An Evaluation of Competing Risks in Studies of Perinatal Mortality and Birth Defects

AN EVALUATION OF COMPETING RISKS IN STUDIES OF PERINATAL MORTALITY AND BIRTH DEFECTS

DOMINIQUE HEINKE

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ABSTRACT

Globally, each year over 4 million infants die during the perinatal period, which includes stillbirth and neonatal death, yet little investment has been made in research or preventative efforts. Birth defects are common among perinatal deaths: major birth defects are identified among 15 to 20% of stillbirths and 20% infant deaths. Due to the interconnections between perinatal outcomes, studies of both perinatal deaths and of risk factors for birth defects may be biased by the occurrence of competing events which may deplete the susceptible population at risk, alter the category of a death without changing the risk of mortality, or may lead to biased risk factor assessments when analyses are conducted among survivors. We therefore sought to evaluate the impact of competing risks in studies of perinatal mortality and birth defects. First, we described the timing and etiology of stillbirths and neonatal deaths in the US during 2014. Then we examined the risk of stillbirth among fetuses with major birth defects and evaluated the effect of termination for pregnancy as a competing risk on observed stillbirth risk estimates. Finally, we evaluated whether risk factor studies of birth defects are biased when conducted among live births only. We found that the risk of stillbirth and first day mortality were higher than late neonatal deaths at all gestational ages and that stillbirth and first day deaths share have a greater etiological overlap than first day deaths and later neonatal deaths. Fetuses with major birth defects were found to have high risks of stillbirth, and that termination of pregnancy may lead to underestimates of stillbirth risk by depleting the susceptible population at risk. Risk factor studies of birth defects conducted only among live births were not found to be

meaningfully biased in most situations, but studies of high mortality defects where the exposure is also very strongly associated with termination of pregnancy and stillbirth may lead to biased results. In studies of perinatal mortality and birth defects, competing risks may act to induce bias under certain circumstances.

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DEDICATED TO THE MEMORY OF KYLE R. GEISER AND TO MARGARET, RICHARD, AND CARLIE GEISER

FOR INSPIRING ME TO WORK TO PROVIDE ANSWERS
TO THOSE WHOSE TRAGEDIES ARE HIDDEN BEHIND WALLS OF SILENCE.

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"There is no heartbeat." With those four words everything stopped.
-Edie Edwards STILLBIRTH ON NOV. 4, 2012[36]

Introduction

For around four million families around the world each year, the hope and anticipation of expecting a child is shattered by death of their baby soon before or after birth, collectively called perinatal deaths. [1,2] These deaths carry significant emotional burdens and morbidity for families, who often feel isolated in their grief.[3] Beyond the individual burden of perinatal deaths, rates of these deaths act as sensitive markers of health system performance and combined represent significant sources of financial burdens to families, health systems, and society.[4] Despite the massive burden of perinatal deaths, governments and organizations at the global, national, and local levels have invested little in their investigation and prevention; for example, although perinatal deaths occur more than 10 times more frequently than sudden infant death syndrome (SIDS), research and public attention are notably less. [1,5,6] Thus, little is known about the causes of most perinatal deaths and progress in preventing such deaths has stalled.

Perinatal deaths are defined as the combination of stillbirths and neonatal deaths. Stillbirth, the death of a viable fetus in utero, is defined in most of the United States (US) as the death of a fetus of 20 weeks or more gestational age (or a weight at birth of 350g or more) before birth; approximately 23,000 US pregnancies end in stillbirth each year. [6] Although the rate of stillbirth in the US declined 8% from 2000 to 2006 (6.6 to 6.1 per 1,000 live births and fetal deaths) progress in preventing stillbirth has slowed, with no change in the rate of stillbirth from 2006 to 2012. [7] Infant deaths, defined as deaths within the first year of life, are divided into the neonatal period (within the first 28 days of life) and the post-neonatal period (after the first 28

days of life). Neonatal deaths are further subdivided into early neonatal deaths (<7 days of life) and late neonatal deaths (7 – 27 days of life). [8] Approximately 23,000 live born infants die before their first birthday in the US each year, of which over 15,000 die within a month of birth.[5] After a dramatic decline during the previous century, infant deaths plateaued in the early 2000s but have since begun to decrease, with data from 2014 showing a rate of 5.84 infant deaths per 1,000 live births. [9,10]

The risk of perinatal death is markedly increased by malformations that develop early in pregnancy that often impair fetal viability. [11,12] Birth defects are any abnormality of the structure or function of the body that originate during gestation; major defects are those with significant functional or cosmetic consequences. In the United States, major structural defects affect approximately three pregnancies for every 100 live births, thus approximately 90,000 cases are identified every year.[13] Major birth defects are identified among 20% of infant deaths and 15% to 20% of stillbirths, making them the leading cause of perinatal deaths. [5,14] For survivors and their families, birth defects often result in substantial medical and emotional burdens as well as important physical and/or intellectual disabilities. [15-17] Although some causes of major birth defects have been identified, the cause of 80% of cases remains unknown. [18]

Efforts to identify modifiable risk factors for birth defects, stillbirth, and neonatal death are complicated by the interconnected nature of perinatal outcomes, which act as competing risks that may bias results under certain circumstances. Competing events are those where the occurrence of one event precludes the occurrence of a subsequent event; a competing risk is

the probability of the occurrence of the competing event. [19] For example, in the context of perinatal mortality, stillbirth is a competing event for live birth and thus neonatal death, as fetuses who die in utero cannot also be live born and subsequently die after birth. In addition to naturally occurring events, medical interventions can act as competing risks in two primary ways: first, termination of pregnancy is a competing event for both stillbirth and live birth/neonatal death; second, medical initiated delivery of a fetus may compete with stillbirth by inducing a live birth. Although medical delivery may be appropriate management which reduces mortality in other cases it may simply "bring birth to the time of death" if the intervention simply changes the outcome category (e.g., moving a stillbirth to a live birth with a subsequent neonatal death) but not mortality. [20,21] Inconsistent categorization of deaths near the time of delivery as stillbirths or neonatal deaths adds further complication to this issue. [22,23]

Competing risks may bias studies of birth defects and perinatal mortality through several different mechanisms: first, by excluding cases with the outcome of interest from those which are observed; second, by removing the highest risk fetuses from the pool at risk ("depletion of succeptibles"); third, by inducing selection bias; and fourth, by shifting to use of etiologically heterogeneous categories in order to compensate for known competing risks. [24-28] As an example of the first and second mechanisms, termination of pregnancy for birth defects competes with stillbirth and live birth for fetuses with birth defects. [29] If birth defect cases are identified only among stillbirths and live births, the number of birth defect cases will be underestimated (mechanism 1), and since termination is generally chosen for the most severe defects at highest risk of mortality, perinatal mortality estimates among live births and

stillbirths will underestimate the "true" risk of mortality since the highest risk cases were removed from the population of fetuses at risk (mechanism 2). [27,30-34] Further, if the choice to terminate a fetus with a severe defect is affected by an exposure of interest and this relationship is analyzed only among live born infants, then selection bias may result (mechanism 3). [35] Finally, analyses combining multiple competing events into a single category, such as perinatal mortality, may combine outcomes with different primary causes, leading to unpredictable biases if an exposure is associated with one event (e.g., stillbirth) but not the other (e.g., neonatal death; mechanism 4). [25]

While these mechanisms have been previously noted by researchers, few studies have evaluated the impact of competing risks in perinatal mortality and birth defects epidemiology. Therefore, we sought to examine the occurrence and impact of competing risks in perinatal and birth defects epidemiology in the following three chapters:

> **Chapter 1.** *Timing and Etiology of Neonatal Death and Stillbirth: A study of 2014 United States Births*
>
> **Chapter 2.** *Risk of stillbirth among fetuses with non-syndromic major birth defects: A population-based study accounting for the influence of competing events*
>
> **Chapter 3.** *Evaluation of selection bias in risk factor studies of birth defects: Evidence from the National Birth Defects Prevention Study*

Understanding the potential for these biases, the magnitude and direction of any resulting bias, the conditions under which these biases are likely to occur, and methods to minimize bias are critical to advancing our understanding of risk factors and thus measures that can be taken to prevent these physically, emotionally, and financially devastating outcomes.

Chapter 1. Timing and etiology of neonatal deaths and stillbirths: a study of united states births in 2014

Dominique Heinke, Paige L Williams, Sonia Hernández-Díaz, Ruth Fretts, and Janet W Rich-Edwards

Abstract

Perinatal death and it's components, stillbirths and neonatal deaths, are important health outcomes. However, there is debate among researchers whether stillbirths and neonatal deaths are similar enough to be combined or should be examined separately. To better understand similarities and differences between these outcomes, we sought to compare mortality rates, risk factors, and cause of death for stillbirths and neonatal deaths by age at death within the United States (US). We evaluated US resident births in 2014 using fetal death and linked birth-infant death certificate data. Perinatal deaths were categorized as stillbirth, first-day (0 - 23 hours), first-week (days 1-6) and first-month (days 7– 27). We examined maternal, infant, and delivery characteristics, gestational timing, and cause of death by age at perinatal death categories. Day-by-day mortality was calculated for neonatal deaths overall and by gestational age at birth. The 38,522 perinatal deaths in 2014 included 60% stillbirths (n=22,994), 23% first-day (n=8,746), 8% first-week (n=2,912) and 8% first-month deaths (n=2,955). 60% of neonatal deaths occurred on the first day. Ninety-three percent of stillbirths and 84% of first-day deaths were attributed to pregnancy complications, disorders of fetal growth, and birth defects versus 42% of first-week, 32% of first-month deaths and 45% of all perinatal deaths combined. We found that most neonatal deaths occurred on the first day, regardless of gestation, and that their major causes of death were more similar to stillbirths than later neonatal deaths or perinatal deaths overall. Consequently, we suggest that first-day mortality be reported and analyzed separately from later neonatal deaths and that use of the composite perinatal death outcome be avoided in risk factor studies.

Introduction

Each year nearly 5 million infants are stillborn or die within a month of birth, yet few global or national research and policy initiatives target prevention of these deaths.[1,37] Recent calls to action have advocated for improved monitoring and research into the causes and risk factors for stillbirth and neonatal deaths. [1,2,37] Beyond acting as epidemiological outcomes, stillbirth and neonatal mortality rates are sensitive markers of health care system performance.[2] However, inconsistency in the reporting and occurrence of stillbirth versus very early infant deaths, which act as competing risks, impairs the ability to identify risk factors on both the individual and systematic level across the development spectrum. [2,38-42]

The time around delivery is one of peak mortality; thus, small shifts in categorization of deaths to one category or the other can lead to large differences in the rates of stillbirth and neonatal death, making meaningful comparisons across locations or over time periods challenging. [38,40,41,43,44] To address these issues, a focus on the composite metric of perinatal death (all stillbirths and neonatal deaths in the first week or first month of life combined) has been suggested. [40,41,45] By capturing all deaths before and after delivery, this measure avoids the inconsistency and possible bias of evaluating either stillbirth or neonatal death alone. However, to the extent that neonatal deaths and stillbirths differ in risk factors and etiology, the combined category of perinatal death may provide little utility as an epidemiologic or system performance metric. [25,46]

Cause of death is known to change with age within in the neonatal period, and the rapid shifts in mortality risk during the first week of life suggest that there may be rapid changes in the main causes of death during this period.[2,44,47] Previous studies have found that the primary causes of neonatal death in the first week differ from those after the first week. [2,47,48] The risk of mortality within a day of birth is substantially higher than any other postnatal day, but only several small studies in low and middle-income countries have evaluated cause of death for first day deaths separately from later neonatal deaths.[2,44,49] These studies found different primary causes of death on the first day than later deaths; to our knowledge, this has not been evaluated in high-income countries. [48,50,51] If the etiology of first-day deaths substantially differs from later neonatal deaths regardless of country income level, the use of the composite perinatal death outcome may need to be reconsidered as it would not meaningfully reflect the etiology of any perinatal deaths.

To investigate the prevalence, etiology, and characteristics of first day death and to help clarify the appropriateness of current definitions of perinatal mortality we sought to examine the relationship of age at death to neonatal mortality rates by maternal, pregnancy, and infant characteristics as well as cause-specific mortality and compare them to stillbirths overall and by gestational age in a recent cohort of births in the United States (US).

Methods

Data source

We used the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) public fetal death and period-linked birth-infant death files to create a

retrospective cohort of all births to US resident mothers in the 50 states and District of Columbia in 2014. Underlying cause of death was obtained from all infant death certificates and from fetal death certificates in states using the 2003 revision of the fetal death certificate and coded using the International Classification of Diseases, Tenth Revision (ICD-10). States using the revised fetal death certificate cover approximately 90% of stillbirths in the US.[52] Cause of death categories based on ICD-Perinatal Mortality (PM) categories are described and summarized in the supplemental materials and Supplemental Table 1.1.[53]

Data Analysis

We included all live births and stillbirths with a plausible gestational age at delivery of at least 20 weeks or, if gestational age was unknown, with a birth weight over 350 g.[54] To avoid a downward bias in gestational age-specific mortality estimates, we followed a published algorithm to identify implausible gestational age estimates and to select a plausible gestational age estimate when available.[55,56] Detailed methods and results of the cleaning and the imputation of missing or invalid gestational age are described in the supplemental materials. Exclusions based on gestational age were applied after first cleaning and imputing missing values. A flow chart describing the final study size is found in supplemental Figure 1.1.

We categorized neonatal deaths by age at death as follows: first-day (0 - 23 hours), first-week (postnatal days 1 - 6), and first-month (postnatal days 7 - 27). The timing of stillbirth relative to delivery was unavailable for a substantial portion of stillbirths (20%) and therefore unable to be incorporated in the analysis. We use “perinatal death” to refer to the combination of stillbirths

and infant deaths up to 28 days. One-year survivors were estimated by excluding all 2014 births who died in 2014 from the total live births.

We calculated cumulative incidence of stillbirth and death for each age at death category of the neonatal period; we follow the convention of referring to these measures as "rates" and note that the time period captured by each category. The denominator for calculating rate of stillbirths was the total number of live births and stillbirths, while for neonatal mortality the denominators were the number of live births surviving to the beginning of the age-at-death category, as described in the supplemental materials. The one-year survival rate was estimated using total births as the denominator. Although gestational age-specific stillbirth rates are most accurately captured using the number of fetuses alive at the beginning of a gestational age category as the denominator ("fetuses at risk"), such an approach is of debatable validity when extended to neonatal mortality. [57-59] Therefore, to facilitate comparisons between the rates of stillbirth and neonatal deaths, we calculated traditional rates based on the number of births during the relevant gestational period for all outcomes.

We summarized selected characteristics which have been previously associated with fetal or infant death and shown to be of high validity as recorded on birth and fetal death certificates.[60,61] We included the following characteristics: Maternal race and ethnicity, maternal age, birth order (including stillbirths), marital status, multiple gestation pregnancy, and method of delivery; payer and Apgar scores at 5 minutes were available only for live births. Small for gestational age was defined as birthweight below the 10th percentile of gestational

age and sex.[62] Statistical contrasts within a very large sample can lead to misleading inferences regarding statistically significant, but clinically trivial differences; therefore we elected to focus on descriptive patterns rather than hypothesis testing.[63,64] All analyses were performed using SAS Studio software Version 3.2 (SAS Institute, Cary NC).

Results

In the US 4,012,945 live births and stillbirths of at least 20 weeks gestational age occurred during 2014. There were 38,512 perinatal deaths, of which 62% (n=23,901) were stillbirths and 38% (n=14,611) were neonatal deaths (Supplemental Figure 1.1). The majority of neonatal deaths occurred on within a day of birth (60% n=8,746) while the remaining deaths occurred with equal frequency during the rest of the first week (20% n=2,912) and the rest of the first month (20% n=2,955). The rate of perinatal death was 9.8 per 1000 total births, which was composed of a neonatal death rate of 4.0 per 1000 live births and a stillbirth rate of 6.1 per 1000 total births. The rate of first-day, first-week, and first-month deaths were 2.2, 0.8, and 0.8 per 1000 live births, respectively (Figure 1.1a).

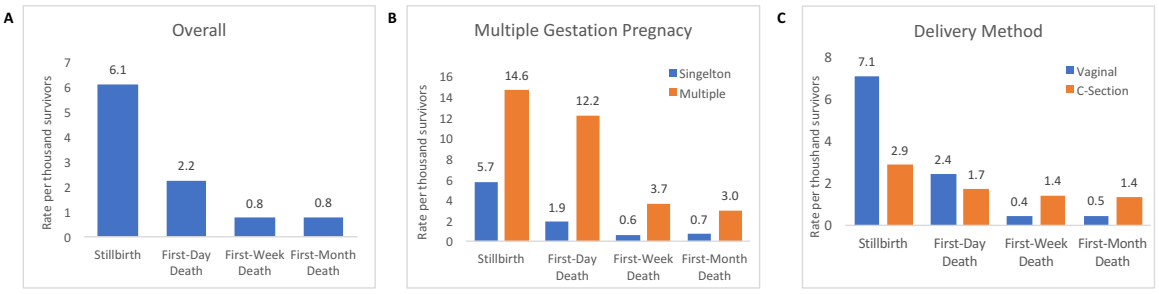


Figure 1.1. Rate of perinatal outcome overall and by multiple pregnancy or delivery method, 2014 United States resident births

The mortality rate by postnatal day during the first postnatal week was highest on the day of birth (22.3 per 10,000 live births) and dropped over 9-fold (2.4 per 10,000 first day survivors) on the second day (Supplemental Table 1.2). The daily mortality rate decreased less rapidly over the remaining first postnatal week. Stratifying by week of gestational age at delivery showed similarly steep declines in the mortality rate between the first and second day across all gestational ages; this occurred despite declines in the peak daily mortality rate with increasing gestational age (Figure 1.2; Supplemental Table 1.2).

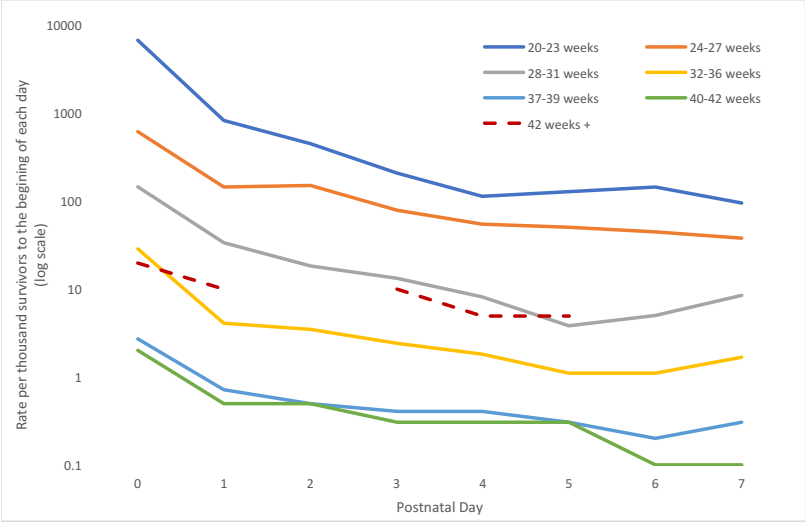


Figure 1.2. Daily mortality rate within the first week of life by category of gestational age at delivery, United States 2014

Mortality rates by age at death and rate of one-year survival by demographic, pregnancy, delivery, and infant characteristics are found in Table 1.1. Within these characteristics and within subgroups, the rate of stillbirth was highest followed by first-day death, then first-week and first-month death. Within each age at death category, the highest mortality rates were seen for mothers who were less than 20 years or older than 35 years, Non-Hispanic Black, who had two or more prior births, were unmarried, and whose payment source was Indian Health

Service, military health coverage, or self-pay, as opposed to Medicaid or private insurance (insurance data available for live births only).

