</i>								
Yes	1,973	17.5	166	19.2	83	20.8	1,807	17.4
No	9,013	80.0	686	79.5	309	77.3	8,327	80.1
Missing	277	2.5	11	1.3	8	2.0	266	2.6
<i>Alcohol consumption during pregnancy</i>								
Yes	4,077	36.2	370	42.9	175	43.8	3,707	35.7
No	6,873	61.0	481	55.7	217	54.5	6,392	61.4
Missing	313	2.8	12	1.4	8	2.0	301	2.9
<i>Pre-pregnancy high blood pressure diagnosis</i>								
Yes	1,507	13.4	127	14.7	61	15.3	1,380	13.3
No	9,694	86.1	736	85.3	339	84.8	8,958	86.2
Don't know/Missing	62	0.6	--	--	--	--	62	0.6
<i>Pre-eclampsia diagnosis</i>								
Yes	996	8.8	79	9.2	37	9.3	917	8.8
No	10,199	90.6	783	90.8	363	90.8	9,416	90.6
Missing	68	0.6	1	0.1	--	--	67	0.6
<i>Gestational diabetes diagnosis</i>								
Yes	772	6.9	63	7.3	30	7.5	709	6.8
No	10,339	91.8	796	92.2	369	92.3	9,543	91.8
Non-gestational diabetes	82	0.7	4	0.5	1	0.3	78	0.8
Missing	70	0.6	--	--	--	--	70	0.7
<i>Parity</i>								
First birth	4,459	39.6	299	33.8	134	33.5	4,160	40.0
2+ births	6,765	60.1	564	66.1	266	66.5	6,201	59.6
Missing	39	0.4	--	--	--	--	39	0.4
<i>Pregnancy planning</i>								
Wanted	5,361	47.6	430	49.8	198	49.5	4,931	47.4
Mistimed	1,883	16.7	125	14.5	53	13.3	1,758	16.9
Unwanted	1,076	9.6	62	7.2	30	7.5	1,014	9.8
Did not care	815	7.2	67	7.8	27	6.8	748	7.2
Refused/Unknown	14	0.1	0	--	0	--	14	0.1
Missing	2,114	18.8	179	20.8	92	23.0	1,935	18.6

Note: Percentage may add up to more than 100% due to rounding

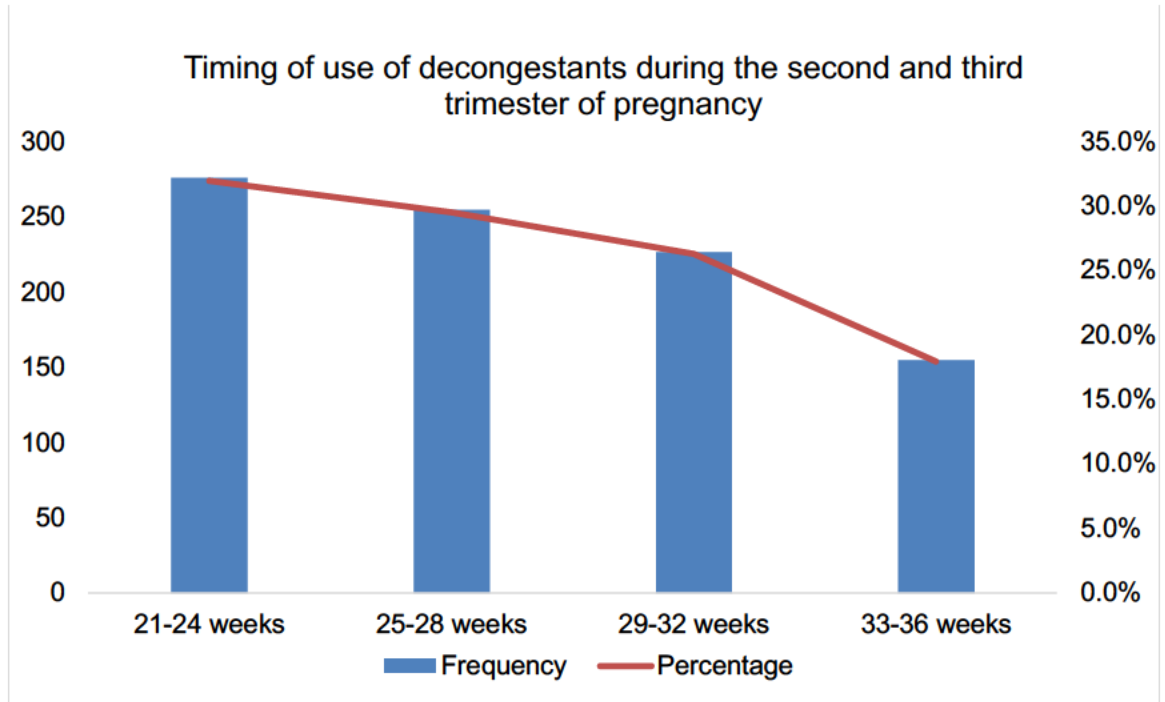
**Table 3.2.** Characteristics of U.S., Singleton, Live Births by Preterm Birth in the National Birth Defects Prevention Study, 1997–2011<sup>a</sup>

	Preterm birth (n=903)		Term birth (n=10,360)	
	No.	%	No.	%
<i>Year of due date</i>				
1997–2001	237	26.3	3,017	29.1
2002–2006	362	40.1	3,709	35.8
2007–2001	304	33.6	3,634	35.1
<i>Study site</i>				
Arkansas	150	16.6	1,258	12.1
California	89	9.9	1,138	11.0
Iowa	106	11.7	1,128	10.9
Massachusetts	89	9.9	1,233	11.9
New Jersey	36	4.0	495	4.8
New York	54	6.0	901	8.7
Texas	134	14.8	1,224	11.8
CDC/Atlanta	102	11.3	1,101	10.6
North Carolina	77	8.5	893	8.6
Utah	66	7.3	989	9.6
<i>Maternal age, years</i>				
< 20	100	11.1	1,035	10.0
20-24	205	22.8	2,367	22.9
25-29	277	30.7	2,855	27.6
30-34	181	20.0	2,701	26.1
35-39	107	11.8	1,181	11.4
40+	33	3.7	221	2.1
<i>Maternal education</i>				
< 12 years	164	18.2	1,653	16.0
12 years	246	27.2	2,377	22.9
13 - 15 years	228	25.3	2,715	26.2
≥ 16 years	235	26.0	3,329	32.1
Missing	30	3.3	286	2.8
<i>Maternal race/ethnicity</i>				
Black	140	15.5	1,105	10.7
Hispanic	227	25.0	2,579	24.9
White	481	53.3	5,989	57.8
Other	56	6.2	680	6.6
Missing	0	---	7	0.1
<i>Maternal BMI, kg/m<sup>2</sup></i>				
Underweight (<18.5)	56	6.2	516	5.0
Normal weight (18.5 – <25)	441	48.8	5,334	51.5

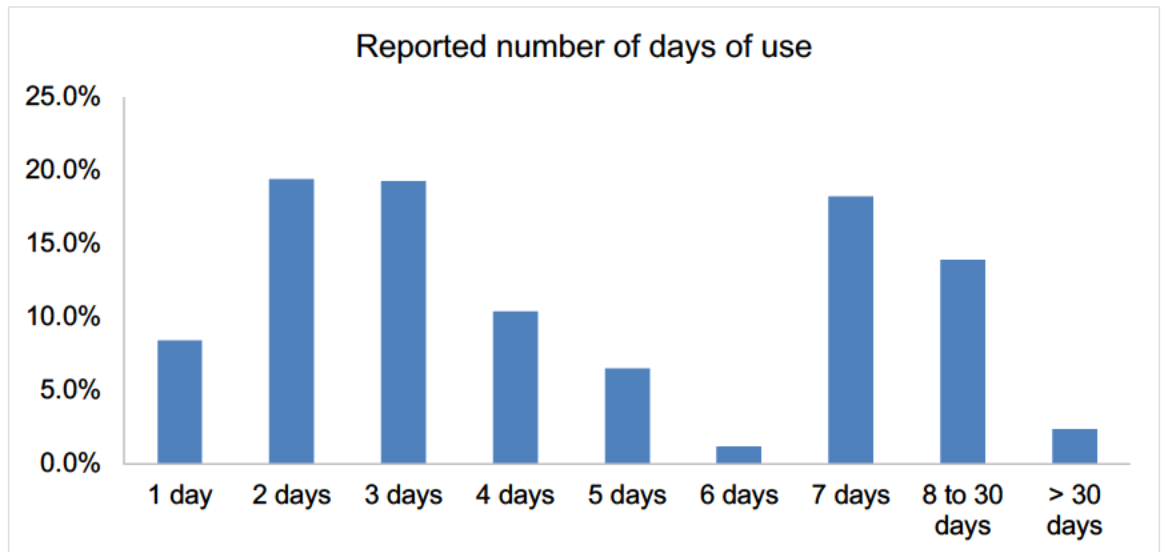
Overweight (25 – <30)	185	20.5	2,254	21.8
Obese (30+)	181	20.0	1,789	17.3
Out of range/Missing	40	4.4	467	4.5
<i>Smoking during pregnancy</i>				
Yes	185	20.5	1,788	17.3
No	692	76.6	8,321	80.3
Missing	26	2.9	251	2.4
<i>Alcohol consumption during pregnancy</i>				
Yes	286	31.7	3,791	36.6
No	586	65.0	6,287	60.7
Missing	31	3.4	282	2.7
<i>Pre-pregnancy high blood pressure diagnosis</i>				
Yes	219	24.3	1,288	12.4
No	678	75.1	9,016	87.0
Don't know/Missing	6	0.7	56	0.6
<i>Pre-eclampsia diagnosis</i>				
Yes	164	18.2	832	8.0
No	730	80.8	9,469	91.4
Missing	9	1.0	59	0.6
<i>Gestational diabetes diagnosis</i>				
Yes	74	8.2	698	6.7
No	799	88.5	9,540	92.1
Non-gestational diabetes	22	2.4	60	0.6
Missing	8	0.9	62	0.6
<i>Parity</i>				
First birth	364	40.3	4,095	39.6
2+ births	532	59.0	6,233	60.2
Missing	7	0.8	32	0.3
<i>Pregnancy planning</i>				
Wanted	410	45.4	4,951	47.8
Mistimed	170	18.8	1,713	16.5
Unwanted	109	12.1	967	9.3
Did not care	63	7.0	752	7.3
Refused/Unknown	1	0.1	13	0.1
Missing	150	16.6	1,964	19.0

<sup>a</sup> Preterm birth includes live births that occurred at gestational ages 24-<37 weeks inclusive.

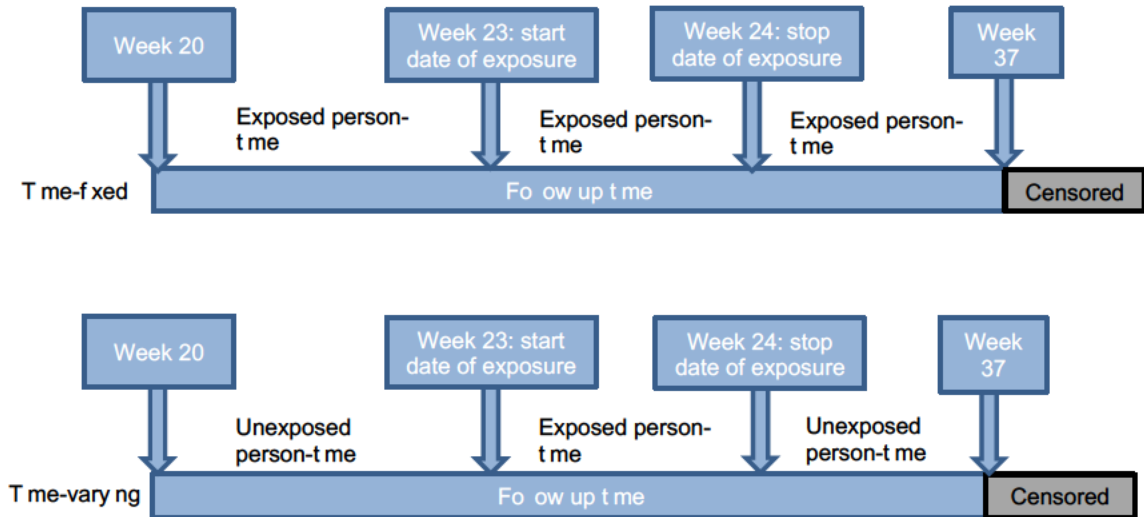
**Figure 3.2.** Timing (non-mutually exclusive) of use among participants reporting exposure to decongestants during the second and third trimester of pregnancy in the National Birth Defects Prevention Study, 1997–2011.



**Figure 3.3.** Distribution of non-consecutive number of days of use among participants reporting exposure to decongestants during the second and or third trimester of pregnancy in the National Birth Defects Prevention Study, 1997–2011



**Figure 3.4.** Example of a participant in the NBDPS that may have immortal person-time be classified as exposed person-time (misclassification bias) in a time-fixed analysis of decongestant use and preterm delivery. Adapted from Lévesque et al.



**Table 3.3.** Hazard Ratio Estimates (and 95% CI) for Decongestant Use and Preterm Birth among U.S, Singleton, Liveborn controls, National Birth Defects Prevention Study, 1997–2011

<b>Timing of decongestant use</b>	<b>Preterm births</b>	<b>HR (95% CI)</b>	<b>aHR<sup>a</sup> (95% CI)</b>	<b>aHR<sup>b</sup> (95% CI)</b>
<b><i>Time fixed</i></b>				
Second/third trimester	69	0.96 (0.73–1.26)	0.96 (0.73–1.27)	0.99 (0.75–1.31)
Third trimester	24	0.74 (0.50–1.11)	0.75 (0.50–1.12)	0.75 (0.49–1.13)
Unexposed	834	---	---	---
<b><i>Time varying</i></b>				
Second/third trimester	69	1.04 (0.79–1.38)	1.07 (0.79–1.44)	1.09 (0.82–1.44)
Third trimester	24	0.87 (0.59–1.30)	0.89 (0.59–1.33)	0.89 (0.59–1.34)
Unexposed	834	---	---	---

<sup>a</sup>Adjusted for age parity smoking alcohol preeclampsia and diabetes diagnosis

<sup>b</sup>Adjusted for age parity smoking alcohol and diabetes diagnosis

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## **4 SELF-REPORTED USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND AMNIOTIC BAND SYNDROME: ASSESSING THE IMPACT OF RECALL BIAS**

### **4.1 INTRODUCTION**

While case-control studies effectively allow research on rare outcomes such as congenital anomalies, exposures during pregnancy are often ascertained retrospectively, at times several years later, resulting in measurement error.<sup>1</sup> If errors in classification occur more frequently in one of the groups being compared, then differential misclassification will occur. Unlike non-differential exposure misclassification, which biases associations towards the null in expectation, differential misclassification may bias estimates in either direction.<sup>2</sup> This may lead to exposures being incorrectly identified as either protective or harmful.

In retrospective case-control studies on the possible teratogenic effects of medications during pregnancy, exposure status based on the mother's recall, may result in a particular scenario of differential misclassification referred to as "maternal recall bias".<sup>3,5</sup> The ensuing bias, resulting from the difference in the accuracy of recall between case and control mothers, stems from the belief that intervening events, such as the birth of a child with a congenital anomaly or other adverse birth outcomes, may impact recall of exposures otherwise forgotten by parents of children born without these conditions.<sup>6,7</sup> Some studies posit that accuracy of recall may be unaffected by the outcome of a pregnancy while others have suggested that mothers of children with congenital anomalies recall

exposures more accurately.<sup>6,8 10</sup>

Given that effects of medications on fetal development are studied primarily and most efficiently through retrospective case-control studies, empirically evaluating the potential impact of recall bias on the magnitude and direction of observed associations of prenatal exposures is crucial.<sup>11</sup> Although both random and systematic error contribute to uncertainty in observational research, the presence of systematic error is often limited to qualitative discussions and relying on heuristics.<sup>12,13</sup> The advent of quantitative bias analysis provides methodological tools to quantitatively estimate the direction, magnitude, and uncertainty associated with misclassification that influences measures of association. More recently, probabilistic bias analysis methods allow researchers to present frequency distribution of corrected measures of association by drawing values for bias parameters (functions to quantify the difference between the expected and observed values of the estimates) from defined probability distributions; repeatedly drawing random samples and explore how various combinations of these parameters would affect results.<sup>14 18</sup>

However, exposure misclassification bias analyses are limited by available data on estimates of the accuracy and validity of self-reported medication use. Existing studies compare self-reported medication use during pregnancy to medical records or prescription drug databases and pharmacy-dispensing records.<sup>19 23</sup> These sources of data may not accurately reflect actual medication use of prescribed medications and lack information on over-the-counter

medications. This gap in available, reliable validation data limits the ability to inform specific bias parameters, in which case multidimensional bias analyses may be used to explore combinations of values for bias parameters and the resulting impact on estimates of the effects of medication use on the risk of congenital anomalies.