The mortality rate at any age in the perinatal period was highest for infants in a multiple gestation pregnancy, born at lower gestational ages, and small for gestational age (Table 1.1). Unlike other characteristics in which sub-categories followed the overall mortality pattern (Figure 1.1a), multiple gestation births had an equivalent rate of stillbirth and first-day death (Figure 1.1b). Cesarean delivery demonstrated a less sharp decline in mortality rates with age at death than other examined characteristics (Figure 1.1c). First week and first-month mortality rates were approximately three times higher for cesarean births than vaginal births. In contrast, the rates of stillbirth and first-day death were approximately twice as high for vaginal births compared to cesarean births. Five-minute Apgar scores strongly correlated with first-day death: infants with low scores (0-3) had a 10-fold higher rate of first-day death than infants with scores of 7 or higher (Table 1.1). Little difference was seen in the rates of first-week and first-month mortality by Apgar score.

Table 1.1. Rate of perinatal outcome by maternal, infant, and delivery characteristics, 2014 United States resident births

	Perinatal Death				
	Stillbirth	**First-Day Death**	**First-Week Death**	**First-Month Death**	**Survived to One Year[b]**
	Rate per 1000 Total Births	Rate per 1000 Live Births	Rate per 1000 First Day Survivors	Rate per 1000 Seven Day Survivors	Rate per 1000 Total Births
	N = 23909	N = 8746	N = 2912	N = 2955	N = 3871776
Overall Rate	6.1	2.2	0.8	0.8	988.3
Mother's Age					
Under 20 years	7.2	2.8	0.9	1.1	984.6
20-24 years	6.1	2.3	0.7	0.9	987.4
25-29 years	5.5	2.1	0.7	0.7	989.2
30-34 years	5.6	2.0	0.7	0.6	989.8
35-39 years	6.9	2.3	0.8	0.8	988.1
Race Ethnicity					
White	5.3	1.8	0.7	0.6	990.4
Black	11.9	4.3	1.1	1.4	979.0
American Indian or AK Native	7.9	2.1	0.6	1.0	985.4
Asian or PI	5.1	1.5	0.5	0.5	991.1
Hispanic	5.2	2.0	0.7	0.7	989.7
More Than One Race[c]	--	2.1	0.9	1.6	978.5
Live Birth Order					
1 Prior Birth	3.4	2.5	0.8	0.8	990.9
2 Prior Births	3.0	1.8	0.6	0.7	995.2
3+ Prior Births	3.6	2.2	0.8	0.8	990.2
Insurance Type[c]					
Medicaid	--	2.4	0.8	1.0	993.1
Private Insurance	--	1.9	0.7	0.6	995.7
Other[d]	--	5.9	1.9	1.6	1987.0
Multiple Pregnancy					
Singelton	5.7	1.9	0.6	0.7	989.3
Multiple	14.6	12.2	3.7	3.0	962.2
Small for Gestational Age					
Not Small for Gestational Age	4.0	1.9	0.6	0.7	991.2
Small for Gestational Age	23.1	4.6	1.7	1.6	964.7
Gestational Age					
20-23 weeks	510.6	325.7	28.4	18.8	107.5
24-27 weeks	162.6	51.0	40.3	39.6	672.0
28-31 weeks	77.5	13.3	7.4	7.1	883.7
32-36 weeks	14.4	2.8	1.4	1.5	975.8
37-39 weeks	1.4	0.3	0.3	0.4	996.2
40-42 weeks	0.8	0.2	0.2	0.2	997.6
42 weeks +	5.9	2.0	2.9	1.0	987.3
Cessarian Delivery					
Vaginal	7.1	2.4	0.4	0.5	988.1
C-Section	2.9	1.7	1.4	1.4	990.0
Five Minute Apgar Score[c]					
7+	--	51.0	27.3	17.7	885.8
3 - 6	--	209.4	32.1	20.5	721.1
0 - 3	--	509.4	35.1	17.5	426.9

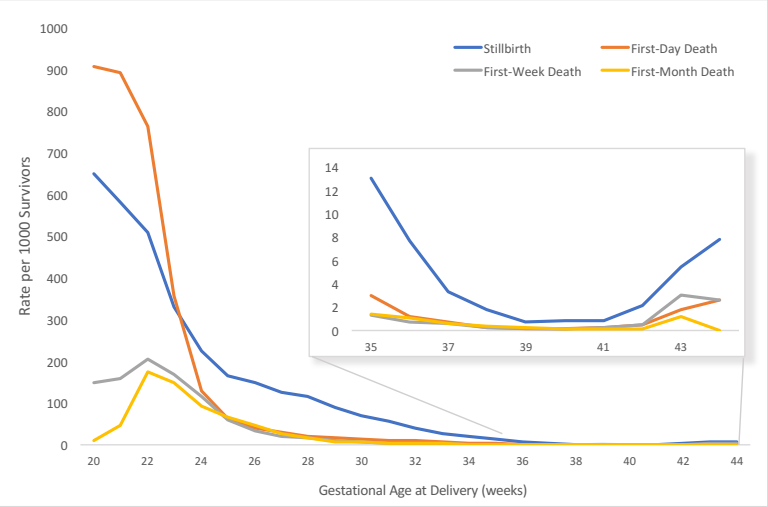
[a] Rate per 1000 survivors in group

[b] One year survival rates among all births at gestational age of 20 weeks or greater or 350g if gestational age was unknown

[c] Not available for stillbirths

[d] Includes Self pay, Indian Health Service, military health care, other government

The rate of each perinatal outcome varied by gestational age at birth (Figure 1.3). Stillbirth and first-day death showed a sharp decline with increasing gestation. First week and first-month death showed an initial increase between weeks 20 and 22 as more infants survived the first day and the first week, followed by a decline with increasing gestation age (Figure 1.3; Supplemental Table 1.2). The greatest rate of decline in mortality for all categories occurred between 22 and 24 weeks. From 24 weeks gestation onward, the stillbirth rate was higher than the neonatal mortality rate for all age groups.

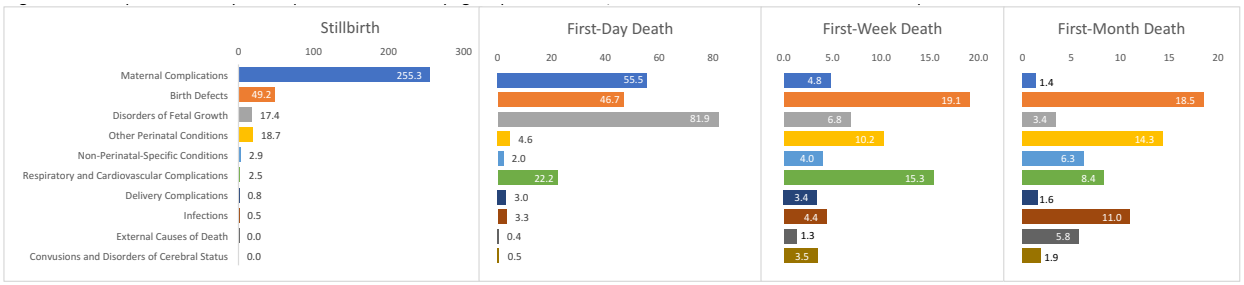


[a] Based on gestational age at delivery, among all infants delivered at that gestational age

Figure 1.3. Gestational age-specific rate of perinatal outcome, 2014 United States resident births

A specified underlying cause of death was available for 98% of neonatal deaths and 70% of stillbirths from states reporting cause of fetal death (Supplemental Table 1.3). The five most common causes of all perinatal deaths were, in descending order, maternal complications, birth defects, disorders of fetal growth, respiratory and cardiovascular complications, and other perinatal conditions (Supplemental Table 1.3). Underlying cause of death varied substantially by

age at death (Figure 1.4). As age at death increased, deaths were distributed among a greater number of cause of death categories: among infants with specified cause of death, 93% of stillbirths and 84% of first day deaths had a cause of death within three categories (maternal complications, disorders of fetal growth, and birth defects) versus 42% of first-week and 32% of first month deaths and 45% of overall perinatal deaths (Supplemental Table 1.3. Results for sub-categories of cause of death can be found in Supplemental Table 1.4.



[a] Rate per 100,000 survivors

[b] Data from areas of the US in which <50% of reported fetal deaths had an unspecified cause of death

[c] Excludes unspecified cause of death (P95, P96, R00-R94, R96-R99)

Figure 1.4. Cause-specific mortality rate of perinatal outcome[a] by age at perinatal death, 2014 United States resident births[b] with a specified cause of death[c]

Discussion

We observed substantial changes in the mortality rate and in cause-specific mortality with age at perinatal death, with the greatest rate of change occurring in the first two days of life. We found that the rate of neonatal mortality was highest the first day of life at all gestational ages, and dropped rapidly from the first to second day, consistent with prior reports across the globe.[44,49,50,65] Mothers of infants who were stillborn or died on the day of birth were similar to mothers of other infants dying in the perinatal period in terms of maternal race, age, and socioeconomic indicators, and these results are consistent with previous reports of risk factors for perinatal death in the US.[6]

We found that the timing of perinatal death varied with delivery method. This finding is likely the result of clinical contexts that require balancing of the benefits of cesarean delivery for the infant against the potential harms to the mother. When infants die before the onset of delivery or have a low probability of survival, such as infants born at a gestational age prior to viability, the balance favors vaginal delivery.[66] However, cesarean delivery may offer an immediate survival advantage for some preterm infants who may develop a fatal condition later in the neonatal period; thus our findings may reflect this as well.[67] Similarly, the equivalent rates of stillbirth and first-day death among multiple gestation births likely reflect a greater physician willingness to intervene to deliver multiples than singletons, thus shifting some multiples from stillbirths to first day deaths.[68] The patterns that we found in the rates of stillbirth and first-day death among infants by delivery method and pregnancy plurality are similar a previous report from a single US state.[41]

We observed that peak gestational age-specific mortality rates occurred before 25 weeks gestational age for all perinatal mortality groups. The inflection point near the line of viability (22-23 weeks) likely reflects both improved biological viability of neonates as well as the willingness to intervene to deliver fetuses at high risk of stillbirth and to perform life-saving interventions starting at this time.[66] The elevated rate of stillbirth compared to neonatal deaths after 24 weeks may reflect a delay between stillbirth and delivery thus gestational age at delivery may misclassify age at death by a week or more, but other factors may be involved. This delay may also overestimate the rate of small for gestational age among stillbirths when using gestational age at delivery, as we have done here.

We found that the major causes of stillbirth and first day death overlapped substantially but are

largely distinct from later neonatal deaths. Furthering previous reports, we found that there are substantial changes in the major causes of death within the early neonatal period. Most stillbirths with a specified cause of death and first-day neonatal deaths were directly due to conditions arising in pregnancy, such as maternal complications and prematurity. In contrast, with the exception of birth defects, the major causes of first-week and -month mortality were varied and more likely to be due to conditions that arise after delivery, such as postnatal infections and respiratory complications. Our results are generally consistent with previous findings based on global data showing that neonatal mortality within the first week is predominantly associated with prematurity and delivery complications while neonatal mortality after the first week is predominately associated with infection and that birth defects are an important cause of death in both periods. [2,47,65,69]

Although we found that the rates and proportions of cause specific mortality for stillbirths and first day deaths are not exactly aligned, most stillbirths and first day deaths were attributed to the same three cause of death categories. Differences in the relative ranking of these major causes may reflect true differences in etiology or differences in how cause of death is reported for stillbirths and first day deaths: a stillbirth following chorioamnionitis at 23 weeks gestational age may be attributed to this condition, but a first day death at the same gestational age may be attributed to prematurity, even though the premature delivery was initiated by chorioamnionitis. This differential reporting occurs despite recommendations within ICD-10 instructions not to attribute cause of death to prematurity unless it is the only fetal or infant condition known.[53] Although differential attribution of cause of death may also exist for later neonatal deaths, the predominance of “prematurity” as an underlying cause of death for first

day deaths suggests that the effect is greatest for this group.

Our findings bear striking similarities to those from developing countries, which found the leading causes of stillbirth to be maternal and placental conditions (e.g., hemorrhage, hypertension) and delivery complications; first day death to be delivery complications, prematurity, and birth defects; and later (first week and first month) deaths to be due to infections and birth defects.[48,50,51] However, the specific infections driving mortality reported in these studies (e.g., tetanus and sepsis) and the predominance of delivery complications as a cause of stillbirth and first-day death in low- and middle-income countries are important differences that reflect the developmental contexts of the studies.

An important implication of our results is that because etiology differs for first-day and later neonatal deaths, the interventions needed to prevent deaths at each time point differs. Yet, first day deaths are currently hidden among all neonatal deaths and within composite perinatal death outcomes leading the resulting analyses of risk factors and causes to be distorted by the combination of outcomes with rapidly changing etiologies. In contrast, the causes of first day deaths overlap substantially with stillbirth, and medical decisions can shift a death from one time period to the other. Yet, these deaths are often treated as different outcomes or combined with all neonatal deaths. This artificial split between stillbirths and first day deaths also hampers the ability to identify the interventions needed to prevent these deaths are likely shared, particularly among preterm births.

Therefore, we suggest that first-day mortality be reported separately from later neonatal mortality. In light of the substantial differences in etiology between stillbirth and later neonatal deaths found in different developmental contexts, we believe the combination of stillbirths and

all first week or first-month deaths as an outcome category is best avoided. When competing risks are a concern, such as when medical decisions on when and how to deliver a high-risk infant may determine whether it is stillborn or dies soon after birth, combining stillbirth and first day deaths may improve comparability by time and place for health system assessments while maintaining a more etiologically homogenous category than overall perinatal death for epidemiological research. However, further research with more detailed cause of death data is needed to confirm the etiological overlap of stillbirth and first-day death before use of a combined category can be suggested for etiological studies.

Strengths and Limitations

Our study has several important strengths. The use of vital statistics data provides a full accounting of all live births and neonatal deaths during the study period and is thus the study population in its entirety rather than a sample of the population. This eliminates selection bias and reflects real-world conditions, thus providing broad generalizability of the results. In addition, we took steps to improve validity and minimize bias, such as having the same inclusion criteria for stillbirths and live births, removing illogical values of gestational age, and replacing missing or illogical gestational age values with imputed values. Cause of death for stillbirths and neonatal deaths is reported by physicians.

Surprisingly, remarkable consistency has been found across countries in the proportion of neonatal deaths occurring on the first day regardless of country income level, neonatal mortality rate, and region.[44,47] Our findings on the causes of death by age at death show substantial similarities to findings from developing countries. Therefore, we expect our main results, that stillbirth and first-day deaths comprise the majority of perinatal deaths and that

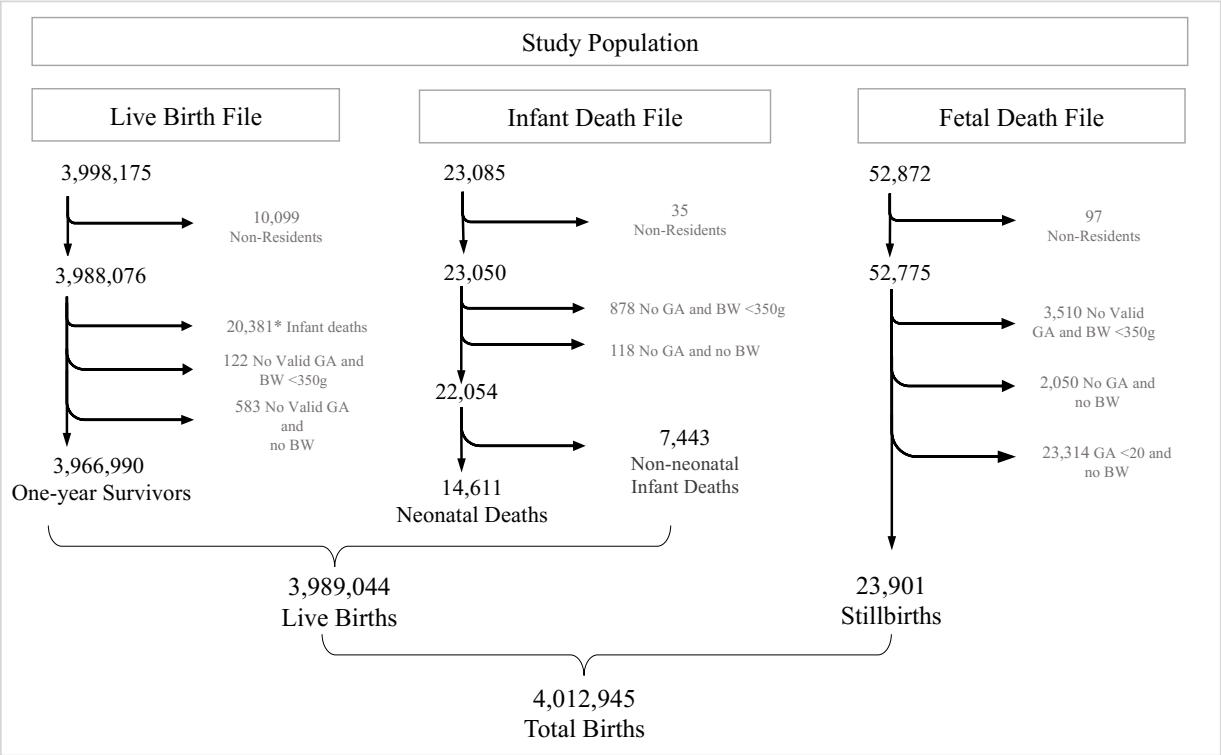
these groups share etiology distinct from later neonatal deaths, to generalize broadly.

There are also several important limitations to our study. Stillbirths are known to be underreported in vital statistics, in part because there is some classification overlap with early neonatal death as well as poor reporting at the margin of the definition of stillbirth.[23,40,41,70] The high degree of overlap in the major causes of death for stillbirth and first-day death suggests that there are common etiologies, regardless of any inconsistency in reporting. The major causes of stillbirth identified in our study are generally consistent with previous studies based on direct examination of stillbirths and medical records, suggesting that underreporting of stillbirths within vital records does not lead to substantial bias.[12,14]

An additional limitation of vital statistics data is incomplete reporting of risk factors and events during pregnancy.[60,61] We have attempted to leverage the strengths of vital statistics data by only using fields shown to have high validity. Although some possible covariates, such as maternal complications, are highly relevant to our question validation studies have found them to be substantially underreported on certificates. [60,61,71] Fortunately, we are able to capture some of the effects of these conditions through the analysis of cause of death data. [72] However, it should be noted that establishing cause of death, particularly for stillbirth is complicated and imprecise. Additionally, due to the large number of stillbirths with an unspecified cause of death and the preponderance of prematurity, a non-specific cause of death, among first day deaths further analysis using a data source with more detailed causal data is needed to determine whether stillbirth and first day death have sufficient etiological commonality to be analyzed as a combined category.

Conclusions

We found substantial changes in the mortality rate and cause-specific mortality with age at perinatal death. Among 2014 US births, we observed the highest mortality rates among stillbirths and first-day neonatal deaths, with mortality rates dropping dramatically after the first day of life. Stillbirth and first day deaths were found to share causes that were largely distinct from those found among later neonatal deaths, therefore use of a composite perinatal death outcome is discouraged. Combining stillbirth and first day deaths may improve comparability by time and place for system assessments while maintaining a more etiologically homogenous category than perinatal death for epidemiological research. However, further research is needed to directly address this question. We suggest that the number, rate, and causes of neonatal death on the day of birth be reported separately from other neonatal deaths when possible. Systematic reporting of first day deaths would bring focus to a period of high mortality that has long been hidden within current statistics.