### MOTIVATING EXAMPLE

We use an example from the literature on medication use during pregnancy and risk of congenital anomalies to ground this exercise. The use of over-the-counter (OTC) medications during pregnancy is common, with analgesics being one of the most prevalent.<sup>24,25</sup> Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are a chemically heterogeneous group of compounds which share common therapeutic and adverse effects. NSAIDs are typically categorized based on chemical structure and selectivity: acetylated salicylates, non-acetylated salicylates, propionic acids, acetic acids, enolic acids, anthranilic acids, naphthylalanine and selective COX-2 inhibitors.<sup>26</sup>

NSAIDs include many OTC and prescription medications; the most routinely used being aspirin, ibuprofen, diclofenac, indomethacin, and naproxen.<sup>27</sup> NSAIDs function by blocking the actions of an enzyme in the body called cyclooxygenase (COX).<sup>28</sup> COX has two function types: COX-1 protects the stomach from acid, and COX-2 is involved in inflammation. Inhibition of the COX-2 mechanism is responsible for the anti-inflammatory properties of NSAIDs while inhibition of the

COX-1 mechanism in the gastrointestinal (GI) tract is believed to be responsible for NSAID-related side effects, including serious GI complications.<sup>29,30</sup>

While generally considered safe at the recommended dosage and frequency, OTC analgesics such as aspirin, non-aspirin NSAIDs, and their combinations with other medications can have adverse events on the cardiovascular system and gastrointestinal tract in adults.<sup>25</sup> During pregnancy, exposure to analgesics and their metabolites may alter fetal physiological function through transplacental transport and pregnancy progression.<sup>25</sup> Animal studies have suggested that COX-1 inhibition may lead to congenital anomalies.<sup>31,32</sup> Exposure to NSAIDs during pregnancy in mice, rats and rabbits increased the incidence of midline defects, diaphragmatic hernias, and ventricular defects. However, the incidence of these defects was higher in aspirin-treated compared to non-aspirin NSAID-treated animals.<sup>31,33 35</sup> Pregnant rats treated with incrementally increasing doses of aspirin from 250–1000 mg/kg, showed a teratogenic dose-response association in early gestation. Large single doses of aspirin (500–625 mg/kg) produced a spectrum of development anomalies, many related to closure defects including craniorachischisis, gastroschisis and umbilical hernia, and cleft lip.<sup>36</sup>

In contrast, evidence on the potential teratogenicity of these medications from human studies is limited and varied.<sup>32,37 40</sup> Some case reports suggest a link between aspirin and indomethacin use and an increased risk of congenital anomalies, while other epidemiologic studies demonstrate no association.<sup>41 44</sup> A

meta-analysis concluded that there was no evidence of an overall increase in the risk of congenital anomalies associated with use of aspirin during pregnancy, with the exception of gastroschisis.<sup>45</sup>

The impact of NSAIDs on pregnancy is important to understand, as despite recommendations to discontinue use in early and late pregnancy, NSAIDs are frequently used in the first trimester of pregnancy to treat fever, inflammation, and pain.<sup>27,46</sup> Prevalence estimates suggest that 1 in 4 women use NSAIDs during pregnancy.<sup>47,48</sup> These medications decrease prostaglandin production, which has the potential to modify transport and implantation of the embryo, placental development, and maintenance of the pregnancy.<sup>49 52</sup> NSAIDs also serve as possible markers of vascular disruption by inhibiting COX-1 and COX-2 and the synthesis and bioavailability of vasodilatory prostaglandins; a group of lipids made at sites of tissue damage or infection that are involved in dealing with injury and illness.<sup>53,54</sup> Prostaglandins control processes such as inflammation, blood flow and formation of blood clots.<sup>55</sup>

Amniotic band syndrome (ABS) falls under an umbrella of several structural abnormalities attributed to vascular disruption during gestation.<sup>54,56 60</sup> Typically evidenced by a deformity mainly of the limbs, ABS often includes the presence of constriction rings, some degree of syndactyly, and occasionally fibrous bands encircling one or more fingers.<sup>61</sup> The proposed mechanism resulting in these deficiencies is a localized disruption of blood flow in embryonic and fetal cells, which alters a previously normal limb structure and can result in cell damage,

hemorrhage and tissue loss.<sup>61,62</sup> During embryonic development, vasculogenesis precedes the differentiation of the mesenchyme into muscle and bone.<sup>63</sup> The embryonic capillary network is the first fully functional tissue system to be developed and determines the vascular anatomy of the limbs.<sup>63,64</sup> Disruptions in the vascular network results in anomalies and may lead to multi-organ system anomalies, including musculoskeletal defects.<sup>63 65</sup> This can occur between the 6<sup>th</sup> and 8<sup>th</sup> week of gestation in the developing limbs when the disruption follows the ingestion of specific exposures.<sup>61,65 68</sup>

Two studies using data from the National Birth Defects Prevention Study (NBDPS) have estimated adjusted odds ratios (aORs) of 1.3 (95% confidence interval [CI]: 0.8, 1.8, [1997–2011]) and 1.4 (95% CI: 0.9, 2.1, [1997–2005]) for associations between use of non-aspirin NSAIDs and ABS.<sup>53,54</sup> A cohort study, using Danish registry data, reported slightly elevated odds of congenital anomalies (aOR 1.27, 95% CI: 0.93, 1.75) in pregnancies prescribed NSAIDs, although these results were aggregated for 46 congenital abnormalities.<sup>41</sup> In contrast, results from a large Norwegian cohort study suggest that exposure to NSAIDs does not seem to be associated with an increased risk of several congenital anomalies. However, due to small numbers of NSAID-exposed infants in individual categories (fewer than three exposed cases), several congenital anomalies, including ABS, were excluded from the analyses.<sup>40</sup>

The reported associations between use of NSAIDs and ABS in NBDPS may be the result of disparate recall among mothers of cases and controls. Particularly,

episodic exposures such as OTC medications, notably NSAIDs, may be reported inaccurately. This analysis revisits the most recently published association between use of NSAIDs and ABS in NBDPS and investigates the impact of exposure misclassification by applying non-probabilistic and probabilistic bias analysis methods using multiple sets of parameter estimates derived from external validation studies.<sup>14,15</sup>

## **4.2 METHODS**

### *4.2.1 Study population*

NBDPS was a multi-site, population-based case-control study, designed to investigate more than 30 major structural anomalies and associated genetic and environmental risk factors. From October 1997 to December 2011, surveillance systems in ten states across the United States (Arkansas, California, Iowa, Georgia, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) were used to identify cases and non-malformed controls. Eligible cases included live born, stillborn ( $\geq 20$  weeks' gestation) and, at selected sites, pregnancies ending in terminations. All clinical information was reviewed by a geneticist for eligibility criteria and classification of cases.<sup>69</sup> Congenital anomalies with a known genetic cause (i.e., single gene disorders or chromosomal disorders) were excluded. Control infants were randomly selected among unaffected live births from birth certificates or hospital birth records in the same region, with an estimated delivery date during the same period as study cases.<sup>70,71</sup> Overall, 67% of eligible

cases and 65% of eligible controls participated in the interviews.<sup>70</sup>

Mothers of eligible cases and controls were sent introductory packets and invited to complete computer-assisted telephone interviews, in English or Spanish, between 6 weeks to 24 months after the estimated delivery date (EDD). Mothers were contacted and interviewed via computer-assisted telephone interviews (CATI) for approximately 60 minutes. The interviews included detailed questions on demographics, reproductive factors, behaviors, illnesses, medications for treatment of reported illnesses (e.g., infections, fevers, injuries) and other exposures that occurred three months before conception through the end of the pregnancy.<sup>70</sup> Pregnancy calendars are built into the CATI to assist with accurate reporting of exposures relative to the timing during pregnancy.

#### *4.2.2 Outcome*

Case classification has been described in detail elsewhere.<sup>70 72</sup> Briefly, cases in NBDPS were classified as isolated, multiple, or complex by study geneticists. Isolated cases refer to cases with single major defects (including single major defects accompanied by minor defects in the absence of a defined syndrome) and multiple major defects in the same organ system. Given the complexity of classification of limb deficiencies, isolated cases are presumed to reduce pathogenetic heterogeneity. The outcome of interest for this current study only includes isolated ABS cases.

Isolated ABS cases involved constriction band(s), cord constriction, unusual syndactylies (particularly acrosyndactyly) and amputations only affecting the limbs

(i.e., no craniofacial disruption or truncal involvement). ABS cases with reported anomalies consistent with limb-body wall complex were not considered. Among the 284 ABS case mothers, we excluded 95 (33%) mothers of infants with non-isolated cases of ABS. We also excluded one (<1%) case with missing information on estimated date of delivery information (EDD). Following exclusions, we included 179 ABS case mothers and 11,500 control mothers.

#### *4.2.3 Exposure*

The exposure of interest in this study is use of non-aspirin NSAIDs in the periconceptual period – defined as the month preceding conception to the third month of pregnancy. Mothers with missing information on exposure to NSAIDs were excluded from the analysis (n = 10). Information on use of non-aspirin NSAIDs was compiled and coded using the Slone Drug Dictionary, linking drug products to their active ingredients.<sup>73</sup> Participants were considered exposed if they reported any use of the following medications (both prescription and OTC) for any indication and in any dose during the exposure window: aceclofenac, choline magnesium trisalicylate, etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, magnesium salicylate, methyl salicylate, nabumetone, naproxen, phenyl salicylate, sodium salicylate, sulindac, tolmetin and zomepirac. In the previous study, aspirin users were considered separately and thus excluded from this analysis.

#### 4.2.4 Covariates

We considered study site, demographic, and clinical characteristics as covariates. Demographic information included maternal age at delivery (< 20, 20–24, 25–29, ≥ 30 years), years of formal education (< 12, 12, 13–15, ≥ 16 years) and race/ethnicity (non-Hispanic Black, non-Hispanic white, Hispanic, Asian, Native American, and other). Mothers reporting Hispanic ethnicity were classified as Hispanic, regardless of reported race. Other variables of interest included anthropometric and reproductive characteristics such as pre-pregnancy body mass index (BMI) (< 18.5, 18.5–< 25, 25–< 30, ≥ 30 kg/m<sup>2</sup> according to the National Institutes of Health categories), number of previous live births (≥ 1, 0) and pregnancy intention and planning at the time that the pregnancy occurred.

In the original analyses by Adrien et al, cigarette smoking and alcohol consumption were included as primary exposures; potential markers of the vascular disruption theory, based on their vasoactivity.<sup>53</sup> In this analysis, we examined alcohol consumption and cigarette smoking during pregnancy as potential confounders of the association between ABS and NSAIDs. Reported alcohol consumption was categorized as binge drinking (≥ 4 drinks/occasion), drinking but not binge drinking (< 4 drinks/occasion), and no drinking. Cigarette smoking was dichotomized into fewer than 15 cigarettes and 15 or more cigarettes per day. Women who reported different average daily amounts of smoking between months during the period of interest were assigned the highest value of reported cigarettes.

#### 4.2.5 Conventional analysis

Descriptive analyses included distribution of maternal factors (i.e., age, BMI, education, race/ethnicity, number of previous births, and pregnancy intention), periconceptional cigarette smoking and alcohol consumption for cases and controls. Original comparative analyses of the study data presented multivariable-adjusted models using Firth's penalized logistic regression models to estimate adjusted odds ratios (aORs) and profile likelihood 95% confidence intervals (CIs) to mitigate bias due to sparse data.<sup>53,74</sup> In the comparative analyses, maternal age at delivery and education were categorized into dichotomous variables (age: < 25, ≥ 25 years; education < 12 and ≥ 12 years). For race/ethnicity, mothers reporting Asian or Native American as their racial identity were reclassified as "Other" due to small cell sizes. The aORs were interpreted as relative risks since the outcome is rare. All statistical analyses were conducted in SAS version 9.4 (Cary, NC).

#### 4.2.6 Adjustment for exposure misclassification

In order to assess the impact of recall bias on the reported associations between NSAIDs and ABS, we considered sensitivity and specificity parameters from external validation studies for reports of medication use during pregnancy for mothers of infants with and without congenital anomalies.<sup>20,21,75</sup> For cases, we used data from a validation study from Eurocat Northern Netherlands, a population-based registry of congenital anomalies that includes 10% of all births in the Netherlands.<sup>21</sup> The study included information from 560 mothers of infants with

any congenital anomaly, from January 2009 through June 2010. However, pharmacy records were used as the “gold standard” measure to assess the sensitivity (0.36) and specificity (0.98) of maternal recall of medication by comparing information to self-administered questionnaires (Table 4.3, *van Gelder et al*).<sup>21</sup>

For controls, we obtained data from a validation study on medication exposures during pregnancy of women with chronic conditions. These women from the United States and Canada were enrolled in one of two MotherToBaby pregnancy studies and diagnosed with chronic conditions (asthma and rheumatoid arthritis) using both continuous and sporadic medications. MotherToBaby studies are prospective cohorts and include a medication-exposed group, a disease matched-group, and a non-diseased comparison group. Pregnant participants are recruited in three cohorts at <20 weeks’ gestation, complete three to four telephone interviews, and consent to release of medical records.<sup>76</sup> Information is collected on all medication, vaccines, dietary supplements, herbal products and other substances used by dose and gestational timing.<sup>76</sup> Validity measures (Se = 0.38, Sp = 0.93) for medication use, such as information on oral NSAIDs, were calculated using agreement between maternal report and obstetrician records (Table 4.3, *Palmsten et al*).

We obtained a second set of bias parameters, Se (0.79) and Sp (0.62), from a validation study using a subset of the *Right from the Start* (RFTS) community-based cohort. Participants in RFTS were recruited from 2000–2012 among people

attempting to conceive without the use of assisted reproductive technologies, in North Carolina, Tennessee, and Texas. A subset of participants enrolled from 2006–2012 to complete web-based daily and weekly diaries, initiated prior to conception. Diary participants were prompted to record entries, including the name and dosages of the medications that they used daily, following a baseline questionnaire. Daily diaries prompted participants to record NSAID use, providing medication names and common name brands (e.g., ibuprofen (Advil/Motrin), naproxen (Aleve), aspirin, ketoprofen (Orudis)). Weekly diaries also included prompts concerning prescription medications. To be included in the analysis, participants had to be adherent to daily diary participation for five out of seven days a week, and at least six of the seven weeks in the exposure window for the weekly diaries. At the third trimester, participants were asked to retrospectively report information on medications during a CATI, targeting NSAID exposure during the periconceptual period. Retrospective information was compared to prospectively collected information from daily dairies (Table 4.3, *Sundermann et al*).<sup>20</sup>

The majority of NBDPS participants report use of OTC (vs. prescription) NSAIDs. Available validation studies on self-reported use of NSAIDs during pregnancy (among cases or controls) relied on two “gold standard” approaches to estimate true NSAID use. The first approach was to use electronic medical records (EMR) and pharmacy records as “gold standard” measurement tools, which do not accurately capture OTC medications. The second relied on contemporaneous diary information, first prompting participants to prospectively document daily and

weekly NSAID use during the first trimester, then asking participants to recall their previously reported use at the end of the first trimester. While this approach does capture use of OTC medications, diary recording is likely to enhance retrospective recall and the interval of recall is shorter than in NBDPS. This second gold standard measure may not be a comparable reflection of the accuracy of exposure ascertainment in NBDPS. Given the aforementioned limitations of these validation data, we could not assume that the Se and Sp were transportable to the desired sensitivity and specificity estimates in NBDPS. While the external validation studies suggest that specificity may be nearly perfect and sensitivity is poor, there is a wide range of uncertainty regarding the values assigned to the parameters. Thus, we conducted multidimensional non-probabilistic quantitative bias analyses to explore combinations of values of the bias parameters. For non-probabilistic bias analyses, we calculate misclassification-adjusted ORs that do not take into account uncertainty in the bias parameters, therefore not allowing us to calculate intervals for the estimate.<sup>15</sup> We assumed both nondifferential and differential misclassification with respect to the outcome. Based on the validation studies used for the probabilistic bias analysis, we first assumed differential misclassification, assigning the same sensitivity to both groups, and greater specificity (+0.05) to the cases. Then we assumed greater sensitivity in the cases, then the controls and assigned the same value for specificity. Values for sensitivity ranged from 0.3 to 0.7 while values for specificity ranged from 0.8 to 1.0.

We conducted a record-level probabilistic bias analysis and assigned

triangular distributions to model the probability density functions for the bias parameters, using the ranges presented in the validation studies as the upper and lower bounds (restricted to fall between zero and 1). We chose the triangular distribution as a realistic distribution close to a normal distribution given that there was no evidence to suggest that the data were not normally distributed. Among the cases, for the sensitivity, we specified a mode of 0.36 (0.16–0.56) and a mode of 0.98 (0.96–0.99) for the specificity based on parameters from van Gelder et al. Among the controls, we specified a mode of 0.38 (0.23–0.55) for the sensitivity and 0.93 (0.88–0.85) for the specificity, based on parameters from Palmsten et al. These were the bias parameters most compatible with the data based on the exposure prevalence. We imputed each parameter 5,000 times and calculated 5,000 ORs.<sup>14,15</sup> We used the method of Fox et al. to account for random error.<sup>77</sup> We present the results as the median OR and the 2.5<sup>th</sup>, 50<sup>th</sup> and 97.5<sup>th</sup> percentile values, reported as a simulation interval (SI).