***Infant deaths in 2014 that occurred among 2014 births; Infant deaths are included in the infant death file based on death occuring in 2014 but birth could have occurred in 2013**

Supplemental Figure 1.1. Construction of the study cohort. GA = gestational age; BW = birth weight.

Supplemental Table 1.1 ICD-10 codes used to create underlying cause of death categories.

Cause of Death	ICD 10 Codes	ICD PM Categories	Description
Maternal Complications	P00 - P03	M1-M4	Premature rupture of membranes, incompetent cervix, multiple pregnancy, maternal hypertensive disorders, maternal conditions unrelated to pregnancy, other maternal complications of pregnancy. Chorioamnionitis, placental complications, intrauterine or breast milk exposure to noxious substances, cord complications, other membrane abnormalities
Disorders of Fetal Growth	P05 - P08	A5, I6, N2	Slow fetal growth and malnutrition, short gestation and low birth weight, long gestation and high birth weight
Complications of Labor and Delivery	P10 - P15, P20 - P21	A3, I3, N4,I2, N3	Antepartum or intrauterine hypoxia, birth trauma
Convusions and Disorders of Cerebral Status	P90 - P91	N5	Convusions, neonatal coma, hypoxic ischemic encephalopathy, other disturbances of cerebral status
Respiratory and Cardiovascular Disorders	P22, P24 - P29	N7	Respiratory distress of newborn, neonatal aspiration syndromes, interstitial emphysema and related conditions, pulmonary hemorrhage, chronic respiratory disease, atelectasis, all other respiratory conditions originating in the perinatal period. Cardiac failure, congestive heart failure, and all other disorders of the cardiovascular system (excluding heart defects).
Infection	P23, P35 - P39, A50, G00 - G03, G04 - G09	A2, I4, N6	Bacterial sepsis of newborn, omphalitis of newborn, congenital pneumonia, all other infections specific to the perinatal period, neonatal teatnus
Birth Defects	Q00 - Q99	A1, I1, N1	Structural birth defects, chromosomal birth defects
Other Perinatal Conditions	P50 - P61, P70 - P78, P80 - P83, P92 - P94	A4, I5, N8	Necrotizing entercolitis, non-immune hydrops fetalis, fetal blood loss, intracranial hemmorage and other conditions specific to the perinatal period
Fetal or Neonatal Death of Unspecified Cause	P95, P96, R00-R94, R96-R99	A6, I7, N10, N11	Unspecified or ill defined cause of fetal or neonatal death
Non-Perinatal-Specific Conditions	A00-A41, A81-A98 B00, B02-B04, B06-B19, B25, B27-34 D00-D48, C00-C80, C88, C90-C97, D50-D76, E00-E88 F01-F99, G00, G03-G04, G06-G11, G12.1-G12.9, G20-G72, G80-G93.9, G95-G98 H00-H57, I00-I28, I30-I31, I33-I38, I40, I42, I44- I51, I60-I99 J22, J30-J39, J43-J44, J47-J68, J70-J98, K00-K38, K40-K46, K50-K92 L00-M99, N00-N15, N17-N23, N25-N95, R00-R53, R55-R94, R96-R99	*	Infectious and parasitic diseases, neoplasms, anemias, hemorrhagic conditions, nutritional deficiencies, endocrine nutritional and metabolic diseases, diseases of the nervous system, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, diseases of the genitourinary system
External Causes of Death	R95, W00-W34, W35-W64, W75, W76-W99, Y00-Y09, Y10-Y36, Y40-Y84, X10-X39, X50-X59, X60-X85-X90-X92, X96-X99, *U01.0-*U01.3,*U01.5-*U01.9	*	Sudden infant death syndrome, accidental death, homicide, neglect abandonment and maltreatment syndromes, complications of medical and surgical care, all other external causes

[a] International Classification of Diseases, Tenth Revision

* Miscelaneous in ICD-PM

Supplemental Table 1.2. Daily mortality rate per 10,000 live birth survivors within the first week of life by gestational age at delivery, 2014 US resident births

	Postnatal Day							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Overall	2.23	0.24	0.18	0.11	0.09	0.07	0.06	0.07
Gestational Age (weeks)								
20	9063.0	1393.4	0.0	95.2	0.0	0.0	0.0	0.0
21	8930.5	1530.1	0.0	64.5	0.0	0.0	0.0	0.0
22	7633.3	1026.2	650.2	215.8	98.0	123.8	100.3	126.6
23	3570.0	649.8	468.9	225.3	133.4	147.5	174.7	101.6
24	1298.4	324.9	361.9	182.7	120.6	118.6	109.4	74.9
25	645.4	156.7	169.4	96.6	73.8	66.4	53.5	43.0
26	408.4	96.4	95.0	50.3	25.3	39.1	25.4	30.1
27	289.0	70.6	51.9	32.8	25.2	11.7	19.4	19.5
28	205.7	61.9	42.6	23.0	11.5	5.0	14.9	21.5
29	150.9	34.5	27.7	12.5	13.9	5.6	2.8	11.1
30	135.8	27.8	11.1	13.4	5.6	2.2	6.7	3.4
31	115.0	21.2	6.5	8.2	4.9	3.3	0.0	4.1
32	92.7	13.7	9.3	5.5	1.6	4.4	1.1	6.0
33	57.7	8.9	6.7	5.6	4.1	1.9	3.3	3.7
34	35.6	5.3	6.3	1.4	2.0	1.2	1.8	1.6
35	29.9	4.0	2.5	2.0	2.3	0.8	1.1	1.5
36	12.1	1.7	1.7	1.9	1.1	0.7	0.5	1.0
37	6.9	1.7	1.2	0.8	0.8	0.7	0.6	0.6
38	2.8	0.8	0.6	0.4	0.5	0.4	0.2	0.3
39	1.6	0.4	0.3	0.3	0.3	0.2	0.2	0.3
40	1.6	0.4	0.4	0.3	0.3	0.2	0.1	0.1
41	2.7	0.5	0.6	0.5	0.3	0.3	0.1	0.0
42	5.2	1.0	1.0	0.3	1.0	1.4	0.0	0.0
43	18.1	6.1	0.0	12.1	6.1	6.1	0.0	0.0
44	26.1	26.2	0.0	0.0	0.0	0.0	0.0	0.0

Supplemental Table 1.3. Proportion of cause of death among stillbirths and neonatal deaths by age at death, and all perinatal deaths combined, among infants with a specified cause of death[a], 2014 US resident births

	Stillbirth[b]		First-Day Death		First-Week Death		First-Month Death		Perinatal Death	
	N	%	N	%	N	%	N	%	N	%
	N = 21022		N = 8740		N = 2902		N = 2950		N = 35614	
Cause of Death										
Maternal Complications	10194	73.8	2195	25.4	190	6.7	58	2.0	12637	44.9
Birth Defects	1938	14.0	1829	21.2	746	26.2	723	24.3	5236	18.6
Disorders of Fetal Growth	687	5.0	3208	37.1	267	9.4	132	4.4	4294	15.3
Other Perinatal Conditions	738	5.3	179	2.1	399	14.0	560	18.8	1876	6.7
Non-Perinatal-Specific Conditions	113	0.8	80	0.9	156	5.5	244	8.2	593	2.1
Delivery Complications	32	0.2	118	1.4	133	4.7	62	2.1	345	1.2
Infections	18	0.1	128	1.5	172	6.0	430	14.4	748	2.7
Respiratory and Cardiovascular Complications	97	0.7	871	10.1	599	21.0	326	11.0	1893	6.7
Convulsions and Disorders of Cerebral Status	0	0.0	21	0.2	136	4.8	74	2.5	231	0.8
External Causes of Death	1	0.0	14	0.2	51	1.8	225	7.6	291	1.0
Unspecified Fetal or Neonatal Death	7204	52.1	97	1.1	53	1.9	116	2.7	7470	26.5

[a] Among infants with a specified cause of death (Stillbirth n=13818; First-Day Death n=8643; First-Week Death n=2849; First-Month Death n=2834)

[b] Cause of death for stillbirths are limited to stillbirths in areas of the US using the 2003 revision of the fetal death certificate, approximately 90% of all US stillbirths in 2014

[c] Perinatal Death defined as stillbirths and all neonatal deaths combined

Supplemental Table 1.4 Number and rate[a] of detailed cause of death by age at perinatal death, 2014 US resident births[b]

		Perinatal Outcome							
		Stillbirth		First Day Death		First Week Death		First Month Death	
Cause of Death	ICD-10 Codes	N	Rate	N	Rate	N	Rate	N	Rate
Maternal Conditions									
Maternal Hypertensive Disorders	P00.0	778	19.7	54	1.4	8	0.2	2	0.1
Other Maternal Medical or Surgical Conditions	P00.1 - P00.9	625	15.9	55	1.4	19	0.5	4	0.1
Incopentent Cervix	P01.0	456	11.6	393	10	7	0.2	1	0
Premature Rupture of Membranes	P01.1	1687	42.8	632	16.1	32	0.8	5	0.1
Multiple Pregnancy	P01.5	411	10.4	94	2.4	10	0.3	6	0.2
Maternal Death	P01.6	14	0.4	4	0.1	2	0.1	1	0
Malpresentation Before Labor	P01.7	4	0.1	8	0.2	1	0	0	0
Other Maternal Complication of Pregnancy	P01.2 - P01.4, P01.8 - P01.9	309	7.8	124	3.2	13	0.3	1	0
Placenta Previa	P02.0	23	0.6	10	0.3	0	0	0	0
Placental Separation and Hemorrhage	P02.1	1620	41.1	277	7.1	33	0.8	17	0.4
Morphologic and Functional Abnormalities of Placenta	P02.2	1255	31.9	12	0.3	4	0.1	1	0
Placental Transfusion Syndromes	P02.3	119	3	35	0.9	13	0.3	4	0.1
Prolapsed Cord	P02.4	152	3.9	16	0.4	5	0.1	1	0
Compression of Umbilical Cord	P02.5	1133	28.8	8	0.2	1	0	1	0
Other Umbilical Cord Conditions	P02.6	594	15.1	7	0.2	1	0	1	0
Chorioamnionitis	P02.7	686	17.4	359	9.2	25	0.6	9	0.2
Other Membrane Abnormalities	P02.8 - P02.9	15	0.4	0	0	0	0	0	0
Malpresentation	P03.0 - P03.1	16	0.4	10	0.3	3	0.1	0	0
Complications of C-Section	P03.4	0	0	0	0	1	0	0	0
Other Delivery Complications	P03.2 - P03.9	160	4.1	74	1.9	8	0.2	2	0.1
Noxious Substances	P04	137	3.5	23	0.6	4	0.1	2	0.1
Disorders of Fetal Growth									
Small for Gestational Age	P05	121	3.1	46	1.2	30	0.8	23	0.6
Prematurity	P07	562	14.3	3162	80.7	236	6.1	109	2.8
Large for Gestatonal Age / Post Term	P08	4	0.1	0	0	1	0	0	0
Delivery Complications									
Birth Trauma	P10 - P15	2	0.1	1	0	6	0.2	4	0.1
Intrauterine Hypoxia	P20	30	0.8	45	1.1	70	1.8	30	0.8
Birth Asphyxia	P21	0	0	72	1.8	57	1.5	28	0.7
Convulsions and Disorders of Cerebral Status									
Convulsions and Other Disorders of Cerebral Status	P90 - P91	0	0	21	0.5	136	3.5	74	1.9
Respiratory and Cardiovascular Conditions									
Respiratory Distress of Newborn	P22	3	0.1	141	3.6	191	4.9	114	2.9
Primary atelectasis	P28.0 - P28.1	2	0.1	146	3.7	47	1.2	16	0.4
Other Respiratory Conditions	P28.9	13	0.3	94	2.4	179	4.6	81	2.1
Cardiovascular Complications	P29.0	79	2	490	12.5	182	4.7	115	3
Infections									
Viral Infections	A50	9	0.2	7	0.2	17	0.4	52	1.3
Other Perinatal Infections	P35, P37 - P39	6	0.2	27	0.7	6	0.2	27	0.7
Meningitis	G00 - G03	0	0	0	0	1	0	13	0.3
Congenital Pneumonia	P23	2	0.1	4	0.1	10	0.3	37	1
Bacterial Sepsis	P36	1	0	90	2.3	138	3.5	299	7.7
Encephelitis	G04 - G09	0	0	0	0	0	0	2	0.1
Other Perinatal Conditions									
Fetal Blood Loss	P50	17	0.4	6	0.2	7	0.2	0	0
Intracranial Hemorrhage	P52	9	0.2	17	0.4	229	5.9	101	2.6
Other Hemorrhage	P51, P53 - P54	3	0.1	14	0.4	31	0.8	19	0.5
Hemolytic Conditions	P55-P56	14	0.4	2	0.1	5	0.1	0	0
Necrotizing Entercolitis	P77	0	0	3	0.1	18	0.5	320	8.2
Hydrops Fetalis (not due to hemolytic disorders)	P83.2	230	5.8	100	2.6	43	1.1	25	0.6
Other Perinatal Conditions (Remainder)	P80 - P83.1, P83.3 - P94, P96	465	11.8	37	0.9	66	1.7	95	2.4
Birth Defects									
Neurological Defects	Q00 - Q07	355	9	336	8.6	127	3.3	86	2.2
Heart Defects	Q20 - Q28	211	5.4	142	3.6	178	4.6	264	6.8
Respiratory Defects	Q30 - Q34	16	0.4	183	4.7	52	1.3	38	1
Digestive Defects	Q35 - Q45	16	0.4	5	0.1	11	0.3	8	0.2
Renal and Urinary Defects	Q60 - Q64	126	3.2	342	8.7	86	2.2	20	0.5
Musculoskeletal Defects	Q65 - Q85	212	5.4	215	5.5	68	1.7	98	2.5
Chromosomal Defects	Q90 - Q99	707	17.9	309	7.9	162	4.2	163	4.2
Other Birth Defects	Q10 - Q18, Q50 - Q56, Q86 - Q89	295	7.5	297	7.6	62	1.6	46	1.2
Unspecified									
Unspecified COD	P95, P96, R00-R94, R96-R99	7204	182.9	97	2.5	53	1.4	116	3
Non-Perinatal Specific									
Non-Perinatal Specific	A, B, C, D, E, G, H, K, L-N U04[c]	113	2.9	80	2	156	4	244	6.3
External									
SIDS	R95, W75	0	0	1	0	38	1	198	5.1
Accidents	V01-X59	1	0	4	0.1	7	0.2	11	0.3
Complications of Medical or Surgical Care	Y40 - Y84	0	0	1	0	3	0.1	2	0.1
Homicide	*U01, X85 - Y09	0	0	8	0.2	3	0.1	14	0.4

[a] Rate per 100,000 survivors in group

[b] Cause of death for stillbirths are limited to stillbirths from 2014 US Fetal Deaths in areas of the US using the 2003 revision of the fetal death certificate

[c] Codes A50, G00 - G03, and G04 - G09 are included in Infections

Chapter 2. Risk of stillbirth among fetuses with non-syndromic major birth defects: a population-based study incorporating estimates of the impact of competing events

Dominique Heinke, Erini Nestoridi, Sonia Hernandez-Diaz, Paige L Williams, Janet W Rich-Edwards, Angela E Lin, Carla M Van Bennekom, Allen A Mitchel, Wendy N Nembhard, Ruth Fretts, Suzan L Carmichael, Drucilla J Roberts, Charles W Duke, and Mahsa M Yazdy

Abstract

The risk of stillbirths in the US population is 0.6%. We sought to estimate the risk of stillbirth among cases of non-syndromic major birth defects and to quantify the impact of elective termination and first day neonatal death on estimates. We included major birth defect cases in the National Birth Defects Prevention Study identified through active population-based surveillance programs in nine US states between 1997 and 2011. Birth defects were confirmed and classified by clinical geneticists after medical records review. Estimates excluded defects unreliably ascertained in stillbirths (e.g., heart defects). We calculated the observed risk of stillbirth, termination-corrected minimum (terminations assumed live born) and maximum (terminations assumed stillborn) risk, and risk of combined mortality (termination, stillbirth, and first-day neonatal death) among cases of specific birth defects surviving ≥ 20 weeks GA overall and stratified by defect pattern. Among 19,718 cases, 843 were stillborn, 698 electively terminated, and 18,186 live born. Observed stillbirth risk ranged from 1.2% for cerebellar hypoplasia to 49.2% for limb-body-wall complex. The difference in minimum and maximum termination-corrected risk estimates ranged from 0.2 percentage points for cleft lip without cleft palate (range: 1.3 – 1.5%) to 35.1 percentage points for limb-body-wall complex (range: 31.9 – 67.0%). Isolated cases had lower risks of stillbirth and combined mortality than multiple defect cases. Stillbirth comprised half or more of the combined mortality for isolated cases of most birth defects. Fetuses with major non-syndromic birth defects have an increased risk of stillbirth which varies by specific defect and is further increased for multiple defect cases. Estimates may aid counseling after prenatal diagnosis; estimates which incorporate competing events can improve counseling and comparisons across studies.

Introduction

Major structural birth defects are common, occurring in one pregnancy for every 33 live births, and are well recognized as a major cause of infant mortality.[5,73] Although major birth defects are identified among fifteen to 20% of stillborn infants, the risk of stillbirth among fetuses with major birth defects has not received the same policy and research attention as the risk of infant mortality.[1,12] Consequently, little is known about the risk of stillbirth among infants with specific birth defects, yet they are needed to provide evidence-based counseling to families with prenatally-diagnosed birth defects and identify opportunities for prevention of stillbirth.[72,74]

Such data are lacking in part due to the substantial challenges of identifying a large representative sample of infants and fetuses with well-characterized defects, many of which are relatively rare, occurring at a rate of fewer than 5 cases per 10,000 live births. [13,73,75] Thus, nearly all published prevalence estimates for stillbirth among infants with specific birth defects are based on small samples of infants identified from a single center or hospital network, yielding unstable estimates with limited generalizability.[76-78] Further, limited sample sizes often preclude estimating the risk of stillbirth for important subgroups, such known genetic or chromosomal origins, specific phenotypes within a defect class, or multiple birth defects.[79]

Estimates of stillbirth risk are further complicated by competing events, which alter the pool of fetuses at risk. Termination of pregnancy for birth defects is more common for fetuses with more severe birth defects and multiple birth defects, and thus may selectively removes cases at

high risk of stillbirth from the population of fetuses at risk. [27,30,80,81] Additionally, variation in the categorization of perinatal deaths as stillbirths or neonatal deaths (e.g., through selective medical delivery of high risk fetuses to avert stillbirth resulting in death soon after delivery) may also act as competing events and thus bias stillbirth risk estimates. [20,21]

All studies, including the few larger population-based studies published, have excluded terminated cases from analyses and no study has accounted for inconsistency in classification of stillbirth versus early neonatal deaths, both of which may have biased stillbirth risk estimates. [22,79,80]

We conducted a population-based cohort study to estimate the risk of stillbirth among infants with selected specific, non-syndromic birth defects using cases from the National Birth Defects Prevention Study. We expand upon previous population-based analyses by estimating the maximum and minimum termination-corrected risk of stillbirth, including estimates for infants with multiple birth defects, and calculating the combined prenatal and immediate neonatal mortality from 20 weeks of gestation through the first day of life.

Methods

Study Population

The National Birth Defects Prevention Study (NBDPS) is a large, population-based collaborative multi-state case-control study of 33 specific major birth defects in the United States (US) from 1997 to 2011.[13] Briefly, birth defect cases were identified using active surveillance systems in all or part of 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah). Each site abstracted and reviewed medical records for all

identified potentially eligible birth defect cases in their respective catchments. Sites reviewed medical records of all identified stillborn infants for evidence of birth defects. Abstracted medical records of all identified birth defect cases were reviewed by physicians with specialist training in birth defects (clinical geneticists) at each site to confirm every reported birth defect diagnosis. Pre-defined information from the abstracted medical records was included in the NBDPS clinical database. Institutional Review Board approval was obtained by all study sites.