## **4.3 RESULTS**

### *Conventional analysis*

Nearly a quarter of controls (22.5%), compared to nearly a third of case mothers (26.5%) reported use of NSAIDs in the periconceptional period (Table 4.1). There was a higher proportion of ABS mothers who were younger and had lower education attainment than mothers of controls. More ABS case mothers identified as non-Hispanic Black, were more likely to be first time mothers, but were

equally as likely as control mothers to report a planned pregnancy. ABS case mothers were more likely to report smoking (26.4%) and alcohol consumption (43.4%) than controls (17.5% and 35.7% respectively) (Table 4.2). For the association between the use of non-aspirin NSAIDs and ABS, the unadjusted OR was 1.29 (95% CI 0.93–1.79). After excluding participants with missing covariate information and adjusting for study location, age, education attainment, self-reported race and parity, the odds ratio for the association for the use of non-aspirin NSAIDs was 1.25 (95% CI 0.84–1.79). After including smoking and alcohol consumption as additional confounders in the model, the adjusted OR was 1.17 (95% CI 0.79–1.69).

#### *Exposure misclassification*

The results of the multidimensional bias analyses assuming differential and nondifferential misclassification are shown in Figure 4.1–Figure 4.4. Results varied according to the scenarios considered, with some overall trends emerging. When we assumed the same sensitivity but greater specificity in the cases, the estimates decreased from 13.71 (Se = 0.30, Sp = 0.85 in the cases) to 1.72 (Se = 0.70, Sp = 1.0 in the cases) (Figure 4.1). Under the assumption of differential misclassification and greater sensitivity in the cases, the adjusted estimates suggested that the observed unadjusted and confounding-adjusted estimates could be biased either away from (Sp  $\geq$  0.9) or towards the null (Sp  $\leq$  0.8). With perfect specificity, estimates ranged from 0.69 (Se = 0.3) to 1.09 (Se = 0.7) (Figure

4.2). As specificity decreased, the resulting bias in the observed estimate increased. When we assumed a specificity of 0.8, bias adjusted-estimates ranged from 1.45 (Se = 0.3) to 2.29 (Se = 0.7). When we assumed greater sensitivity in the controls, the resulting bias-adjusted estimated suggested that the observed estimate was biased towards the null, to varying degrees, under all assumptions for specificity (Figure 4.3). Even under the assumption of perfect specificity, bias-adjusted estimates ranged from 9.87 (Se = 0.3) to 1.63 (Se = 0.7).

When we assumed nondifferential misclassification, results were also compatible with the observed unadjusted and confounding-adjusted estimates being biased towards the null. The bias adjusted estimates ranged from 1.35 (Se = 0.7, Sp = 1.0) to 8.49 (Se = 0.3, Sp = 0.8) (Figure 4.4). We observed one phenomenon that should be noted. When sensitivity was quite poor (<0.4), despite increases in specificity, the resulting adjusted estimates suggested large amounts of bias towards the null in the unadjusted and confounding-adjusted estimates. With poor sensitivity, as specificity decreased, the bias adjusted estimates could be more than 10-fold the observed unadjusted estimate.

In the probabilistic analysis, approximately 18% of iterations produced an error. The external validation studies indicated differential misclassification, suggesting low, albeit similar, sensitivity between the cases and controls, and better specificity among the cases. The resulting bias-adjusted estimates from the probabilistic analyses also suggested that the unadjusted and confounding-adjusted estimates were biased towards the null. The record level bias-adjusted

OR was 3.19 (95% SI 0.49–36.13) (Figure 4.5).

#### **4.4. DISCUSSION**

We implemented non-probabilistic and probabilistic adjustments of differential misclassification of exposure to evaluate the results of a study of the association between NSAIDs and amniotic band syndrome. When we explored the impact of differential misclassification, assuming better classification in the cases, the adjusted estimates were compatible with either bias away or bias towards the null. We observed that nondifferential misclassification as expected, resulted in bias towards the null in the observed association of ABS and NSAIDs. To some degree, the specificity value had a greater impact on the estimates than losses of sensitivity. However, when sensitivity was below 0.4, resulting in truly exposed women being classified as unexposed, the estimates suggested very large amounts of bias towards the null. These results suggest that the previously observed association between ABS and NSAIDs is may not be due to misclassification and may in fact be biased towards the null; however, the magnitude of the true effect depends on the extent of misclassification, which cannot be estimated from previous validation studies.

Our attempts to adjust for exposure misclassification were limited by several factors. The majority of the available validation studies on NSAID use during pregnancy compare medical or pharmacy records data to maternal reports. Comparing prescription records to self-report data often shows substantial

disagreement between the two information sources.<sup>21,78</sup> Medications acquired OTC are not captured in prescription records, therefore studies using administrative records would consider people unexposed when they are truly exposed (decreased sensitivity). Additionally, information on use of NSAIDs reflected in medical charts may reflect a patient population using higher doses of NSAIDs or at a greater frequency. Pregnancy is a major predictor for medication discontinuation, thus pregnant people may also be classified incorrectly as exposed when they have in fact discontinued or reduced medication use.<sup>79</sup>

Information on medication use in NBDPS captures information on both prescription and OTC medication use. Using bias parameters informed by pharmacy records limits our ability to effectively ascertain the potential effects of recall bias for a medication that is largely used intermittently.<sup>80</sup> We could not assume that the external validity parameters were applicable to the NBDPS study population. The purpose of bias analyses is not always to estimate the true association, particularly given the lack of good validation data. Valuable contributions include observing changes in results under realistic assumptions about mechanisms of bias. Therefore, we tested a limited number of the many possible assumptions, and if incorrect, can cause substantial error and our results would not reflect the true estimate. While multidimensional bias analyses allowed us to assess how robust the observed measure of association is to changes in the bias parameter values, we also assigned equal weight to each corrected measure of association, similar to specifying a uniform probability distribution.<sup>15,77</sup>

Probabilistic bias analyses allow researchers to specify which values for bias parameters are more or less likely based on the assigned probability distributions.<sup>15,77</sup>

Studies on the accuracy of recall of medication use during pregnancy suggest that while specificity is often high, sensitivity may be low, particularly with medications taken intermittently, such as analgesics.<sup>21,78</sup> Participants may be unaware and not report medications that are not specifically labelled as NSAIDs or include combinations of NSAID and non-NSAID in a singular medication. Several factors affect recall of exposures beyond frequency and type of medication, such as age, education, or other pre-pregnancy behaviors associated with social desirability.<sup>81</sup> Higher levels of education are consistent with better recall and educational attainment was higher in the controls than the cases in our data.<sup>82</sup> In our analyses, we made the simplifying assumption that bias parameters varied by case-control status. While estimating bias parameters conditional on other variables may provide better adjustment for bias, further parsing out our small sample size might have introduced additional bias to the analysis or resulting in non-estimable ORs.<sup>83</sup>

Other methods to address misclassification of maternal recall of early pregnancy exposures have been undertaken, including stratification by length of recall period<sup>59,84</sup> or restricting the analyses by length of recall (between 6–42 weeks between the estimated date of the delivery and the interview).<sup>85</sup> Some have made adjustments for misclassification using Bayesian analysis methods.<sup>86</sup> Others

eschew the more computationally demanding implementation of probabilistic bias analyses and provide simpler methods to compute bounds that can be used to compare the effect of bias due to misclassification.<sup>87,88</sup> Though we were limited in our analyses, additional complexities can be added to address other biases such as unmeasured confounding or selection bias. Studies of medications as risk factors may still be prone to confounding by indication. Additionally, the vasoactive properties of NSAIDs are dose-dependent and we were unable to assess whether differences in observed and corrected estimated differed by ingested dose.

Our study underlines the need for validation studies of medication use during pregnancy, such as OTC analgesics. Under the assumption of recall bias, our results suggested that decreases in sensitivity may be drastically biasing results towards the null. Even under the expectation of nondifferential misclassification which tends to bias results towards the null, under the “worst case” scenario assumption used in this study, our results suggest that we may be failing to detect meaningful risks. We highlight the importance of considering sources of systematic bias as well as confounding. Future analyses exploring medications used episodically would benefit from quantitative bias analyses to explore the effects of misclassification. An additional consideration from these results is that the effect of confounding may be less important than the effect of misclassification, particularly with poor sensitivity in these data.

**Table 4.1.** Characteristics of Mothers of ABS<sup>a</sup> Cases and Controls in the Analysis, National Birth Defects Prevention Study, 1997–2011

	Isolated ABS ( <i>n</i> = 189)		Controls ( <i>n</i> = 11,829)	
	No.	%	No.	%
Non-aspirin NSAID				
Yes	50	26.5	2,658	22.5
Missing/Unknown	10	5.3	329	2.8
Maternal age, years				
< 20	34	18.0	1,177	10.0
20-24	65	34.4	2,668	22.6
25-29	41	21.7	3,271	27.7
30+	49	25.9	4,713	39.8
Maternal BMI, kg/m <sup>2</sup>				
Underweight (<18.5)	10	5.3	599	5.1
Normal weight (18.5 – <25)	103	54.5	6,045	51.1
Overweight (25 – <30)	30	15.9	2,557	21.6
Obese (30+)	34	18.0	2,074	17.5
Out of range/Missing	12	6.4	554	4.7
Maternal education, years				
≤ 12	97	51.3	4,630	39.1
13–15	45	23.8	3,079	26.0
≥ 16	40	21.2	3,775	31.9
Missing	7	3.7	345	2.9
Maternal race/ethnicity				
Black	44	23.3	1,308	11.1
White	93	49.2	6,836	57.8
Hispanic	36	19.1	2,908	24.6
Asian	7	3.7	353	3.0
Native American	1	0.5	51	0.4
Other racial categories/Missing	8	4.2	373	3.2
Number of previous live births				
None	110	58.2	4,664	39.4
1+	75	39.7	7,114	60.1
Missing	4	2.1	51	0.4
Pregnancy intention				
Wanted <sup>b</sup>	135	71.4	8,486	71.7
Unwanted	21	11.1	1,115	9.4
Missing/Refused/Unknown	33	17.5	2,228	18.8

<sup>a</sup>Amniotic band syndrome, <sup>b</sup> Includes "mistimed" and "did not care" responses

**Table 4.2.** Periconceptual Health Behaviors among Mothers of ABS<sup>a</sup> Cases and Non-malformed Controls, National Birth Defects Prevention Study, 1997–2011

<b>Exposures</b>	<b>Isolated ABS (n = 189)</b>		<b>Controls (n = 11,829)</b>	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>
Maternal smoking				
≥ 15 cigarettes/day	15	7.9	580	4.9
< 15 cigarettes/day	35	18.5	1,495	12.6
No smoking	132	69.8	9,454	79.9
Missing/Unknown	7	3.7	300	2.5
Alcohol drinking				
Binge drinking (≥ 4 drinks)	34	18.0	1,431	12.1
Drinking but not binge drinking	48	25.4	2,788	23.6
No drinking	98	51.9	7,210	61.0
Missing/Unknown	9	4.8	400	3.4

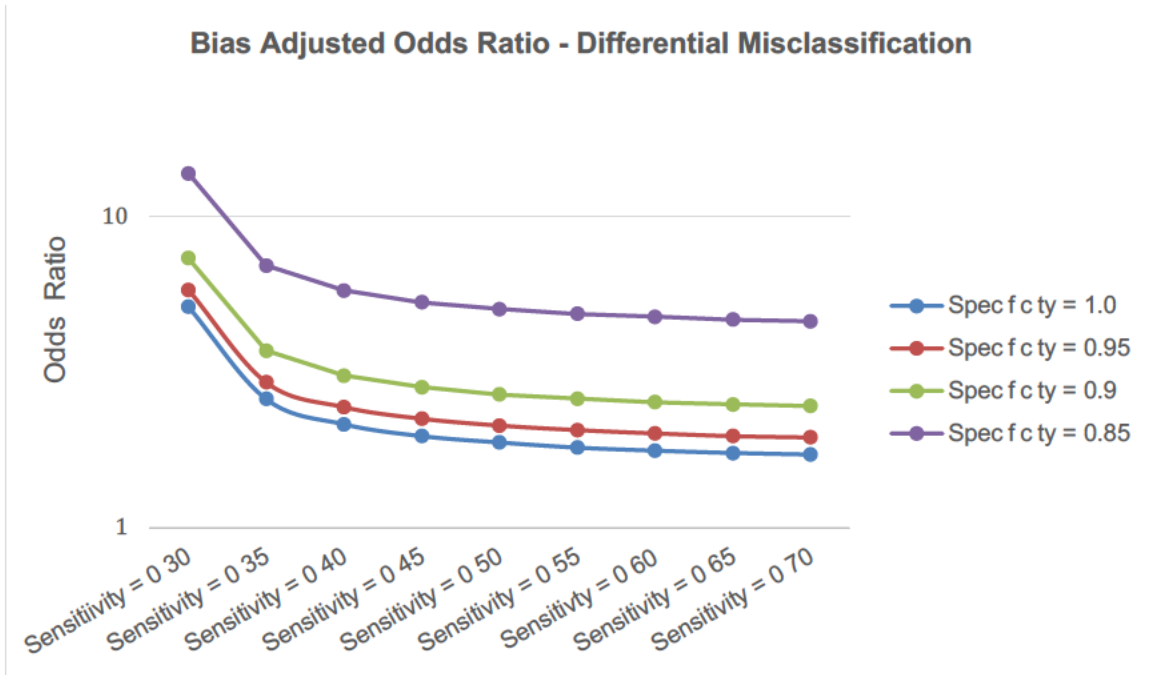
<sup>a</sup>Amniotic band syndrome

**Table 4.3.** Validation studies of reported sensitivity and specificity values for reported maternal recall for exposure to analgesics during pregnancy among mothers of infants with and without birth defects

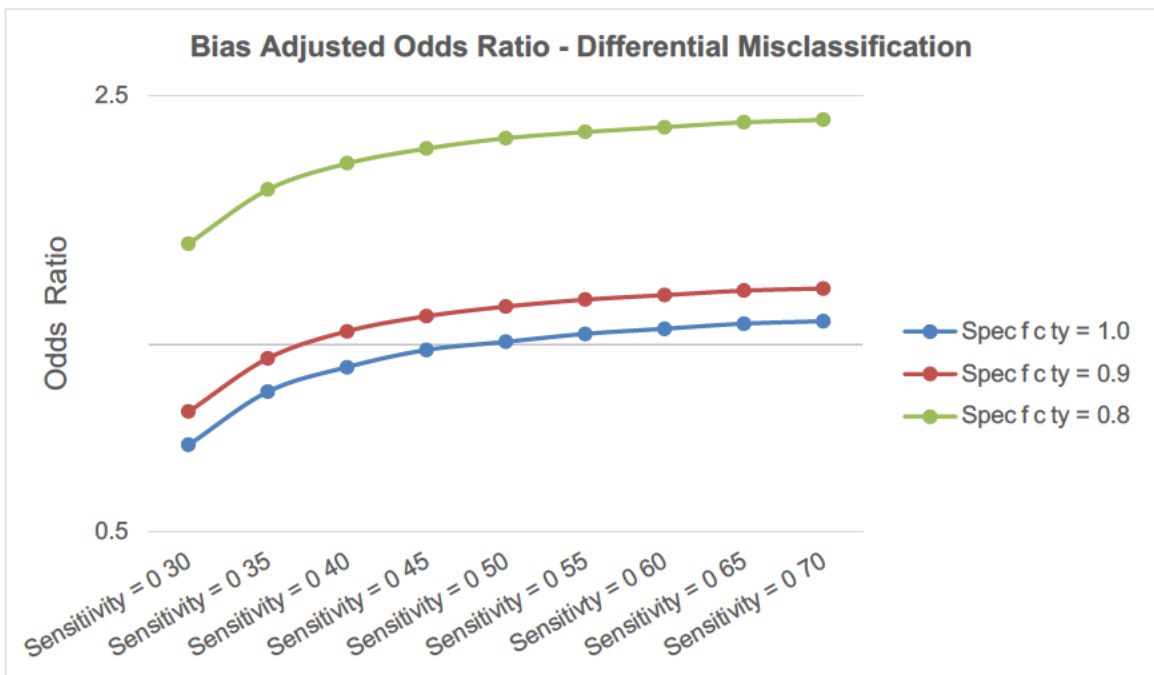
Validity Measures							
Congenital anomaly		Nonmalformed births					
Authors	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Medication	Source Population	"Gold standard" measurement tool (s)
<i>van Gelder MMHJ et al.</i>							
	0.36 (0.16–0.56)	0.98 (0.96–0.99)	--	--	NSAIDs	Netherlands	Pharmacy records
<i>Palmsten et al.</i>							
			0.38 (0.23–0.55)	0.93 (0.88–0.95)	oral NSAIDs	United States and Canada	Medical records
<i>Sundermann et al</i>							
	--	--	0.79	0.62	NSAIDs	United States	Prospective diary entries

CI: Confidence Interval; Eurocat – NNL: European Registration of Congenital Anomalies and Twins Northern Netherlands (EUROCAT NNL).