Eligibility

Birth defect cases with a known or strongly suspected single gene or chromosomal disorders ("syndromic cases") were ineligible for the NBDPS; genetic studies were not required for eligibility. Cases with a pregnancy outcome of live birth, termination, or stillbirth (fetal death at ≥20 weeks gestational age at delivery or a birth weight of ≥500g), were eligible for inclusion in the study; spontaneous losses <20 weeks gestational age were ineligible. We included all cases in the clinical database meeting our study criteria regardless of gestational age.

Defect Classification

All cases in the NBDPS clinical database were further reviewed by study clinical geneticists who evaluated whether each NBDPS-eligible birth defect case met standard study criteria for inclusion in birth defect-specific etiologic analyses and classified each by birth defect pattern (isolated, multiple, sequence, complex) according to a standard algorithm which has been described in detail.[82] For our analyses, we considered fetuses with a classification other than isolated to have multiple birth defects, and we further categorized the latter according to the most severe defect present. Severity categories (moderate, serious, or severe) were based on both the average risk of mortality among

infants with a particular defect and the degree of disability or long-term care necessary for survivors, similar to previously-published severity scales (Table 2.1); assignment was independent of an individual infant's clinical course. [32] In the assignment of severity, all major birth defects were considered, whether or not a defect was among those classified as NBDPS eligible (supplemental materials).

Table 2.1. Severity categorization of birth defects

Severity Category	Description	Defects
Severe	Fatal, supportive measures only	Anencephaly, bilateral renal agenesis, limb-body-wall complex, hydranencephaly, vein of Galen malformation, tracheal atresia, agyria
Serious	May be correctable, most infants have long-term needs	Amniotic band syndrome, aniridia, anophthalmia, anotia, arthrogryposis, biliary atresia, bladder extrophy, cloacal extrophy, double outlet right ventricle, ectopia cordis, encephalocele, heterotaxia with congenital heart defect, holoprosencephaly, hypoplastic left heart syndrome, limb reductions (moderate-severe), lisencephaly, sacral agenesis, single ventricle, spina bifida
Moderate	Most correctable, many infants have long-term needs	Aortic valve stenosis, atrial septal defect, atrioventricular canal, choanal atresia, cleft lip and/or palate, coarctation of the aorta, cataract, glaucoma/anterior chamber defects, clubfoot, coloboma, craniosynostosis, Dandy-Walker malformation, diaphragmatic hernia, esophageal atresia, Ebstein anomaly, gastroschisis, obstructive genitourinary defects, Hirschsprung, hydrocephalus, hypospadias (second, third degree), intestinal atresia, imperforate anus/stenosis, interrupted aortic arch, limb reduction (mild – moderate), intestinal malrotation, microcephaly, microtia, omphalocele, pulmonary sequestration, pulmonary atresia/stenosis, tethered spinal cord, tetralogy of Fallot, total/partial anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia/stenosis, truncus arteriosus, ventricular septal defect

Analyses

Construction of the analytic cohort is described in Figure 2.1. We excluded cases with an unknown pregnancy outcome, a gestational age that could not reliably be determined to be above or below 20 weeks, gestational age below 20 weeks, and from study sites that only included live births (New Jersey, New York before 2000). [13] Gestational age was obtained from medical or vital records and reviewed for consistency with birth weight and/or pregnancy outcome (supplemental materials). Infants and fetuses with multiple birth defects were

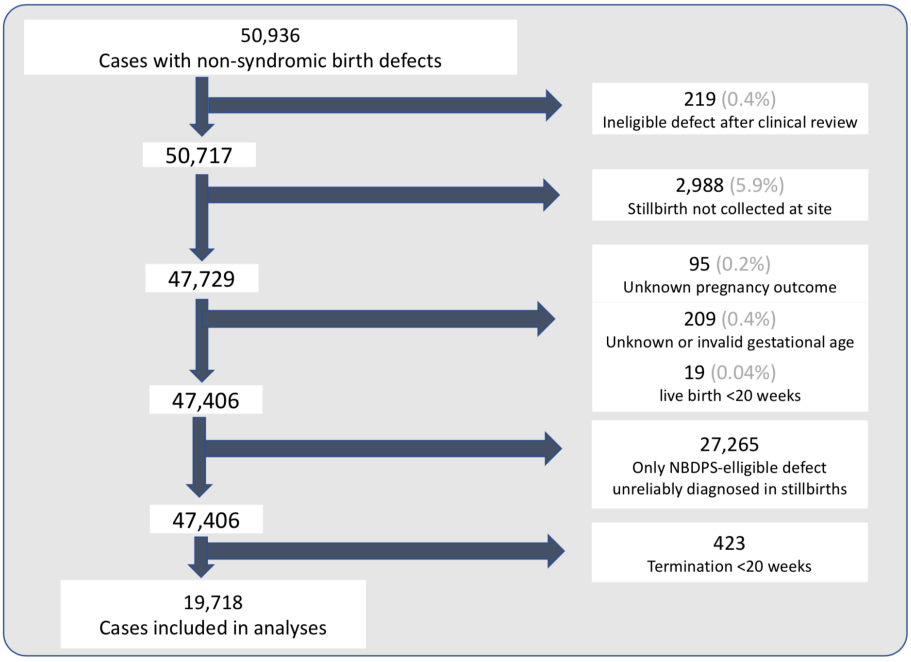


Figure 2.1. Construction of the study cohort.

included in the analysis of each eligible birth defect. We restricted our analyses to those NBDPS-eligible birth defects reliably identified by prenatal ultrasound or external physical examination; estimates were not calculated for defects that may only be identified or confirmed by autopsy (heart defects), are most often diagnosed based on postnatal signs/symptoms (biliary atresia, craniosynostosis), or may be difficult to observe in small or macerated fetuses (hypospadias, glaucoma, cataracts, anophthalmia/microphthalmia, anotia/microtia, choanal atresia). [83-85] Cases whose only NBDPS-eligible defect was among those were thus excluded from analyses; those who also had an additional NBDPS-eligible defect were included in the analysis of that specific defect. Risks were calculated when there were at least 10 cases with a specific birth defect in the category of interest.

Observed stillbirth risk

For the purposes of this analysis we considered the birth defect case population to be a cohort of fetuses with birth defects at risk of stillbirth (gestational age at birth of ≥20 weeks or birthweight ≥500g; see Figure 2.2). We calculated the observed risk of stillbirth for each defect as the number of stillbirths divided by the total number of live births and stillbirths, which we report as a percent. We then calculated estimates after stratifying by isolated vs multiple birth defects; multiple defect cases were further stratified by severity.

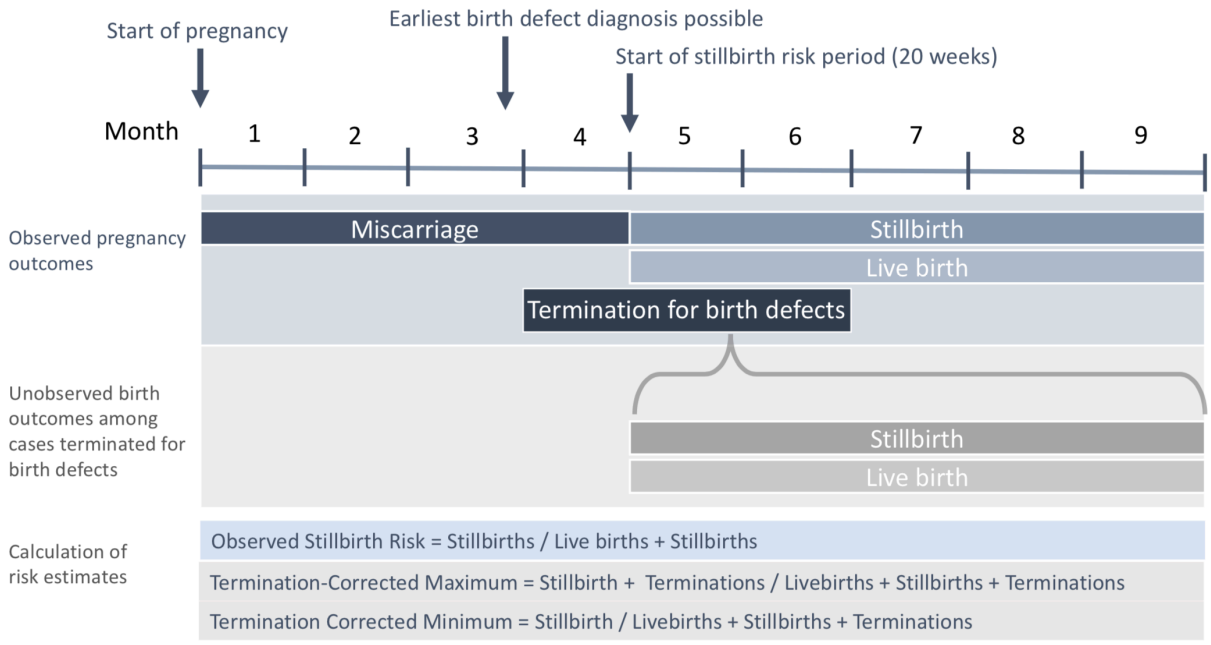


Figure 2.2. Observed and unobserved pregnancy outcomes among birth defect cases and their relation to calculated risk estimates

Termination-corrected stillbirth risk

We evaluated the possible bias introduced by termination of birth defect cases by estimating the minimum and maximum risk of stillbirth given our observed data. We used two extreme hypothetical situations to represent the risk of stillbirth had no terminations occurred: First, to

estimate the minimum stillbirth risk, we assumed all terminated cases would have survived to live birth. Thus, the minimum termination-corrected risk was calculated as the number of stillborn cases divided by the total number of cases (live born, stillborn, terminated. Second, to estimate the maximum termination-corrected risk, we assumed all terminated cases would have resulted in stillbirth. Thus, the maximum termination-corrected risk was calculated as the number of stillborn cases plus all terminated cases, divided by total number of cases (live born, stillborn, terminated). Both estimates are reported as percentages.

Combined prenatal and first day neonatal mortality

To account for both possible forms of competing risks (termination and misclassification of neonatal deaths) we estimated the combined mortality occurring during pregnancy or on the day of birth (termination, stillbirth, neonatal death <1 day) as a proportion of the total case population with a specific birth defect. We restricted to first day neonatal deaths because the risk of miss-categorization is highest for deaths occurring very soon after birth. Because time of birth and death were not available, we considered an infant to have died on the day of birth if the date of birth and date of death were the same. Estimates were also stratified by type of mortality in order to evaluate the relative contribution of each type of mortality. All analyses were conducted using SAS version 9.3 (SAS, Cary, NC).

Results

Of the 19,718 cases meeting our study criteria, 4.3% were stillborn (n=843) and 3.5% (n=689) underwent termination for birth defects. Among the live births, 1.7% (n=307) infants died on the day of birth. Most fetuses and infants (77.8%, n=15,667) had an isolated birth defect.

Among fetuses and infants with multiple major birth defects (n=4473), 58.1% had the most severe defect classified as moderate, 35.3% as serious, and 6.7% as severe.

Observed stillbirth risk

The observed risk of stillbirth by defect is shown in Figure 2.3 (Supplemental Table 2.1). The risk ranged from 1.2% among fetuses with cerebellar hypoplasia to 49.2% among fetuses with limb-body-wall complex. The highest prevalence estimates were among fetuses with severe defects considered to be universally fatal: limb-body-wall complex, anencephaly, and bilateral renal agenesis. With few exceptions, fetuses with isolated birth defects had a lower observed risk of stillbirth than fetuses with multiple birth defects (Figure 2.4, Supplemental Table 2.2).

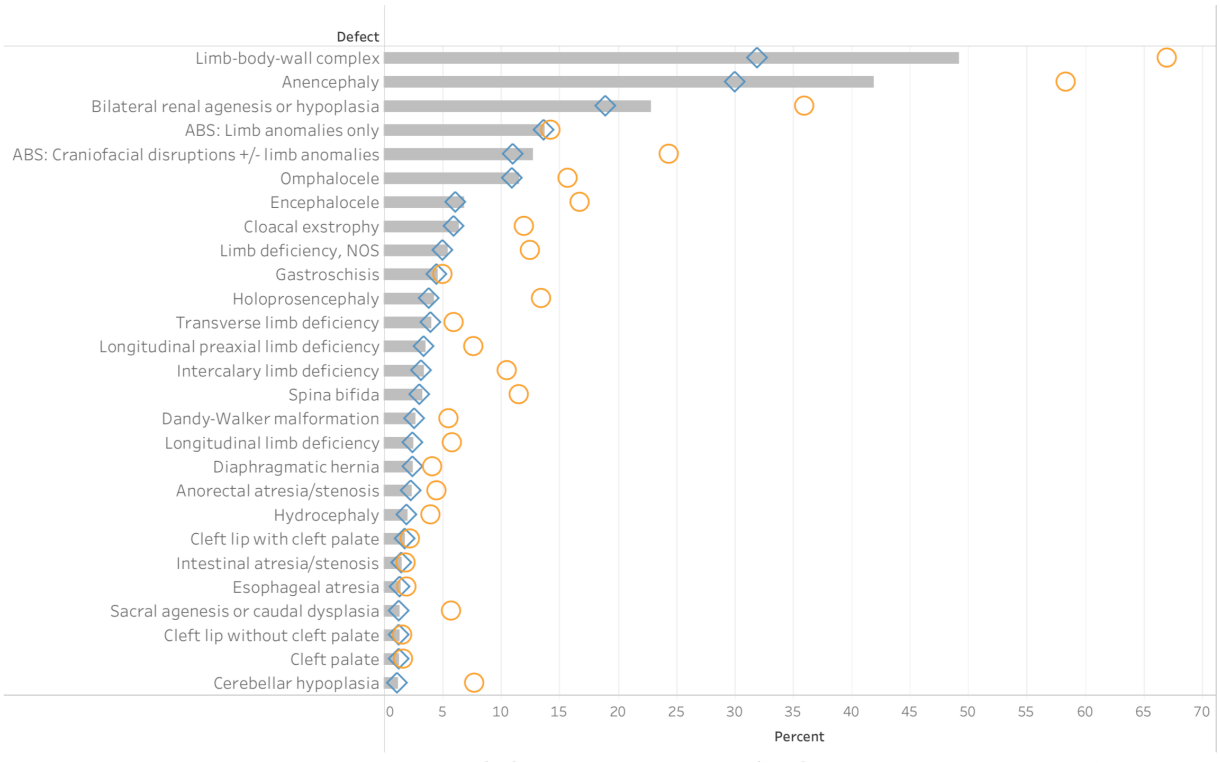


Figure 2.3. Observed and minimum and maximum termination-corrected risk of stillbirth per 100 non-syndromic birth defect cases. Bars represent observed risk; diamond represents minimum termination-corrected risk; circle represents maximum termination-corrected risk. Cases with multiple birth defects are included in each category for which they have an eligible defect; within a defect category a case is

(Figure 2.3 continued) represented only once. Defects are ordered by observed prevalence of stillbirth. ABS = amniotic band syndrome; NOS = not otherwise stated.

Among fetuses with isolated defects, the highest risk of stillbirth remained among those with universally fatal defects, the highest of which was limb-body-wall complex at 34.2%. Either no stillbirths or only one stillbirth occurred among the isolated cases of four defects: sacral agenesis (n=17), cerebellar hypoplasia (n=46), intercalary limb deficiency (n=61), and limb deficiency, not otherwise specified (NOS; n=28). Stratification according to severity revealed, in general, that the risk of stillbirth increased as defect severity increased (Figure 2.4, Supplemental Table 2.2).

Termination-corrected stillbirth risk

The minimum termination-corrected stillbirth risk was within 0.4 percentage points of the observed risk for most defects (Figure 2.3, Supplemental Table 2.1). Terminations had a greater influence on the maximum termination-corrected risk than the minimum: a 1% risk of termination led to a one percentage point increase in the maximum-corrected risk, whereas a termination risk of 10% was needed to generate the same change in the minimum-corrected risk. The difference in the minimum and maximum termination-corrected for overall stillbirth risk ranged from a low of 0.2 percentage points for cleft lip without cleft palate (range: 1.3 – 1.5) to a high of 35.1 percentage points for limb-body-wall complex (range: 31.9 – 67.0). There was little difference between the observed and maximum termination-corrected risk estimates for most isolated cases of birth defects (Figure 2.4, Supplemental Table 2.2). However, when a difference was noted, the magnitude by which the maximum termination-corrected estimate exceeded the observed was unrelated to the value of the observed risk. For most birth defects,

the maximum risk estimates were greater among fetuses with multiple birth defects than among those with isolated defects and were positively correlated with severity category (Figure 2.4, Supplemental Table 2.2).

Figure 2.4. Observed and minimum and maximum termination-corrected stillbirth risk per 100 non-syndromic birth defect cases by birth defect pattern and highest severity. Bars represent observed risk; diamond represents minimum termination-corrected risk; circle represents maximum termination-corrected risk. Defects are ordered by observed prevalence of stillbirth among isolated cases. Cases with multiple birth defects are included in each defect category for which they have an eligible defect. Within a defect category a case is represented only once. ABS = amniotic band syndrome; NOS = not otherwise stated.

Combined prenatal and first day neonatal mortality

Risk of combined mortality overall was over 50% for bilateral renal agenesis, anencephaly, and limb-body-wall complex and less than 5% for infants with hydrocephaly, bladder extrophy, esophageal and intestinal atresia, and oral clefts (Figure 2.5, Supplemental Table 2.3). Among those with isolated birth defects, stillbirth comprised 20% (spina bifida) to 100% (esophageal, intestinal, anorectal atresia, and cleft lip with cleft palate) of the risk of combined mortality for those birth defects where at least one stillbirth occurred. With the exception of diaphragmatic hernia, holoprosencephaly, neural tube defects, bilateral renal agenesis, and limb-body-wall complex stillbirth comprised at least half of the combined mortality risk. Fetuses and infants with multiple defects had a higher risk of combined mortality than those with isolated defects, regardless of the severity level of the other defects; among multiple birth defect cases, risk of combined mortality was positively correlated with severity, largely due to increases in the risk of termination (Figure 2.6, Supplemental Table 2.4).

Discussion

In this population-based study of over 20,000 fetuses and infants with at least one of 27 specific specialist- confirmed non-syndromic birth defects, the risk of stillbirth ranged from 1.2% to 49.2%, exceeding the 0.6% risk of stillbirth in the general US population by 2 to 84 times.[6] The same phenomenon was observed for fetuses with isolated defects, with the exception of fetuses with isolated cleft lip without cleft palate or cleft palate alone. Observed risk of stillbirth was higher for fetuses with multiple compared to isolated defects and was further positively associated with severity category. Similar patterns were observed for combined prenatal and

first-day neonatal mortality; of note, stillbirth made up half or more of the total combined mortality for cases with most isolated birth defects.

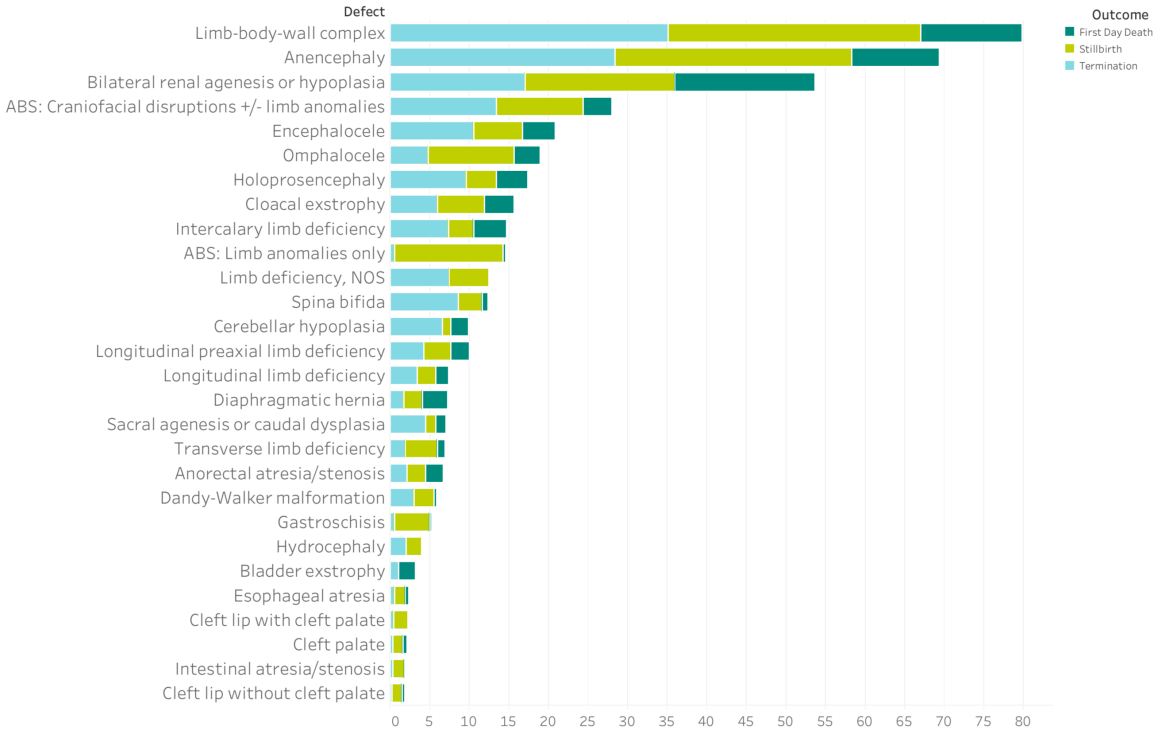


Figure 2.5. Observed risk of combined mortality (termination, stillbirth, or first day neonatal death) per 100 non-syndromic birth defect cases. Proportion of total outcomes (termination, stillbirth, first day neonatal death, survival to second neonatal day) are represented by the bars: termination = light blue, stillbirth = light green, first day death = dark green, remainder of scale represents survival to the first day. The proportion of each mortality outcome of all mortality outcomes is represented by the relative size of the colored bar to the total size of the length of the colored bar. Defects are ordered by prevalence of combined prenatal and first day mortality. Cases with multiple birth defects are included in each defect category for which they have an eligible defect Within a defect category a case is represented only once. ABS = amniotic band syndrome; NOS = not otherwise stated.

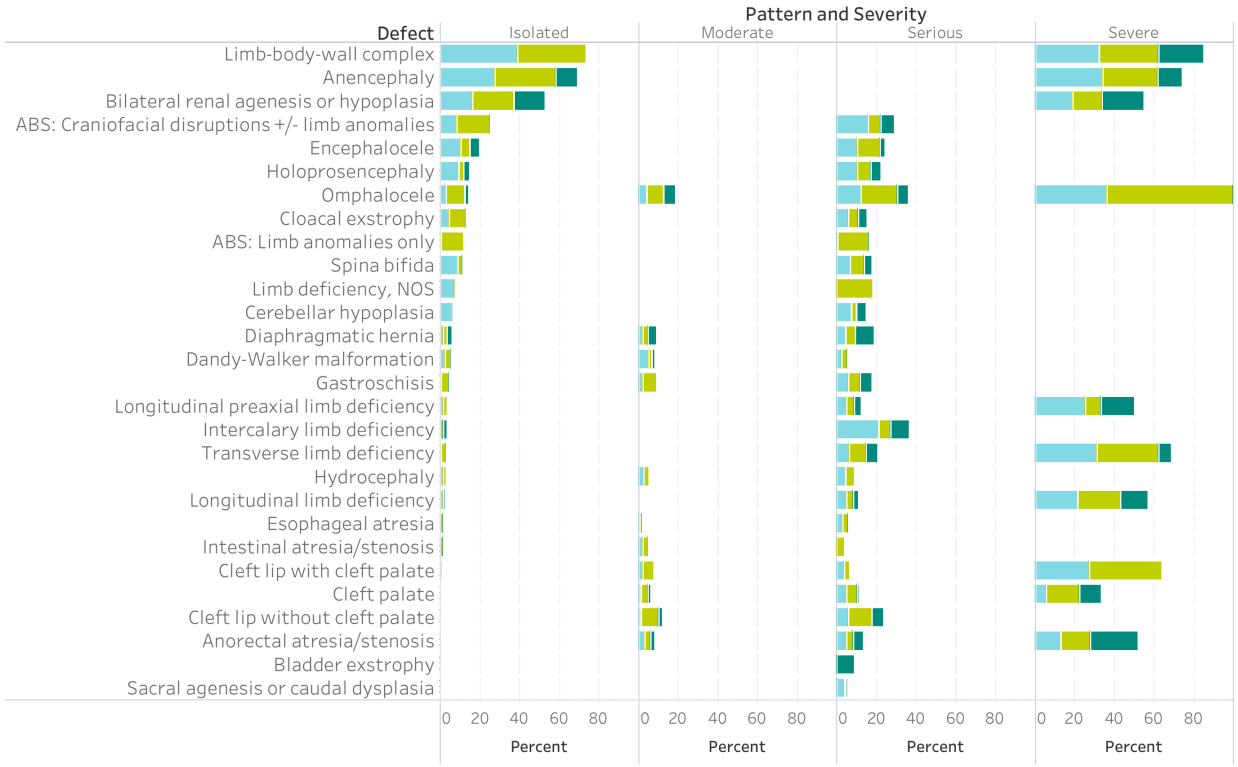


Figure 2.6. Observed risk of combined mortality (termination, stillbirth, or first day neonatal death) per 100 non-syndromic birth defect cases by birth defect pattern and highest severity. Proportion of total outcomes (termination, stillbirth, first day neonatal death, survival to second neonatal day) are represented by the bars: termination = light blue, stillbirth = light green, first day death = dark green, remainder of scale represents survival to the first day. The proportion of each mortality outcome of all mortality outcomes is represented by the relative size of the colored bar to the total size of the length of the colored bar. Defects are ordered by observed total combined mortality among isolated cases. Cases with multiple birth defects are included in each defect category for which they have an eligible defect. Within a defect category a case is represented only once. ABS = amniotic band syndrome; NOS = not otherwise stated.

Risk of termination also increased with multiple birth defects and further with severity, suggesting that termination leads to the “depletion of succeptibles”. Consideration of the impact of termination on stillbirth risk estimates demonstrated that observed estimates are more likely to underestimate than overestimate the actual risk of stillbirth when terminated

cases are excluded from analyses. That higher risk fetuses are more likely to be terminated, further suggests that true risks of stillbirth are more likely to towards the maximum estimate than the minimum. Additionally, we found that the magnitude of the change in estimate from the observed risk to the maximum termination-corrected risk was unrelated to the observed risk of stillbirth; thus, as demonstrated by results for cerebellar hyperplasia (observed risk =1.2, maximum-termination-corrected risk =7.7%), the true risk of stillbirth for birth defects with high risks of termination may be substantially larger than suggested by the observed risk.

Strengths and weaknesses of the study

A major strength of our study is that we used all identified cases of well characterized, specific birth defects in a population-based case-control which allowed us to ensure that we have a large, reasonably complete cohort of infants with birth defects from the catchment areas of the study sites and that all cases received equivalent review for case confirmation and consistent classification. Although the restriction of this study to non-syndromic cases precluded risk estimates for this group, these disorders may increase the risk of stillbirth even when structural birth defects are absent and most infants and fetuses with major defects do not have a known syndrome. [18] Thus it is also an important strength.

Our study has several limitations. Although our overall sample size is large, limited data were available for some sub-analyses, leading to unstable estimates. First day mortality is based on the date of death rather than a 24-hour period, and thus represents a minimum risk. Cases of birth defects which undergo termination are more difficult to identify than those resulting in live birth or stillbirth, and were not enrolled by all study sites, thus are under-captured by our

study; the degree of under-capture is unknown. Therefore, the true maximum and minimum termination-corrected risks are likely to be even further from the observed risk than our estimates.

Birth defects may be less likely to be diagnosed or confirmed in terminated, stillborn, or live born infants who die on the day of birth relative to their cohorts who survive the first day, in part because most of these infants do not undergo autopsy or even post-mortem physical examinations. [86] This could lead to differential diagnosis or confirmation of birth defects according to pregnancy outcome leading to biased estimates of stillbirth risk. However, a recent study found that, among stillborn infants undergoing autopsy, most major birth defects, excluding certain heart defects, were also identified by other means. [83] We excluded defects not reliably diagnosed in stillborn and terminated infants from our analyses, minimizing the risk that our estimates suffer from this bias. Nonetheless, for certain birth defects, gastrointestinal atresias in particular, postnatal symptoms in live born survivors or the presence of more obvious defects (e.g., limb deficiencies) may lead physicians to look for commonly co-occurring birth defects. [87,88] Therefore, our results may underestimate the risk of stillbirth among infants with gastrointestinal atresias, especially when they occur as isolated birth defects.

Because little is known about factors that influence the risk of stillbirth among fetuses with birth defects it is unclear to whom our estimates may generalize. However, the termination-corrected estimates reduce the sensitivity of our results to the underlying rate of termination in our population, thus improving generalizability to populations with different termination rates.

Despite these limitations, our study increases knowledge about the risk of stillbirth among infants with birth defects and advances the methods for conducting research on perinatal mortality risks in this population. First, identification of cases through active population-based surveillance systems helps assure that our estimates are not biased by population characteristics and referral patterns that may affect single center or hospital network-based studies and ensure inclusion of as complete of a cohort as possible.[76,89] Second, compared to previously published studies, our very large sample, with over 10,000 more cases of the commonly examined defects as the largest previously published study, allowed us to generate more stable estimates, the first stillbirth risk estimates for some very rare birth defects (e.g., cloacal extrophy), and to stratify risk estimates for common birth defects by phenotype and birth defect pattern.[79,80] For example, the largest study identified by a systematic review and meta-analysis of stillbirth among fetuses with gastroschisis included 274 cases and a risk of 14.6% compared to our sample of 2,214 cases and an observed risk of 4.5% (of note, our prevalence was the same as the pooled estimate from the meta-analysis).[77]

Fourth, we examined the possible bias introduced by termination of pregnancy and addressed the possible influence on estimates by introducing minimum and maximum termination-corrected risk estimates. Compared to the usual method of estimating a single stillbirth risk based on live births and stillbirths, this method improves both generalizability across populations and comparability between studies by providing the range of stillbirth risk consistent with the observed risk of termination of pregnancy for a specific defect. For example, although our observed risk estimates differ substantially for many defects compared

to those found by Groen et al. in the only other large population-based study of stillbirth among fetuses with birth defects, many of Groen's estimates fall within our maximum and minimum range. [79] Thus, although, Groen's estimate for isolated holoprosencephaly of 11.5 differs from our observed 4.3%, it falls within our termination-correction range of 3.9 - 13.5%, suggesting that differences in the risk of termination are is a plausible explanation for the difference in estimates. For the birth defects for which our range did not capture Groen's estimate (isolated cases of gastroschisis, omphalocele, hydrocephaly, and bilateral renal agenesis), other explanations are more likely; in either instance disparities in risk estimates may reflect unstable estimates due to small sample sizes, bias due to excluding terminated cases, or true differences in risk.

Third, we did not produce estimates for birth defects that are likely to be underdiagnosed among infants who undergo termination, are stillborn, or die on the day of birth. In contrast, Groen et al included these defects, resulting in implausibly low estimates for defects such as congenital cataract (0%), choanal atresia (0%), and hypospadias (0.02%).[79] Accurate estimates for these types of defects would require a study design in which a cohort of stillborn infants are actively examined for the presence of these defects.

Finally, this is the first study to estimate combined prenatal and first day mortality to aid in accounting for any possible misclassification of stillbirths and early neonatal deaths. Additionally, this estimate allowed for comparisons of the mortality due to stillbirth versus termination or first day neonatal morality. These comparisons identified several birth defects

that have a particularly high burden of stillbirth relative to other forms of perinatal mortality (e.g., gastroschisis), suggesting defects that could be targeted for research into stillbirth prevention. Of the birth defects identified as having a disproportionately high risk of stillbirth, most are unlikely to directly cause mortality (e.g., isolated limb defects) suggesting that the risk of stillbirth among at least some fetuses with birth defects may share a common pathway with the development of the defect or that these fetuses are particularly vulnerable to risk factors for stillbirth unrelated to their defect.

Estimates generated in this study can assist clinicians caring for patients with prenatally diagnosed birth defects as a basis for parental counselling on the risk of mortality during pregnancy and within a day of delivery. Although we found elevated risks of stillbirth for fetuses with non-syndromic major birth defects, results provide some reassurance since most such fetuses survive to live birth and through the high-risk period of the first day of life. However, it is important that parents be counseled that any major birth defect is associated with an increased risk of stillbirth compared to the general population, on the risk identified for their child's specific birth defect or defects, and on any clinical measures available to minimize stillbirth risk. This will aid families in making medical plans and arrangements for services that will best fit their needs.[90]

Results of our study also suggest that estimates or the risk of stillbirth among fetuses with major birth defects which are calculated based on observed stillbirths and live births may substantially underestimate the true risk of stillbirth for birth defects with even moderate risks

of termination. Our data also supports previous findings that high-risk fetuses with more severe defects and multiple birth defects are selectively removed from the pool of fetuses at risk by termination. [30,34] Therefore, differences in termination risk may substantially alter estimates of risks of all perinatal outcomes among fetuses with birth defects and thus may affect comparisons between studies. In studies of risk factors for stillbirth, especially among fetuses with birth defects, exclusion of terminated cases could lead to substantial bias if termination rates differ between exposed and unexposed groups. Termination-corrected minimum and maximum estimates may help to address this issue and thus improve interpretation of study results.

For policy makers and researchers, our results also highlight the need for greater research into risk factors for stillbirth among fetuses with ultimately fatal and non-fatal birth defects. In our study, unexpectedly, fetuses with isolated cases of birth defects that do not directly affect vital organs, such as limb defects, were at an increased risk of stillbirth compared to infants in the general population. These findings raise the question of whether certain birth defects may increase risk of stillbirth through indirect means, or whether the birth defects and increased risk of stillbirth might share common causes. Further exploration into the mechanisms that lead to this increased risk may identify opportunities to improve survival for some infants with major birth defects. Future studies should expand investigations into areas such as associated conditions and causes of stillbirth, modifiable risk factors, and clinical care measures (e.g., enhanced prenatal monitoring and early delivery) to prevent stillbirth among fetuses with major birth defects. We encourage researchers to include termination-corrected estimates to

account for the prevalence of termination and provide more meaningful mortality and risk estimates.

Supplemental Table 2.1. Observed and minimum and maximum termination-corrected prevalence of stillbirth per 100 non-syndromic birth defect cases

Defect	Observed Stillbirths	Observed Fetuses at Risk	Stillbirths + Terimations	Total Cases	Minimum Termination-Corrected	Observed	Maximum Terminaton-Corrected	Difference between Minimum and Maximum
Limb-body-wall complex	30	61	63	94	31.9	49.2	67.0	35.11
Anencephaly	258	616	502	860	30.0	41.9	58.4	28.37
Bilateral renal agenesis or hypoplasia	62	272	118	328	18.9	22.8	36.0	17.07
ABS: Limb anomalies only	47	342	49	344	13.7	13.7	14.2	0.58
ABS: Craniofacial disruptions +/- limb anomalies	9	71	20	82	11.0	12.7	24.4	13.41
Omphalocele	67	583	96	612	10.9	11.5	15.7	4.74
Encephalocele	22	321	60	359	6.1	6.9	16.7	10.58
Cloacal exstrophy	8	126	16	134	6.0	6.3	11.9	5.97
Limb deficiency, NOS	2	37	5	40	5.0	5.4	12.5	7.50
Gastroschisis	100	2214	111	2225	4.5	4.5	5.0	0.49
Holoprosencephaly	10	235	35	260	3.8	4.3	13.5	9.62
Transverse limb deficiency	41	1008	61	1028	4.0	4.1	5.9	1.95
Longitudinal preaxial limb deficiency	14	400	32	418	3.3	3.5	7.7	4.31
Intercalary limb deficiency	3	88	10	95	3.2	3.4	10.5	7.37
Spina bifida	51	1566	198	1713	3.0	3.3	11.6	8.58
Dandy-Walker malformation	7	263	15	271	2.6	2.7	5.5	2.95
Longitudinal limb deficiency	17	683	41	707	2.4	2.5	5.8	3.39
Diaphragmatic hernia	30	1231	51	1252	2.4	2.4	4.1	1.68
Anorectal atresia/stenosis	36	1531	70	1565	2.3	2.4	4.5	2.17
Hydrocephaly	15	767	31	783	1.9	2.0	4.0	2.04
Cleft lip with cleft palate	34	1936	43	1945	1.7	1.8	2.2	0.46
Intestinal atresia/stenosis	13	878	16	881	1.5	1.5	1.8	0.34
Esophageal atresia	13	954	18	959	1.4	1.4	1.9	0.52
Sacral agenesis or caudal dysplasia	2	150	9	157	1.3	1.3	5.7	4.46
Cleft lip without cleft palate	20	1554	24	1558	1.3	1.3	1.5	0.26
Cleft palate	29	2321	37	2329	1.2	1.2	1.6	0.34
Cerebellar hypoplasia	1	85	7	91	1.1	1.2	7.7	6.59

ABS = amniotic band syndrome, NOS = not otherwise specified

Total cases = Live births + Stillbirths + Terminations

Observed Prevalence = Stillbirths / Live births + Stillbirths
Maximum Termination-Corrected = Stillbirth + Terminations / Livebirths + Stillbirths + Terminations
Minimum Termination Corrected = Stillbirth / Livebirths + Stillbirths + Terminations

Supplemental Table 2.2. Observed and minimum and maximum termination-corrected stillbirth prevalence per 100 non-syndromic birth defect cases by birth defect pattern and highest severity