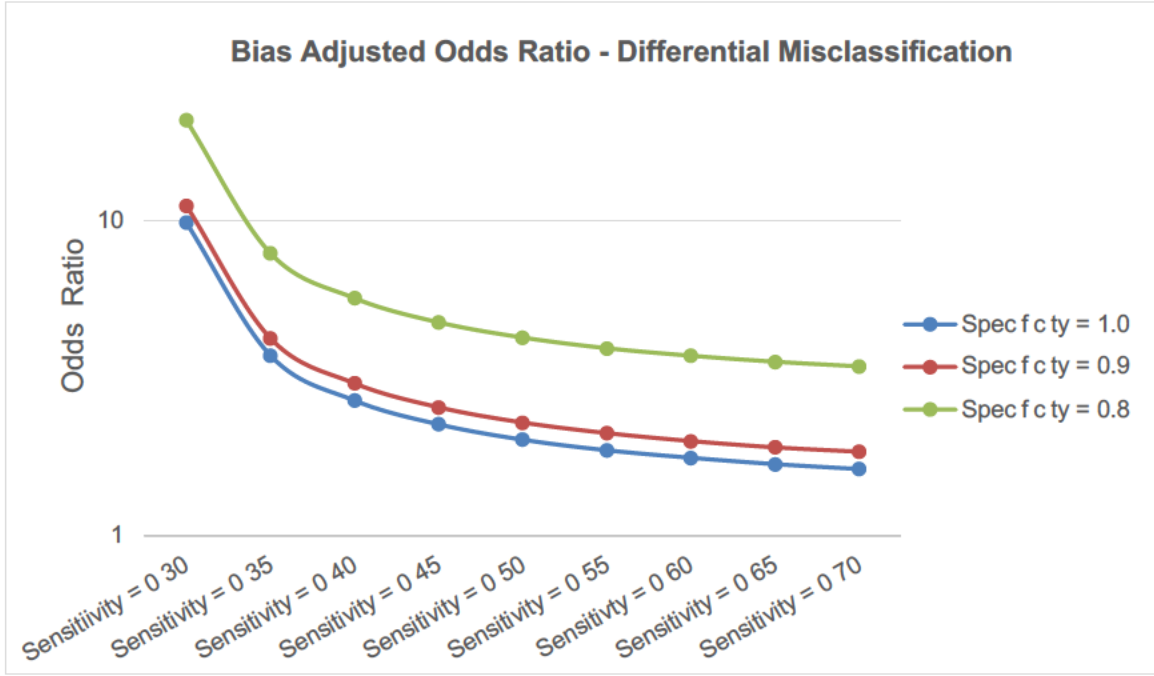
**Figure 4.1.** Adjusted estimate(s) for differential misclassification, assigning same sensitivity (0.3–0.7) and lower specificity (0.8–0.95) to the controls and Se/Sp +0.05 to the cases



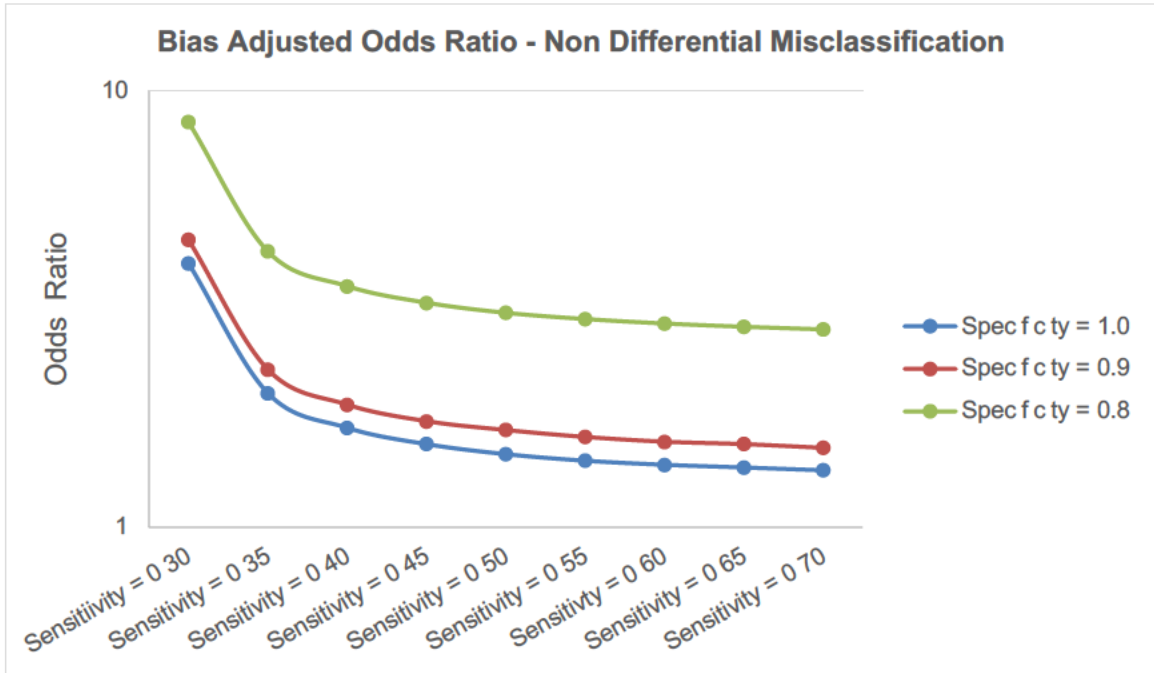
**Figure 4.2.** Adjusted estimate(s) for differential misclassification, assigning lower sensitivity to the controls (0.3–0.7) and Se +0.10 to the cases



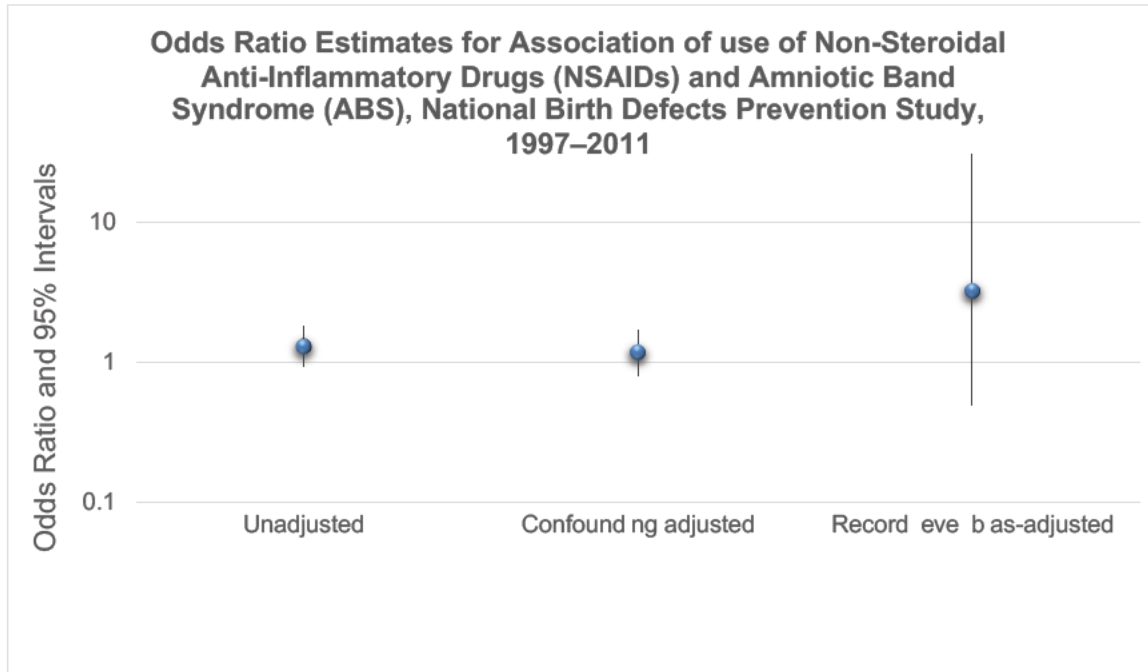
**Figure 4.3.** Adjusted estimate(s) for differential misclassification, assigning lower sensitivity to the cases (0.3–0.7) and Se +0.10 to the controls



**Figure 4.4.** Adjusted estimate(s) for non-differential exposure misclassification



**Figure 4.5.** Comparison of odds ratio and 95% intervals in conventional, confounding-adjusted, and probabilistic bias-adjusted analyses



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## CONCLUSION

This dissertation examined the association between three commonly used medications during pregnancy and fetal outcomes. Specifically, we studied various proposed mechanisms of systematic bias in previous studies to quantitatively examine their impact on estimates of association. Using data from the National Birth Defects Prevention Study (NBDPS), we studied the presence and impact of 1) selection bias due to differential participation on the association between use of ondansetron in the first trimester and cleft palate, 2) immortal-time bias on the association of decongestant use in late pregnancy and preterm delivery, and 3) differential misclassification on the association of use of non-steroidal anti-inflammatory drugs (NSAIDs) and amniotic band syndrome. Overall, we found that evidence of the impact of these mechanisms of bias was limited. Results suggested that use of certain medications such as ondansetron and NSAIDs in the first trimester may be associated with an increased risk of congenital anomalies. We also found that use of decongestants was not associated with a decreased risk of preterm delivery.