Defect	Pattern and Severity	Observed Stillbirths	Observed Fetuses at Risk	Stillbirths + Terminations	Total Cases	Minimum Termination-Corrected Prevalence	Observed Prevalence	Maximum Termination-Corrected Prevalence	Minimum and Maximum Difference
Limb-body-wall complex	Isolated	14	25	30	41	34.1	56.0	73.2	39.0
	Severe	16	36	33	53	30.2	44.4	62.3	32.1
Anencephaly	Isolated	231	552	442	763	30.3	41.8	57.9	27.7
	Severe	27	64	60	97	27.8	42.2	61.9	34.0
ABS: Limb anomalies only	Isolated	18	160	19	161	11.2	11.3	11.8	0.6
	Serious	29	182	30	183	15.8	15.9	16.4	0.5
Omphalocele	Isolated	34	344	44	354	9.6	9.9	12.4	2.8
	Moderate	16	183	24	191	8.4	8.7	12.6	4.2
	Serious	10	49	17	56	17.9	20.4	30.4	12.5
	Severe	7	7	11	11	63.6	100.0	100.0	36.4
Cloacal exstrophy	Isolated	4	45	6	47	8.5	8.9	12.8	4.3
	Serious	4	79	9	84	4.8	5.1	10.7	6.0
	Severe	0	2	1	3		0.0		
Encephalocele	Isolated	12	242	40	270	4.4	5.0	14.8	10.4
	Serious	10	78	19	87	11.5	12.8	21.8	10.3
	Severe	0	1	1	2		0.0		
Gastroschisis	Isolated	86	2023	91	2028	4.2	4.3	4.5	0.2
	Moderate	11	158	14	161	6.8	7.0	8.7	1.9
	Serious	2	32	4	34	5.9	6.3	11.8	5.9
	Severe	1	1	2	2		100.0		
Holoprosencephaly	Isolated	5	166	22	183	2.7	3.0	12.0	9.3
	Serious	5	68	13	76	6.6	7.4	17.1	10.5
	Severe	0	1	0	1		0.0		
Dandy-Walker malformation	Isolated	5	167	9	171	2.9	3.0	5.3	2.3
	Moderate	1	59	4	62	1.6	1.7	6.5	4.8
	Serious	1	37	2	38	2.6	2.7	5.3	2.6
Transverse limb deficiency	Isolated	22	846	27	851	2.6	2.6	3.2	0.6
	Serious	14	151	24	161	8.7	9.3	14.9	6.2
	Severe	5	11	10	16	31.3	45.5	62.5	31.3
Spina bifida	Isolated	34	1343	165	1474	2.3	2.5	11.2	8.9
	Serious	16	216	32	232	6.9	7.4	13.8	6.9
	Severe	1	7	1	7		14.3		
Diaphragmatic hernia	Isolated	18	914	31	927	1.9	2.0	3.3	1.4
	Moderate	8	272	13	277	2.9	2.9	4.7	1.8
	Serious	2	41	4	43	4.7	4.9	9.3	4.7
	Severe	2	4	3	5		50.0		
Longitudinal preaxial limb deficiency	Isolated	3	149	5	151	2.0	2.0	3.3	1.3
	Serious	10	242	23	255	3.9	4.1	9.0	5.1
	Severe	1	9	4	12	8.3	11.1	33.3	25.0
Intercalary limb deficiency	Isolated	1	61	1	61	1.6	1.6	1.6	0.0
	Serious	2	26	9	33	6.1	7.7	27.3	21.2
	Severe	0	1	0	1		0.0		
Hydrocephaly	Isolated	8	545	15	552	1.4	1.5	2.7	1.3
	Moderate	4	158	8	162	2.5	2.5	4.9	2.5
	Serious	3	63	6	66	4.5	4.8	9.1	4.5
	Severe	0	1	2	3		0.0		
Esophageal atresia	Isolated	5	393	5	393	1.3	1.3	1.3	0.0
	Moderate	4	457	6	459	0.9	0.9	1.3	0.4
	Serious	3	97	6	100	3.0	3.1	6.0	3.0
	Severe	1	7	1	7		14.3		
Intestinal atresia/stenosis	Isolated	9	713	9	713	1.3	1.3	1.3	0.0
	Moderate	3	137	6	140	2.1	2.2	4.3	2.1
	Serious	1	25	1	25	4.0	4.0	4.0	0.0
	Severe	0	3	0	3		0.0		
Longitudinal limb deficiency	Isolated	4	371	9	376	1.1	1.1	2.4	1.3
	Serious	10	301	26	317	3.2	3.3	8.2	5.0
	Severe	3	11	6	14	21.4	27.3	42.9	21.4
Cleft lip with cleft palate	Isolated	16	1663	16	1663	1.0	1.0	1.0	0.0
	Moderate	13	219	17	223	5.8	5.9	7.6	1.8
	Serious	1	46	3	48	2.1	2.2	6.3	4.2
	Severe	4	8	7	11	36.4	50.0	63.6	27.3
Anorectal atresia/stenosis	Isolated	2	675	2	675	0.3	0.3	0.3	0.0
	Moderate	20	635	38	653	3.1	3.1	5.8	2.8
	Serious	6	174	15	183	3.3	3.4	8.2	4.9
	Severe	8	47	15	54	14.8	17.0	27.8	13.0
Cleft lip without cleft palate	Isolated	6	1431	6	1431	0.4	0.4	0.4	0.0
	Moderate	9	102	10	103	8.7	8.8	9.7	1.0
	Serious	2	16	3	17	11.8	12.5	17.6	5.9
	Severe	3	5	5	7		60.0		
Cleft palate	Isolated	8	1836	8	1836	0.4	0.4	0.4	0.0
	Moderate	14	394	17	397	3.5	3.6	4.3	0.8
	Serious	4	74	8	78	5.1	5.4	10.3	5.1
	Severe	3	17	4	18	16.7	17.6	22.2	5.6
Cerebellar hypoplasia	Isolated	0	43	3	46	0.0	0.0	6.5	6.5
	Moderate	0	4	0	4		0.0		
	Serious	1	38	4	41	2.4	2.6	9.8	7.3
Limb deficiency, NOS	Isolated	0	26	2	28	0.0	0.0	7.1	7.1
	Serious	2	11	2	11	18.2	18.2	18.2	0.0
Sacral agenesis or caudal dysplasia	Isolated	0	17	0	17	0.0	0.0	0.0	0.0
	Serious	1	127	6	132	0.8	0.8	4.5	3.8
	Severe	1	6	3	8		16.7		

ABS = amniotic band syndrome, NOS = not otherwise specified

Total cases = Live births + Stillbirths + Terminations

Observed Prevalence = Stillbirths / Live births + Stillbirths
Maximum Termination-Corrected = Stillbirth + Terminations / Livebirths + Stillbirths + Terminations
Minimum Termination-Corrected = Stillbirth / Livebirths + Stillbirths + Terminations

Supplemental Table 2.3. Observed number and risk of termination, stillbirth, first day neonatal death, or survival to second postnatal day per 100 non-syndromic birth defect cases

Defect	Pattern and Severity	Observed Stillbirths	Observed Fetuses at Risk	Stillbirths + Terminations	Total Cases	Minimum Termination-Corrected Prevalence	Observed Prevalence	Maximum Termination-Corrected Prevalence	Minimum and Maximum Difference
Limb-body-wall complex	Isolated	14	25	30	41	34.1	56.0	73.2	39.0
	Severe	16	36	33	53	30.2	44.4	62.3	32.1
Anencephaly	Isolated	231	552	442	763	30.3	41.8	57.9	27.7
	Severe	27	64	60	97	27.8	42.2	61.9	34.0
ABS: Limb anomalies only	Isolated	18	160	19	161	11.2	11.3	11.8	0.6
	Serious	29	182	30	183	15.8	15.9	16.4	0.5
Omphalocele	Isolated	34	344	44	354	9.6	9.9	12.4	2.8
	Moderate	16	183	24	191	8.4	8.7	12.6	4.2
	Serious	10	49	17	56	17.9	20.4	30.4	12.5
	Severe	7	7	11	11	63.6	100.0	100.0	36.4
Cloacal exstrophy	Isolated	4	45	6	47	8.5	8.9	12.8	4.3
	Serious	4	79	9	84	4.8	5.1	10.7	6.0
	Severe	0	2	1	3		0.0		
Encephalocele	Isolated	12	242	40	270	4.4	5.0	14.8	10.4
	Serious	10	78	19	87	11.5	12.8	21.8	10.3
	Severe	0	1	1	2		0.0		
Gastroschisis	Isolated	86	2023	91	2028	4.2	4.3	4.5	0.2
	Moderate	11	158	14	161	6.8	7.0	8.7	1.9
	Serious	2	32	4	34	5.9	6.3	11.8	5.9
	Severe	1	1	2	2		100.0		
Holoprosencephaly	Isolated	5	166	22	183	2.7	3.0	12.0	9.3
	Serious	5	68	13	76	6.6	7.4	17.1	10.5
	Severe	0	1	0	1		0.0		
Dandy-Walker malformation	Isolated	5	167	9	171	2.9	3.0	5.3	2.3
	Moderate	1	59	4	62	1.6	1.7	6.5	4.8
	Serious	1	37	2	38	2.6	2.7	5.3	2.6
Transverse limb deficiency	Isolated	22	846	27	851	2.6	2.6	3.2	0.6
	Serious	14	151	24	161	8.7	9.3	14.9	6.2
	Severe	5	11	10	16	31.3	45.5	62.5	31.3
Spina bifida	Isolated	34	1343	165	1474	2.3	2.5	11.2	8.9
	Serious	16	216	32	232	6.9	7.4	13.8	6.9
	Severe	1	7	1	7		14.3		
Diaphragmatic hernia	Isolated	18	914	31	927	1.9	2.0	3.3	1.4
	Moderate	8	272	13	277	2.9	2.9	4.7	1.8
	Serious	2	41	4	43	4.7	4.9	9.3	4.7
	Severe	2	4	3	5		50.0		
Longitudinal preaxial limb deficiency	Isolated	3	149	5	151	2.0	2.0	3.3	1.3
	Serious	10	242	23	255	3.9	4.1	9.0	5.1
	Severe	1	9	4	12	8.3	11.1	33.3	25.0
Intercalary limb deficiency	Isolated	1	61	1	61	1.6	1.6	1.6	0.0
	Serious	2	26	9	33	6.1	7.7	27.3	21.2
	Severe	0	1	0	1		0.0		
Hydrocephaly	Isolated	8	545	15	552	1.4	1.5	2.7	1.3
	Moderate	4	158	8	162	2.5	2.5	4.9	2.5
	Serious	3	63	6	66	4.5	4.8	9.1	4.5
	Severe	0	1	2	3		0.0		
Esophageal atresia	Isolated	5	393	5	393	1.3	1.3	1.3	0.0
	Moderate	4	457	6	459	0.9	0.9	1.3	0.4
	Serious	3	97	6	100	3.0	3.1	6.0	3.0
	Severe	1	7	1	7		14.3		
Intestinal atresia/stenosis	Isolated	9	713	9	713	1.3	1.3	1.3	0.0
	Moderate	3	137	6	140	2.1	2.2	4.3	2.1
	Serious	1	25	1	25	4.0	4.0	4.0	0.0
	Severe	0	3	0	3		0.0		
Longitudinal limb deficiency	Isolated	4	371	9	376	1.1	1.1	2.4	1.3
	Serious	10	301	26	317	3.2	3.3	8.2	5.0
	Severe	3	11	6	14	21.4	27.3	42.9	21.4
Cleft lip with cleft palate	Isolated	16	1663	16	1663	1.0	1.0	1.0	0.0
	Moderate	13	219	17	223	5.8	5.9	7.6	1.8
	Serious	1	46	3	48	2.1	2.2	6.3	4.2
	Severe	4	8	7	11	36.4	50.0	63.6	27.3
Anorectal atresia/stenosis	Isolated	2	675	2	675	0.3	0.3	0.3	0.0
	Moderate	20	635	38	653	3.1	3.1	5.8	2.8
	Serious	6	174	15	183	3.3	3.4	8.2	4.9
	Severe	8	47	15	54	14.8	17.0	27.8	13.0
Cleft lip without cleft palate	Isolated	6	1431	6	1431	0.4	0.4	0.4	0.0
	Moderate	9	102	10	103	8.7	8.8	9.7	1.0
	Serious	2	16	3	17	11.8	12.5	17.6	5.9
	Severe	3	5	5	7		60.0		
Cleft palate	Isolated	8	1836	8	1836	0.4	0.4	0.4	0.0
	Moderate	14	394	17	397	3.5	3.6	4.3	0.8
	Serious	4	74	8	78	5.1	5.4	10.3	5.1
	Severe	3	17	4	18	16.7	17.6	22.2	5.6
Cerebellar hypoplasia	Isolated	0	43	3	46	0.0	0.0	6.5	6.5
	Moderate	0	4	0	4		0.0		
	Serious	1	38	4	41	2.4	2.6	9.8	7.3
Limb deficiency, NOS	Isolated	0	26	2	28	0.0	0.0	7.1	7.1
	Serious	2	11	2	11	18.2	18.2	18.2	0.0
Sacral agenesis or caudal dysplasia	Isolated	0	17	0	17	0.0	0.0	0.0	0.0
	Serious	1	127	6	132	0.8	0.8	4.5	3.8
	Severe	1	6	3	8		16.7		

ABS = amniotic band syndrome, NOS = not otherwise specified

Total cases = Live births + Stillbirths + Terminations

Observed Prevalence = Stillbirths / Live births + Stillbirths
Maximum Termination-Corrected = Stillbirth + Terminations / Livebirths + Stillbirths + Terminations
Minimum Termination-Corrected = Stillbirth / Livebirths + Stillbirths + Terminations

Supplemental Table 2.4. Observed number and risk of termination, stillbirth, or first day neonatal death per 100 non-syndromic birth defect cases by defect pattern and highest severity

	Pattern and Severity / Outcome															
	Isolated				Moderate				Serious				Severe			
Defect	Termination	Stillbirth	First Day Death	Survivor to Day Two	Termination	Stillbirth	First Day Death	Survivor to Day Two	Termination	Stillbirth	First Day Death	Survivor to Day Two	Termination	Stillbirth	First Day Death	Survivor to Day Two
Limb-body-wall complex	16 39.0	14 34.1	0 0.0	11 26.8									17 32.1	16 30.2	12 22.6	8 15.1
Anencephaly	211 27.7	231 30.3	83 10.9	238 31.2									33 34.0	27 27.8	12 12.4	25 25.8
Bilateral renal agenesis	34 16.2	44 21.0	33 15.7	99 47.1									22 18.6	18 15.3	25 21.2	53 44.9
ABS: Craniofacial +/- limb anomalies	3 8.3	6 16.7	0 0.0	27 75.0					7 15.6	3 6.7	3 6.7	32 71.1				
Encephalocele	28 10.4	12 4.4	13 4.8	217 80.4					9 10.3	10 11.5	2 2.3	66 75.9	1	0	0	1
Holoprosencephaly	17 9.3	5 2.7	5 2.7	156 85.2					8 10.5	5 6.6	4 5.3	59 77.6	0	0	1	0
Omphalocele	10 2.8	34 9.6	6 1.7	304 85.9	8 4.2	16 8.4	11 5.8	156 81.7	7 12.5	10 17.9	3 5.4	36 64.3	4 36.4	7 63.6	0 0.0	0 0.0
Cloacal exstrophy	2 4.3	4 8.5	0 0.0	41 87.2					5 6.0	4 4.8	4 4.8	71 84.5	1	0	1	1
ABS: Limb anomalies only	1 0.6	18 11.2	0 0.0	142 88.2					1 0.5	29 15.8	1 0.5	152 83.1				
Spina bifida	131 8.9	34 2.3	3 0.2	1306 88.6					16 6.9	16 6.9	9 3.9	191 82.3	0	1	2	4
Limb deficiency, NOS	2 7.1	0 0.0		26 92.9					0 0.0	2 18.2		9 81.8	1	0		0
Cerebellar hypoplasia	3 6.5	0 0.0	0 0.0	43 93.5	0	0	0	4	3 7.3	1 2.4	2 4.9	35 85.4				
Diaphragmatic hernia	13 1.4	18 1.9	22 2.4	874 94.3	5 1.8	8 2.9	12 4.3	252 91.0	2 4.7	2 4.7	4 9.3	35 81.4	1	2	2	0
Dandy-Walker malformation	4 2.3	5 2.9	0 0.0	162 94.7	3 4.8	1 1.6	1 1.6	57 91.9	1 2.6	1 2.6	0 0.0	36 94.7				
Gastroschisis	5 0.2	86 4.2	2 0.1	1935 95.4	3 1.9	11 6.8	1 0.6	146 90.7	2 5.9	2 5.9	2 5.9	28 82.4	1	1	0	0
Transverse limb deficiency	5 0.6	22 2.6	0 0.0	824 96.8					10 6.2	14 8.7	9 5.6	128 79.5	5 31.3	5 31.3	1 6.3	5 31.3
Longitudinal preaxial limb deficiency	2 1.3	3 2.0	0 0.0	146 96.7					13 5.1	10 3.9	8 3.1	224 87.8	3 25.0	1 8.3	2 16.7	6 50.0
Intercalary limb deficiency	0 0.0	1 1.6	1 1.6	59 96.7					7 21.2	2 6.1	3 9.1	21 63.6	0	0	0	1
Hydrocephaly	7 1.3	8 1.4		537 97.3	4 2.5	4 2.5		154 95.1	3 4.5	3 4.5		60 90.9	2	0		1
Longitudinal limb deficiency	5 1.3	4 1.1	0 0.0	367 97.6					16 5.0	10 3.2	9 2.8	282 89.0	3 21.4	3 21.4	2 14.3	6 42.9
Esophageal atresia	0 0.0	5 1.3	0 0.0	388 98.7	2 0.4	4 0.9	4 0.9	449 97.8	3 3.0	3 3.0	0 0.0	94 94.0	0	1	0	6
Intestinal atresia/stenosis	0 0.0	9 1.3	0 0.0	704 98.7	3 2.1	3 2.1	1 0.7	133 95.0	0 0.0	1 4.0	0 0.0	24 96.0	0	0	1	2
Cleft lip with cleft palate	0 0.0	16 1.0		1647 99.0	4 1.8	13 5.8		206 92.4	2 4.2	1 2.1		45 93.8	3 27.3	4 36.4		4 36.4
Cleft lip without cleft palate	0 0.0	6 0.4	1 0.1	1424 99.5	1 1.0	9 8.7	2 1.9	91 88.3	1 5.9	2 11.8	1 5.9	13 76.5	2	3	1	1
Cleft palate	0 0.0	8 0.4	3 0.2	1825 99.4	3 0.8	14 3.5	7 1.8	373 94.0	4 5.1	4 5.1	1 1.3	69 88.5	1 5.6	3 16.7	2 11.1	12 66.7
Anorectal atresia/stenosis	0 0.0	2 0.3	0 0.0	673 99.7	18 2.8	20 3.1	13 2.0	602 92.2	9 4.9	6 3.3	9 4.9	159 86.9	7 13.0	8 14.8	13 24.1	26 48.1
Sacral agenesis or caudal dysplasia	0 0.0	0 0.0	0 0.0	17 100.0					5 3.8	1 0.8	1 0.8	125 94.7	2	1	1	4
Bladder exstrophy	0 0.0		0 0.0	70 100.0					0 0.0		2 8.7	21 91.3	1		0	1

ABS = amniotic band syndrome, NOS = not otherwise specified

Chapter 3. Evaluation of selection bias in studies of risk factors for birth defects among live births: evidence from the National Birth Defects Prevention Study

Dominique Heinke, Janet W Rich-Edwards, Paige L Williams, Sonia Hernandez-Diaz, Marlene Anderka, Sarah Fisher, Tania Desrosiers, Gary Shaw, Paul Romitti, Mark Canfield, and Mahsa M Yazdy

Abstract

Prior research suggests that risk factor studies of birth defects are affected by selection bias when restricted to live births. However, the degree of bias in estimating association measures in actual studies has not been quantified. Using data from the National Birth Defects Prevention Study, we evaluated the association of established risk factors with defects reflecting a range of prenatal loss due to stillbirth and termination: anencephaly (>50% affected pregnancies); spina bifida, encephalocele, and omphalocele (moderate); and cleft palate (<1%). We considered exposures with a range of strength of association with birth defects and corresponding risk of prenatal loss: smoking (moderate/moderate), antiepileptic drug (AED) use (strong /moderate), and multiple gestation (strong/strong). We used logistic regression to estimate ORs and 95% CIs adjusted for maternal age, race/ethnicity, and pre-pregnancy folic acid use. Potential selection bias was evaluated by comparing ORs across models which included only live births, live births and stillbirths, and all outcomes (live births, stillbirths, and terminations). No differences were observed in ORs among live births only compared to those among all outcomes for AED use, smoking, or multiple gestation for each defect examined, except anencephaly: the OR for multiple gestation was twice as high among live births (aOR=4.9, 95% CI: 3.2, 7.4) as among all outcomes (2.4; 1.7, 3.4) but an interpretation of increased risk remained; small numbers precluded examining AED use for anencephaly. These observations indicate that results from analyses conducted only among live births were not measurably affected by selection bias, even when the exposure was expected to be associated with prenatal loss. However, selection bias may occur when the birth defect is strongly associated with pregnancy loss and the exposure is strongly associated with stillbirth or termination of affected fetuses.

Introduction

Epidemiologic studies of birth defects are particularly vulnerable to selection bias because, unlike most outcomes, many cases of birth defects are excluded from the cohort of pregnancies when they do not survive until birth.[26,91,92] Up to 90% of malformed fetuses are lost between prenatal diagnosis and live birth, primarily due to termination for birth defects, leading to underestimation of the risks when only prevalence at live birth is evaluated. [27,32,34] In etiologic studies, selection bias, also called collider stratification bias, is dependent not only on the loss of cases, but also an association of the exposure with the loss of cases, as shown in Figure 3.1.[91] Simulation studies by Hook and Regal and a literature-based bias analysis by Cragan and Khoury have demonstrated that estimates among live births can be biased towards or away from the null, leading researchers to conclude that etiologic studies of birth defects suffer from selection bias when restricted to only live births. [26,35,93]

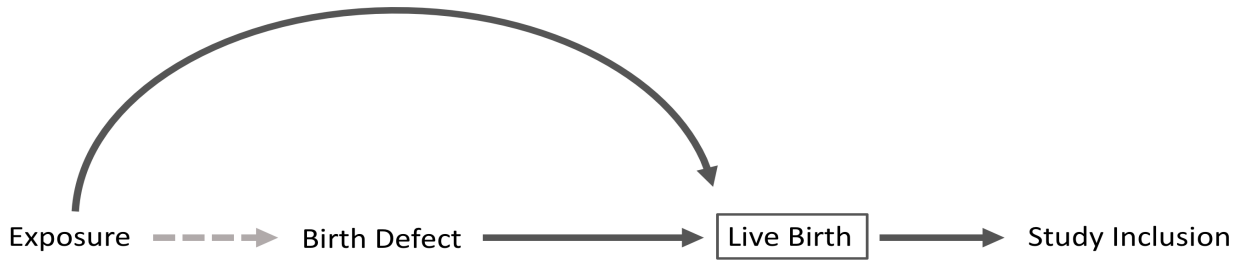


Figure 3.1. Directed Acyclic Graph of Hypothetical Selection Bias in Studies of Birth Defects. The solid arrows represent associations; the dotted arrow represents the question of interest. The box around "Live Birth" represents conditioning on the outcome of pregnancy being live birth. Conditioning on live birth opens a "backdoor pathway" between the birth defect and the exposure resulting in selection bias through collider stratification bias.

However, the generalizability of prior simulation study results on the impact of fetal losses on etiologic research on birth defects to real studies is dependent on the plausibility of the

assumptions utilized. Incorrect assumptions may lead researchers astray.[94] Thus, evaluation of this question using observational data is critical. One study of first trimester exposure to folic acid antagonist medications found that the odds ratio of neural tube defects was 6.3 when terminations were included and 0.51 (based on 2 cases) when only live births and stillbirths were included. The bias was induced by an extremely large and differential termination probability for fetuses with neural tube defects exposed (96%) and unexposed (16%). While this dramatic result suggests evidence of severe selection bias, several methodological issues, including possible differential misclassification of the outcome and inclusion of medications used to induce termination in the exposure, suggest these results cannot be relied upon as evidence that all studies excluding terminated cases are biased. [95] Other studies have reported lower probability of terminations for most specific birth defects and non-differential for exposures such as maternal depression. [34,96]

Although many studies of birth defects include terminated cases, other data sources large enough to investigate risk factors for these rare outcomes, such as administrative claims data, or pregnancy cohorts that enroll women late in gestation, such as pregnancy registries, are often limited to live births. [97-99] Thus, the quantification of the bias introduced by restriction to live births would inform the validity of these data sources for etiologic research on birth defects. As the cause of 80% of birth defect cases remains unknown, a better understanding of if and when selection bias occurs in studies of birth defects among live births may open up further opportunities for investigation.[18]

Therefore, we sought to investigate the occurrence of selection bias in epidemiologic studies using data from a large population-based case-control study of birth defects in the United

States. To evaluate the occurrence of selection bias, we compared results from analyses where the case population was restricted to live births only to results from analyses among live births and stillbirths, and among live births, stillbirths and terminations. Further, to better understand the conditions that may generate selection bias, we evaluated how characteristics of the exposures and defects under evaluation affect the occurrence and magnitude of bias using defects and exposures with a range of associations with fetal loss.

Methods

Study Population

The National Birth Defects Prevention Study (NBDPS) is a large, population-based collaborative multi-state case-control study of major birth defects in the United States. Study methods, including changes over time, have been described in detail previously.[13] Briefly, birth defect cases were identified using active surveillance systems in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah). During the study period, the inclusion of cases by pregnancy outcome differed by site and over time: most sites collected all pregnancy outcomes through their entire study participation; New Jersey collected live births only for its entire study participation; New York collected live births only for the first 27 months of study participation, then included all birth outcomes; only live births and stillbirths were collected for a period of time before collection of all birth outcomes by Georgia (15 months) and Massachusetts (13 years 3 months).[13]

Birth defect cases with a known cause (i.e., single gene or chromosomal disorders) were ineligible. Medical records of cases were reviewed for eligibility and defects were classified by

clinical geneticists using standard criteria.[82] Eligible cases could be live born, stillborn, or elective terminations; spontaneous losses < 20 weeks gestational age were excluded. We used the following definitions for pregnancy outcomes: stillbirths were spontaneous fetal deaths in utero with a gestational age at delivery of at least 20 weeks gestation (or ≥500g if gestational age was unknown), elective terminations were fetal deaths due to the intentional termination of pregnancy, and live births were infants with signs of life at the time of delivery. Cases with an unknown outcome (n=10) were excluded. Controls were live born infants without major birth defects randomly selected from the same geographical location and time period as the cases through either vital statistics record or through birth hospitals.

All eligible mothers were interviewed by telephone within 24 months of their estimated date of delivery about demographic, reproductive factors, pregnancy history, health behaviors, and lifestyle characteristics. Mothers of both cases and controls were ineligible to participate in the interview if the infant was not in the mother's legal custody, the mother was deceased or incarcerated, did not speak English or Spanish, or if she had already participated during a previous pregnancy.

Analyses

Selected Defects and Exposures

To evaluate the effect of the strength of association of the outcome with the selection mechanism, we selected birth defects to represent a range of fetal loss due to elective termination or stillbirth: anencephaly represents a high prevalence of fetal loss; spina bifida, encephalocele, and omphalocele represent moderate prevalence of fetal loss; and cleft palate

(without cleft lip) represents a low prevalence of fetal loss.[34] To evaluate the effect of the strength of the association of the exposures with the outcome and the selection mechanism, we selected exposures with a range of associations: Smoking has a moderate association with oral clefts, no association with omphalocele, and no association with neural tube defects; there is no known association with termination for birth defects.[100 101 102 103-105] Antiepileptic drugs (AEDs) have a strong association with neural tube defects and may be associated with termination for birth defects. [106-109] Multiple gestation pregnancies have a moderate association with anencephaly and omphalocele and a strong association with termination for birth defects. [110,111]

We examined first trimester maternal smoking (any smoking vs no smoking during the first trimester), first trimester use of any AED (use at any time in the first trimester vs no use during the three months before pregnancy and throughout pregnancy), and multiple gestation pregnancy (multiple gestation vs singleton pregnancy). AEDs were defined as any medication containing clonazepam, divalproex sodium, gabapentin, oxcarbazine, phenytoin, phenobarbital, primidone, diazepam, topiramate, levetiracetam, lamotrigine, valproic acid, or carbamazepine. Multiple gestation pregnancies were based on maternal interview or if a response was missing from the interview, information abstracted from medical records or vital records. If more than one infant from a multiple set had eligible birth defects, the oldest eligible infant was chosen to be included in the study. Mothers missing data on smoking, AED use, or multiple gestation pregnancy were excluded from those respective analyses. We examined the prevalence of the exposures by pregnancy outcome among cases.

Statistical Models

We ran firth logistic regression models to estimate the prevalence odds ratio (POR) and 95% profile-likelihood confidence intervals (95% CI) for each exposure – defect pair. Selection on outcome was introduced by restricting analyses following case groups: “live births only”, “live births and stillbirths”, and “live births, stillbirths, and terminations”. We adjusted models for the following covariates simultaneously: maternal age category, maternal race, and pre-pregnancy use of folic acid (yes/no). Because underpowered analyses with unstable estimates make comparisons between models difficult to interpret, we excluded analyses among exposure-defect pairs with less than 5 exposed cases among live births only. We evaluated the effect of potential clustering by study center using binomial mixed models with a random intercept for study center. To simplify analyses, we assumed no misclassification of exposure or the outcome and no unmeasured confounding, although we acknowledge that some amount of these sources of bias are present. [104] Estimates were considered to be different if the 95% CI of models among all outcomes (live births, stillbirths, and terminations) excluded the POR when restricted to live births, or among live births and stillbirths.

Sensitivity Analyses

Because some centers only contributed live births or live births and stillbirths during all or part of the study period, inclusion of these centers in analyses may over-representing exposure distributions among live and/or stillborn infants, and thus may introduce selection bias even when terminated cases are included. Therefore, we evaluated whether estimates that include only cases and controls from time periods where centers collected all pregnancy outcomes

differ from those which includes all study centers, we restricted to sites and time periods where all outcomes where collected ("All Outcome Sample"). To evaluate whether alterations in the termination rate among singleton pregnancies compared to multiple gestation pregnancies (increased rate) and cases with isolated birth defects compared to multiple birth defects (decreased rate) affected the occurrence or degree of selection bias, we restricted analyses to singleton pregnancies and then to isolated defect cases; analyses of exposure to multiple gestation were excluded from sensitivity analysis for singleton pregnanices.[112] Finally, since interview participation may differ by pregnancy outcome, we compared the risk of each outcome by interview status for each birth defect. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Risk of termination varied by defect (Table 3.1), with the highest risk for anencephaly (43.3%, n=248) and the lowest for cleft palate (0.4%, n=27). Risk of termination was slightly higher among non-interviewed cases (Supplemental Table 3.1). The risk of termination and stillbirth for all defects was slightly lower among pregnancies with AED exposure (Figure 3.2a), but was slightly higher among smokers for all defects except encephalocele and omphalocele (Figure 3.2b), and was lower for multiple gestation pregnancies for all defects except cleft palate (Figure 3.2c). Among omphalocele and cleft palate cases with multiple birth defects, the risk of termination was higher than for those with isolated defects, but the reverse was true for encephalocele cases; there was no difference for anencephaly and spina bifida cases (Figure 3.2d).

Table 3.1. Risk of live birth, stillbirth, and termination for each birth defect

	Live Birth		Stillbirth		Termination		Total Cases
	N	%	N	%	N	%	N
Defect							
Neural tube defects	1545	70.8	197	9.0	439	20.1	2181
Anencephaly	219	33.4	153	23.3	284	43.3	656
Spina bifida	1141	88.2	30	2.3	122	9.4	1293
Encephalocele	185	79.7	14	6.0	33	14.2	232
Cleft palate	1607	98.5	17	1.0	7	0.4	1631
Omphalocele	381	85.8	36	8.1	27	6.1	444

Results of models accounting for clustering within study centers did not differ from those that did not, but convergence of mixed models could not be achieved for all analyses (Supplemental Tables 3.2 – 3.7); therefore, we present here results from fixed effect logistic regression models. Estimates among live births did not differ from estimates among live births and stillbirths, or among all outcomes for the association of AED use, smoking, or multiple gestation and any examined defect, except anencephaly (Figure 3.3). For anencephaly and smoking, the estimate among live births (aPOR = 0.5, 95% CI: 0.3, 0.8) was lower than among all outcomes (aPOR = 0.7, 95% CI: 0.5, 0.9) and the point estimate among live births was only included as the lower estimate of the 95% CI for all outcomes. For anencephaly and multiple gestation, the POR was twice as high among live births (aPOR = 4.9, 95% CI: 3.2, 7.4) as among all outcomes (aPOR = 2.4, 95% CI: 1.7, 3.4); although the lower bound of the 95% CI among live births just overlapped with the top interval among all outcomes, the point estimate for live births was excluded. No difference in the occurrence or magnitude of the bias was seen in any sensitivity analyses (Supplemental Tables 3.2 – 3.7).

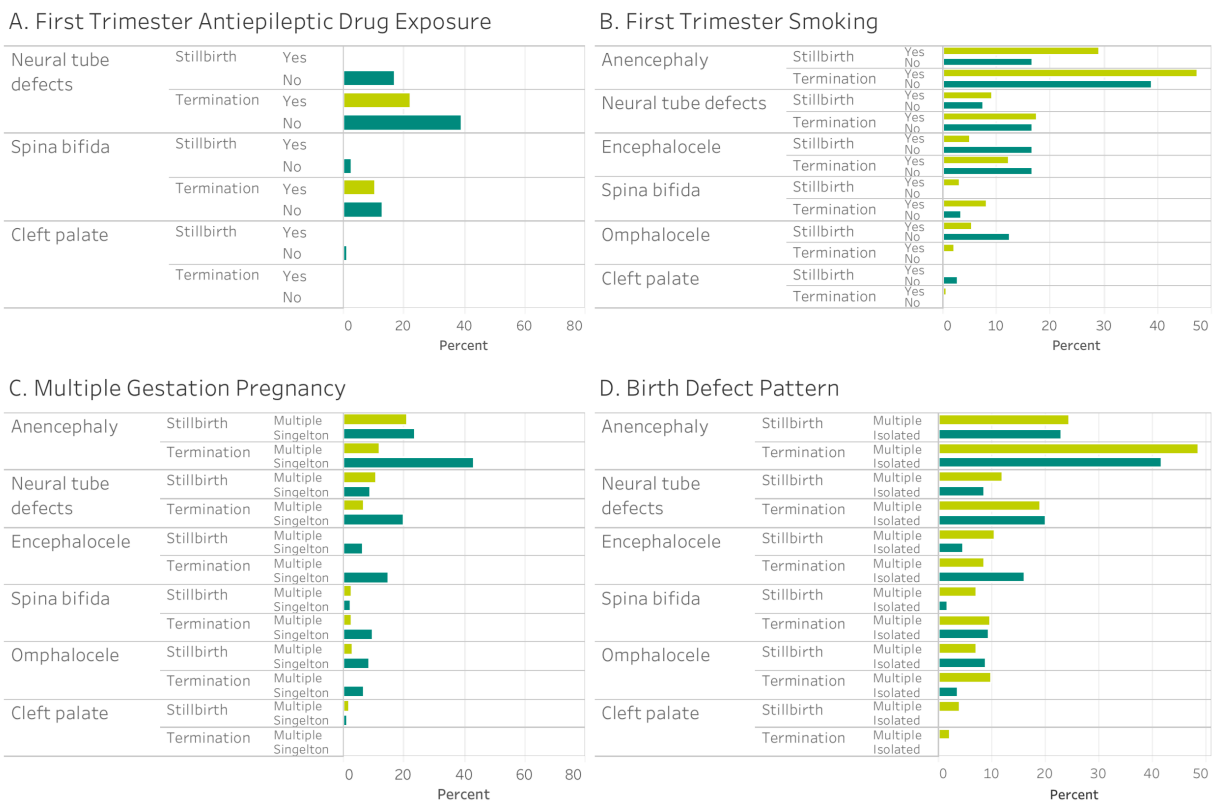


Figure 3.2. Percentage of cases with first trimester exposure to antiepileptic drugs or smoking, part of a multiple gestation pregnancy, or with isolated birth defects by birth defect and pregnancy outcome.

Discussion

Estimated relative odds of birth defects generated among live births did not differ substantially from those generated among all outcomes for most birth defects and exposures we examined. This was true in most circumstances, even when the exposure was associated with the defect and also strongly associated with the prevalence of termination. Only in the most extreme circumstance, here the relationship of multiple gestation to risk of anencephaly, did the estimates among live births differ substantially from those which also included stillbirths and terminations. However, even in this instance, the direction of the relationship was correct but the strength of the association was overstated when restricting to only live births. Restricting

analyses to sub-populations either with lower risks of termination or with more complete capture of birth defect cases did not lead to meaningful differences in estimates.

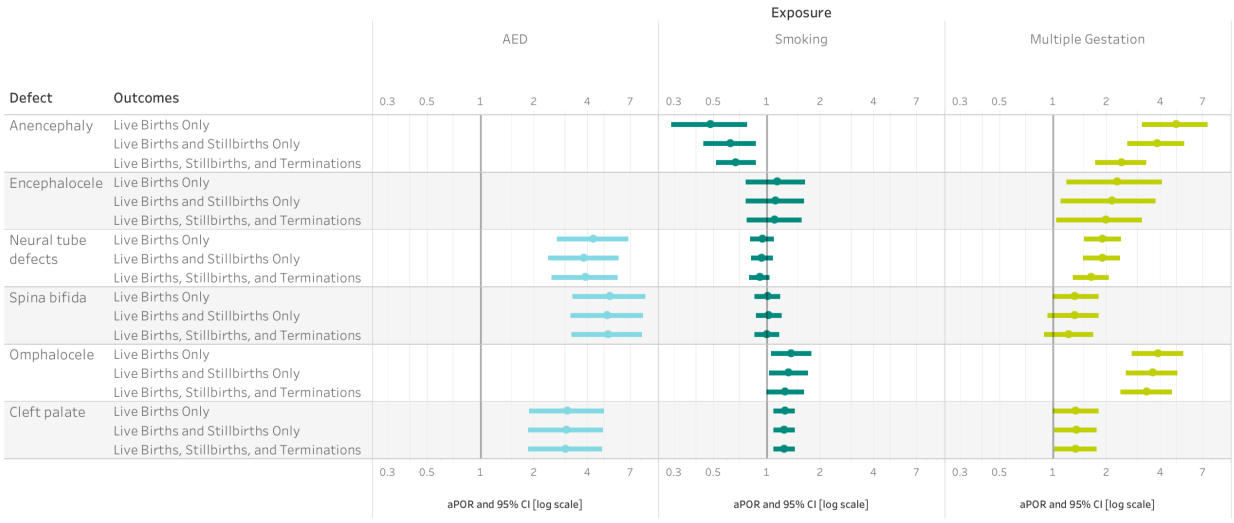


Figure 3.3. Results of adjusted logistic regression models of the relationship of selected birth defects and first trimester maternal AED use, smoking, or multiple gestation pregnancy among live births, live births and stillbirths, and all outcomes. aPOR =, AED = antiepileptic drug. Reference line at aPOR = 1 represents no association. Circles represent point estimate of the adjusted prevalence odds ratio (aPOR), horizontal lines represent the 95% confidence interval (95% CI). Dots below the reference line represent decreased risk; dots above the reference line represent increased risk. Horizontal lines that do not cross the reference line represent results significant at alpha=0.05.

Our results are consistent with previous findings by Cragan and Kourey showing that the occurrence and degree of bias depends on the prevalence of termination for the defect and the relationship of the exposure with termination. [93] However, because observed data contain more sources of error than simulated data, we primarily considered whether estimates differed enough to change the interpretation of the direction and magnitude of association. Thus, results of our study suggest that, although they may suffer from some degree of selection bias as noted by Cragan and Kourey, most etiological studies of birth defects will reach nearly

identical conclusions on the direction and magnitude of association when conducted only among live births.

In contrast to the strong selection bias found by Levy et al., we did not find evidence of selection bias in medication studies of birth defects, here AEDs, were conducted among live births only.[109] Further, even in the instance where we did identify evidence of meaningful selection bias, the level of bias we identified was both much smaller in magnitude and did not change the direction of the association. Thus, our results suggest that selection bias of the magnitude reported in that study is highly unusual and unlikely to affect most studies of birth defects.