In the first study, we used study records to estimate the probability of participation conditional on a vector of covariates associated with the use of ondansetron and cleft palate.<sup>1</sup> Using conditional contrasts, we attempted to build inverse probability of participation weights (IPW) to address potential selection bias in a previous NBDPS study.<sup>1 3</sup> We found limited evidence of selection bias when comparing our weighted and unweighted estimates. The major limitation was that

the information available on the non-participants was limited and our models to predict participation may have been mis-specified. Our measured variables were weak predictors of participation; the concordance statistic, also known as c-statistic for our model predicting participation was 0.7. Therefore, the composite weights that we created may not properly address selection bias.

The possibility of bias in the results on the association of ondansetron and cleft palate in NBDPS were first noted when compared to the results from the Birth Defects study (BDS). Estimates from BDS were compatible with a protective or null association (aOR =0.5, 95% 0.3–1.0). Current literature on the risk associated with use of ondansetron in the first trimester is consistent with results from NBDPS, suggesting increased risks of cleft palate.<sup>5</sup>

In the second study, we used the controls from NBDPS to constitute a retrospective cohort. We compared using a time-fixed to a time-varying approach when assessing the association between a time-varying exposure and a time-dependent outcome.<sup>6</sup> We found that decongestant use in the second and/or third trimester of pregnancy was not associated with a reduced risk of preterm delivery. When comparing a time-fixed to a time-varying approach, we noted that results from the time-fixed approach suggested downward bias in the hazard ratio when compared to the time-varying approaches. Our results were consistent with previous literature suggesting that the protective effect of decongestant use on preterm delivery noted in previous studies may be the result of incorrectly classifying exposure person-time.<sup>7</sup> However we did not observe the same large

protective effect in our time-fixed approach as was previously noted in BDS.<sup>8,9</sup>

In the third study, we examined the impact of differential recall of episodic, over-the-counter medications and amniotic bands syndrome (ABS).<sup>10,11</sup> Previous analyses indicated a slight increase in risk of ABS associated with use of NSAIDs in the periconceptional period. Using quantitative bias analyses, we explored various scenarios of misclassification.<sup>12-14</sup> We noted that specificity had a greater impact on the estimates than losses in sensitivity. Results from our bias analysis suggested that the previously observed association between ABS and NSAIDs may in fact be biased towards the null. However, the magnitude of the true effect depended on the extent and mechanism of misclassification, which we could not estimate from the available validation studies. Our study underlined the need for validation studies of medication use during pregnancy. In the absence of these studies, or the inability to conduct them, considering bias and/or simulation studies to outline combinations of scenarios and better inform conclusions on the effects of these medications on pregnancy outcomes.

In conclusion, certain commonly used medications during pregnancy may be associated with increased risk of adverse pregnancy outcomes. Exploring the impact of mechanisms of systematic bias and explicitly stating the assumptions of these analyses are crucial to bolster available evidence. Therapeutic treatment during pregnancy is complex, can be fraught and evidence on safety and teratogenicity is limited. There is an increasing need to improve evidence on the impact of medications on pregnancy and fetal outcomes.

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## APPENDIX 1

### Participation Status of Interviewed and non-Interviewed in the National Birth Defects Prevention Study (NBDPS), 1997–2011

	Interviewed (n = 44,089)		Non-interviewed (n = 25,817)	
	No.	%	No.	%
Interview complete, buccal cell collection pending	5,278	12.0	--	--
Interview complete, buccal cell collection complete	25,332	57.5	--	--
Interview complete, declined buccal cell collection	9,393	21.3	--	--
Interview partial, final status	1,689	3.8	--	--
Hard refusal to interview	--	--	6,373	24.7
Soft refusal to interview	--	--	4,382	17.0
Not able to locate for interview	--	--	6,720	26.0
Excluded from interview for social reasons (e.g., adoption, etc.)	--	--	2,665	10.3
Not Interviewed due to ascertainment after 24 months post-EDD	--	--	4,344	16.8
Interview complete, buccal cell collection not requested	2,275	5.2	--	--
Excluded from interview, twin/sibling/duplicate case	--	--	49	0.2
Excluded from interview, twin	--	--	93	0.4
Excluded from interview, sibling	--	--	325	1.3
Excluded from interview, duplicate case	--	--	79	0.3
Interview complete, buccal cell collection requested later	54	0.1	--	--
Interview complete, buccal cell collection completed later	45	0.1	--	--
Not stated/missing	23	0.1	787	3.1

*EDD = Estimated date of delivery*

## APPENDIX 2

Multidimensional bias analysis to assess the impact of nondifferential and differential misclassification of periconceptional exposure to NSAIDs<sup>a</sup> among Mothers of ABS<sup>b</sup> Cases, NBDPS<sup>c</sup>, 1997–2011

<b>ABS (n=179)</b>		<b>Controls (n=11,500)</b>								
	<b>Sensitivity</b>	0.30	0.30	0.30	0.40	0.40	0.40	0.50	0.50	0.50
	<b>Specificity</b>	0.80	0.90	1.00	0.80	0.90	1.00	0.80	0.90	1.00
<b>Sensitivity</b>	<b>Specificity</b>	<b>Bias-adjusted odds ratio (95% confidence intervals)</b>								
0.30	0.80	8.41	2.01	1.14	20.66	4.93	2.80	32.91	7.85	4.46
0.30	0.90	19.01	4.54	2.58	46.70	11.14	6.33	74.39	17.75	10.08
0.30	1.00	29.62	7.07	4.01	72.75	17.36	9.85	115.88	27.64	15.69
0.40	0.80	1.44	0.34	0.20	3.54	0.84	0.48	5.64	1.34	0.76
0.40	0.90	3.26	0.78	0.44	8.00	1.91	1.08	12.74	3.04	1.73
0.40	1.00	5.07	1.21	0.69	12.46	2.97	1.69	19.85	4.74	2.69
0.50	0.80	0.79	0.19	0.11	1.94	0.46	0.26	3.08	0.74	0.42
0.50	0.90	1.78	0.42	0.24	4.37	1.04	0.59	6.97	1.66	0.94
0.50	1.00	2.77	0.66	0.38	6.81	1.63	0.92	10.85	2.59	1.47

<sup>a</sup> Nonsteroidal anti-inflammatory drug, <sup>b</sup> Amniotic band syndrome, <sup>c</sup> National Birth Defects Prevention

Multidimensional bias analysis to assess the impact of nondifferential and differential misclassification of periconceptional exposure to NSAIDs<sup>a</sup> among Mothers of ABS<sup>b</sup> Cases, NBDPS<sup>c</sup>, 1997–2011

<b>ABS* (n=179)</b>		<b>Controls* (n=11,500)</b>								
	<b>Sensitivity</b>	0.60	0.60	0.60	0.70	0.70	0.70	0.80	0.80	0.80
	<b>Specificity</b>	0.80	0.90	1.00	0.80	0.90	1.00	0.80	0.90	1.00
<b>Sensitivity</b>	<b>Specificity</b>	<b>Bias-adjusted odds ratio (95% confidence intervals)</b>								
0.60	0.80	2.91	0.69	0.39	3.70	0.88	0.50	4.49	1.07	0.61
0.60	0.90	6.58	1.57	0.89	8.37	2.00	1.13	10.15	2.42	1.37
0.60	1.00	10.25	2.45	1.39	13.03	3.11	1.76	15.81	3.77	2.14
0.70	0.80	2.22	0.53	0.30	2.82	0.67	0.38	3.42	0.82	0.46
0.70	0.90	5.02	1.20	0.68	6.38	1.52	0.86	7.74	1.85	1.05
0.70	1.00	7.81	1.86	1.06	9.93	2.37	1.35	12.05	2.88	1.63
0.80	0.80	1.79	0.43	0.24	2.28	0.54	0.31	2.77	0.66	9.70
0.80	0.90	4.05	0.97	0.55	5.15	1.23	0.70	6.25	1.49	2.32
0.80	1.00	6.31	1.51	0.85	8.02	1.91	1.09	1.49	0.85	1.32

<sup>a</sup> Nonsteroidal anti-inflammatory drug, <sup>b</sup> Amniotic band syndrome, <sup>c</sup> National Birth Defects Prevention Study

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**CURRICULUM VITAE**