Our study also has several limitations. Miscarried cases were not captured due to both technological and practical limitations, thus we were unable to evaluate selection bias due to exclusion of these cases. The protective effect of smoking on anencephaly in our study and others may be an example of this type of section bias if smoking leads to higher rates of miscarriage among anencephaly cases and the true association is null. [35,103,104] Small numbers of live born anencephaly cases exposed to AEDs means that we cannot rule out that substantial selection bias may occur in such analyses. Additionally, although most states included terminated cases of birth defects, it is not possible to know what proportion of all terminated cases were captured by state surveillance systems. If capture of terminated cases differs by exposure status, then results may underestimate the impact of selection bias in studies of birth defects. Although self-reported medication use is subject to errant recall, recall for antiepileptic

drugs has been found to be near-perfect compared to prenatally reported medication use and dispensing records. [113,114] Additionally, self-report of smoking during pregnancy correlates well with biomarker-based estimates of smoking and thus is likely to provide a reasonable estimate of exposure. [115,116] Recall bias is a particular concern in retrospective studies of birth defects cases, however, these concerns appear to be more theoretical than actual, and bias has been shown to manifest only in extreme circumstances. [75]

Our study has several strengths. Examination of selection bias in studies of birth defects within this large, population-based case-control study allowed us to directly examine several different scenarios using observed data rather than relying on assumptions that may not generalize to actual data.[94] Further, we selected exposures with well established relationships to the defects under study, and our results are consistent with previous reports conducted in various settings. [103,104,107,108,110,117-119] Additionally consistent methods of case identification, medical records review, classification, and exposure collection ensure the quality of information does not vary by the pregnancy outcome of birth defect cases in our study. Finally, we selected an exposure and birth defects with varying relationships with termination for birth defect, allowing us to represent a spectrum of possible scenarios in which selection bias may occur, rather than what happens for a single exposure-birth defect combination.

Our results are generalizable only to analyses of specific birth defects. If a study among live births only uses the outcome of all birth defects combined, the degree of selection bias will depend on the strength of the association between the exposure and high mortality defects as

well as the risk of termination for those high mortality birth defects in the underlying study population. Thus, the potential for unpredictable selection bias to provides further reason to avoid using all birth defects as an outcome in etiologic studies.[120] Additionally, our results imply that epidemiological studies of other outcomes with high mortality (e.g., pancreatic cancer) may be vulnerable to selection bias when survival time substantially impacts study participation and is strongly associated with an exposure of interest.

As the relationship between a given exposure and termination for birth defects, as well as the overall risk of termination for a specific birth defect, may change across contexts the magnitude of selection bias is also expected to vary. Our results suggest that in general, studies of birth defects with a high risk of termination, such as anencephaly or limb-body-wall complex, are at risk of substantial selection bias under some circumstances, whereas birth defects with low risk of termination, such as oral clefts and most heart defects, are unlikely to be affected by severe selection bias except in truly extreme circumstances. [30] Further, high risks of termination may lead to too few cases of a specific birth defect for analysis when studies are restricted to live births. Thus, although many studies of birth defects with a high termination risk have a low risk of substantial selection bias when conducted only among live births, precision is greatly improved when cases with all pregnancy outcomes are included. Additional research into predictors of termination for birth defects would aid researchers in evaluating the potential for risk in their analyses.

In conclusion, we found substantial selection bias only when the exposure was strongly associated with the risk of termination among cases of a specific birth defect. When the exposure was not strongly associated with the risk of termination among birth defect cases or when termination was not highly common among cases of a particular defect, we did not find evidence of meaningful selection bias in studies of birth defects restricted to live births only. Inclusion of birth defect cases that undergo termination or are stillborn in studies decreases the risk of selection bias and improves precision of estimates. However, when this is not possible, researchers should consider excluding analyses of high mortality defects when conducting analyses only among live births to minimize the risk biased estimates. Further research into predictors of termination among cases of specific birth defects would aid researchers in conducting assessments of the likelihood of selection bias in studies restricted to live births.

Supplemental Table 3.1. Proportion of pregnancy outcomes for each birth defect by interview status.

	Pregnancy Outcome											
	Live Birth				Stillbirth				Termination			
	Interviewed		Not Interviewed		Interviewed		Not Interviewed		Interviewed		Not Interviewed	
	N	%	N	%	N	%	N	%	N	%	N	%
Defect												
Neural tube defects	1545	70.8	770	59.9	197	9.0	139	10.8	439	20.1	360	28
Anencephaly	219	33.4	163	30.8	153	23.3	109	20.6	284	43.3	244	46.1
Spina bifida	1141	88.2	478	81.2	30	2.3	21	3.6	122	9.4	87	14.8
Encephalocele	185	79.7	131	75.3	14	6.0	10	5.7	33	14.2	32	18.4
Cleft palate	1607	98.5	838	97.6	17	1.0	13	1.5	7	0.4	6	0.7
Omphalocele	381	85.8	189	77.8	36	8.1	32	13.2	27	6.1	22	9.1

Supplemental Table 3.2. Results of main and sensitivity analyses of adjusted logistic regression models of the relationship of selected birth defects and first trimester AED exposure among live births, live births and stillbirths, and all outcomes.

		Included Outcomes					
		Live Births		Live Births and Stillbirths		Live Births, Stillbirths, and Terminations	
Defect	**Sample**	**N Exposed**	**OR (95% CI)**	**N Exposed**	**OR (95% CI)**	**N Exposed**	**OR (95% CI)**
Neural tube defects	Overall	28	4.31 (2.69, 6.75)	28	3.83 (2.4, 6)	36	3.89 (2.53, 5.91)
	Isolated Defect	22	3.93 (2.35, 6.37)	22	3.53 (2.11, 5.71)	28	3.51 (2.19, 5.49)
	Singeltons	28	4.53 (2.82, 7.11)	28	4.02 (2.51, 6.3)	36	4.05 (2.63, 6.16)
	All Outcomes Sample	24	4.46 (2.66, 7.29)	24	3.89 (2.33, 6.37)	32	3.95 (2.48, 6.23)
Anencephaly	Overall	2	NE	2	NE	6	NE
	Isolated Defect	2	NE	2	NE	6	NE
	Singeltons	2	NE	2	NE	6	NE
	All Outcomes Sample	2	NE	2	NE	6	NE
Spina bifida	Overall	26	5.36 (3.3, 8.49)	26	5.2 (3.21, 8.24)	29	5.21 (3.27, 8.13)
	Isolated Defect	20	4.72 (2.76, 7.76)	20	4.61 (2.7, 7.58)	21	4.32 (2.56, 7.05)
	Singeltons	26	5.54 (3.41, 8.78)	26	5.36 (3.3, 8.51)	29	5.35 (3.36, 8.37)
	All Outcomes Sample	22	5.5 (3.23, 9.12)	22	5.3 (3.11, 8.79)	25	5.31 (3.2, 8.66)
Encephalocele	Overall	0	NE	0	NE	1	NE
	Isolated Defect	0	NE	0	NE	1	NE
	Singeltons	0	NE	0	NE	1	NE
	All Outcomes Sample	0	NE	0	NE	1	NE
Cleft palate	Overall	24	3.08 (1.87, 4.92)	24	3.05 (1.86, 4.87)	24	3.03 (1.85, 4.85)
	Isolated Defect	18	2.8 (1.6, 4.68)	18	2.79 (1.6, 4.66)	18	2.79 (1.6, 4.66)
	Singeltons	21	2.77 (1.64, 4.52)	21	2.74 (1.62, 4.47)	21	2.73 (1.62, 4.45)
	All Outcomes Sample	15	2.6 (1.41, 4.57)	15	2.57 (1.39, 4.52)	15	2.56 (1.38, 4.49)
Omphalocele	Overall	2	NE	2	NE	2	NE
	Isolated Defect	1	NE	1	NE	1	NE
	Singeltons	1	NE	1	NE	1	NE
	All Outcomes Sample	0	NE	0	NE	0	NE

[a] AED = antiepileptic drugs. Firth logistic regression models and profile likelihood 95% confidence intervals adjusted for maternal age category, race/ethnicity, and pre-pregnancy exposure to folic acid. Overall sample includes all eligible cases and controls. Isolated Defect sample is restricted to cases with isolated birth defects and all controls. Singeltons sample was restricted to singelton pregnancies. All Outcome Sample excludes cases and controls from sites during times when all outcomes (live births, stillbirths, and terminations) were collected. NE = not estimated.

Supplemental Table 3.3. Results of main and sensitivity analyses of adjusted logistic regression models of the relationship of selected birth defects and multiple gestation pregnancy among live births, live births and stillbirths, and all outcomes.

		Included Outcomes					
		Live Births		Live Births and Stillbirths		Live Births, Stillbirths, and Terminations	
Defect	Sample	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)
Neural tube defects	Overall	79	1.88 (1.45, 2.41)	89	1.89 (1.48, 2.39)	99	1.64 (1.3, 2.05)
	Isolated Defect	69	1.88 (1.43, 2.43)	77	1.88 (1.45, 2.41)	86	1.63 (1.28, 2.07)
	All Outcomes Sample	58	1.84 (1.36, 2.45)	68	1.89 (1.43, 2.48)	78	1.65 (1.27, 2.13)
Anencephaly	Overall	26	4.93 (3.16, 7.42)	35	3.85 (2.63, 5.47)	42	2.44 (1.73, 3.35)
	Isolated Defect	24	5.05 (3.17, 7.71)	31	3.81 (2.54, 5.53)	38	2.48 (1.73, 3.47)
	All Outcomes Sample	19	4.7 (2.79, 7.49)	28	3.85 (2.51, 5.69)	35	2.44 (1.67, 3.46)
Spina bifida	Overall	42	1.33 (0.95, 1.82)	43	1.32 (0.94, 1.8)	45	1.23 (0.89, 1.67)
	Isolated Defect	37	1.32 (0.92, 1.83)	38	1.32 (0.93, 1.84)	39	1.21 (0.85, 1.68)
	All Outcomes Sample	30	1.27 (0.85, 1.83)	31	1.27 (0.85, 1.82)	33	1.19 (0.81, 1.7)
Encephalocele	Overall	11	2.31 (1.19, 4.07)	11	2.15 (1.11, 3.78)	12	1.99 (1.05, 3.41)
	Isolated Defect	8	2.24 (1.02, 4.27)	8	2.13 (0.97, 4.05)	9	1.97 (0.94, 3.63)
	All Outcomes Sample	9	2.53 (1.21, 4.7)	9	2.33 (1.11, 4.31)	10	2.14 (1.06, 3.85)
Cleft palate	Overall	65	1.34 (1.02, 1.75)	66	1.35 (1.02, 1.76)	66	1.34 (1.02, 1.75)
	Isolated Defect	49	1.23 (0.9, 1.65)	49	1.22 (0.89, 1.64)	49	1.22 (0.89, 1.64)
	All Outcomes Sample	47	1.51 (1.09, 2.06)	48	1.53 (1.1, 2.07)	48	1.52 (1.09, 2.06)
Omphalocele	Overall	42	3.91 (2.75, 5.44)	43	3.64 (2.57, 5.03)	43	3.39 (2.4, 4.68)
	Isolated Defect	19	2.84 (1.71, 4.48)	19	2.58 (1.55, 4.05)	19	2.46 (1.48, 3.87)
	All Outcomes Sample	29	4.06 (2.67, 5.98)	30	3.73 (2.47, 5.46)	30	3.42 (2.27, 5)

[a] Firth logistic regression models and profile likelihood 95% confidence intervals adjusted for maternal age category, race/ethnicity, and pre-pregnancy exposure to folic acid. Overall sample includes all eligible cases and controls. Isolated Defect sample is restricted to cases with isolated birth defects and all controls. All Outcome Sample excludes cases and controls from sites during times when all outcomes (live births, stillbirths, and terminations) were collected. If multiple fetuses in a multiple gestation pregnancy had eligible defects the oldest fetus was selected for inclusion.

Supplemental Table 3.4. Results of main and sensitivity analyses of adjusted logistic regression models of the relationship of selected birth defects and a first trimester smoking among live births, live births and stillbirths, and all outcomes.

		Included Outcomes					
		Live Births		Live Births and Stillbirths		Live Births, Stillbirths, and Terminations	
Defect	Sample	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)
Neural tube defects	Overall	245	0.95 (0.81, 1.1)	276	0.94 (0.82, 1.08)	335	0.91 (0.8, 1.03)
	Isolated Defect	210	0.93 (0.79, 1.09)	235	0.92 (0.79, 1.07)	283	0.87 (0.76, 1)
	Singeltons	238	0.98 (0.84, 1.14)	266	0.97 (0.84, 1.12)	323	0.93 (0.81, 1.06)
	All Outcomes Sample	203	0.92 (0.78, 1.08)	234	0.93 (0.79, 1.08)	292	0.89 (0.78, 1.03)
Anencephaly	Overall	18	0.48 (0.29, 0.77)	40	0.62 (0.44, 0.86)	76	0.67 (0.52, 0.86)
	Isolated Defect	16	0.47 (0.27, 0.76)	35	0.6 (0.41, 0.85)	66	0.64 (0.49, 0.83)
	Singeltons	15	0.46 (0.26, 0.77)	34	0.59 (0.4, 0.83)	69	0.66 (0.5, 0.85)
	All Outcomes Sample	16	0.53 (0.3, 0.87)	38	0.68 (0.47, 0.96)	74	0.72 (0.55, 0.92)
Spina bifida	Overall	193	1.01 (0.85, 1.19)	200	1.02 (0.87, 1.21)	218	1 (0.85, 1.17)
	Isolated Defect	169	1 (0.83, 1.19)	173	1 (0.84, 1.19)	186	0.97 (0.81, 1.14)
	Singeltons	189	1.04 (0.88, 1.23)	196	1.05 (0.89, 1.24)	214	1.03 (0.87, 1.2)
	All Outcomes Sample	157	0.95 (0.79, 1.14)	164	0.97 (0.81, 1.16)	181	0.95 (0.8, 1.13)
Encephalocele	Overall	34	1.14 (0.76, 1.65)	36	1.12 (0.76, 1.62)	41	1.11 (0.77, 1.57)
	Isolated Defect	25	1.17 (0.73, 1.81)	27	1.19 (0.76, 1.81)	31	1.13 (0.74, 1.67)
	Singeltons	34	1.23 (0.82, 1.8)	36	1.21 (0.82, 1.76)	40	1.16 (0.8, 1.64)
	All Outcomes Sample	30	1.19 (0.78, 1.78)	32	1.17 (0.77, 1.73)	37	1.16 (0.79, 1.66)
Cleft palate	Overall	343	1.26 (1.1, 1.44)	344	1.25 (1.09, 1.43)	346	1.25 (1.1, 1.43)
	Isolated Defect	281	1.26 (1.09, 1.46)	281	1.26 (1.09, 1.46)	281	1.26 (1.09, 1.46)
	Singeltons	331	1.27 (1.11, 1.45)	332	1.26 (1.1, 1.44)	334	1.26 (1.1, 1.44)
	All Outcomes Sample	256	1.24 (1.06, 1.45)	257	1.23 (1.05, 1.43)	259	1.23 (1.06, 1.43)
Omphalocele	Overall	86	1.37 (1.06, 1.77)	91	1.32 (1.03, 1.69)	93	1.27 (1, 1.62)
	Isolated Defect	45	1.14 (0.8, 1.59)	48	1.1 (0.78, 1.52)	49	1.08 (0.77, 1.48)
	Singeltons	75	1.35 (1.03, 1.77)	79	1.29 (0.98, 1.67)	81	1.23 (0.95, 1.59)
	All Outcomes Sample	70	1.44 (1.08, 1.91)	75	1.39 (1.05, 1.81)	77	1.32 (1, 1.72)

[a] Firth logistic regression models and profile likelihood 95% confidence intervals adjusted for maternal age category, race/ethnicity, and pre-pregnancy exposure to folic acid. Overall sample includes all eligible cases and controls. Isolated Defect sample is restricted to cases with isolated birth defects and all controls. Singeltons sample was restricted to singelton pregnancies. All Outcome Sample excludes cases and controls from sites during times when all outcomes (live births, stillbirths, and terminations) were collected.

Supplemental Table 3.5. Results of main and sensitivity analyses of adjusted mixed effect regression models of the relationship of selected birth defects and multiple gestation pregnancy among live births, live births and stillbirths, and all outcomes.

		Included Outcomes					
		Live Births Only		Live Births and Stillbirths Only		Live Births, Stillbirths, and	
Defect	**Sample**	**N Exposed**	**OR (95% CI)**	**N Exposed**	**OR (95% CI)**	**N Exposed**	**OR (95% CI)**
Neural tube defects	Overall	79	1.94 (1.51, 2.5)	89	NC	99	1.73 (1.37, 2.19)
	Isolated Defect	69	1.93 (1.48, 2.52)	77	NC	86	1.73 (1.35, 2.21)
	All Outcomes Sample	58	1.85 (1.37, 2.48)	68	1.9 (1.44, 2.51)	78	NC
Anencephaly	Overall	26	5 (3.25, 7.69)	35	NC	42	2.63 (1.87, 3.68)
	Isolated Defect	24	5.07 (3.24, 7.94)	31	NC	38	2.68 (1.88, 3.81)
	All Outcomes Sample	19	4.72 (2.87, 7.77)	28	3.88 (2.57, 5.87)	35	2.44 (1.69, 3.52)
Spina bifida	Overall	42	1.36 (0.98, 1.89)	43	NC	45	1.27 (0.92, 1.75)
	Isolated Defect	37	1.35 (0.95, 1.91)	38	NC	39	1.25 (0.89, 1.75)
	All Outcomes Sample	30	1.26 (0.86, 1.86)	31	1.26 (0.86, 1.85)	33	1.18 (0.81, 1.71)
Encephalocele	Overall	11	NC	11	2.07 (1.11, 3.86)	12	NC
	Isolated Defect	8	2.12 (1.03, 4.39)	8	2.01 (0.98, 4.16)	9	1.88 (0.95, 3.72)
	All Outcomes Sample	9	2.42 (1.22, 4.82)	9	2.22 (1.12, 4.41)	10	2.05 (1.07, 3.93)
Cleft palate	Overall	65	1.34 (1.02, 1.75)	66	1.34 (1.02, 1.76)	66	1.34 (1.02, 1.75)
	Isolated Defect	49	1.21 (0.89, 1.65)	49	1.21 (0.89, 1.65)	49	1.21 (0.89, 1.65)
	All Outcomes Sample	47	1.52 (1.1, 2.1)	48	1.53 (1.12, 2.11)	48	1.52 (1.11, 2.09)
Omphalocele	Overall	42	3.89 (2.76, 5.48)	43	3.62 (2.58, 5.07)	43	3.39 (2.42, 4.74)
	Isolated Defect	19	2.78 (1.71, 4.52)	19	2.52 (1.56, 4.09)	19	2.41 (1.49, 3.91)
	All Outcomes Sample	29	4.05 (2.7, 6.08)	30	3.72 (2.49, 5.54)	30	3.42 (2.3, 5.1)

[a] Mixed effect regression models and 95% confidence intervals with a random intercept for study center adjusted for fixed effects of maternal age category, race/ethnicity, and pre-pregnancy exposure to folic acid. Overall sample includes all eligible cases and controls. Isolated Defect sample is restricted to cases with isolated birth defects and all controls. All Outcome Sample excludes cases and controls from sites during times when all outcomes (live births, stillbirths, and terminations) were collected. If multiple fetuses in a multiple gestation pregnancy had eligible defects the oldest fetus was selected for inclusion. NC = no convergence.

Supplemental Table 3.6 Results of main and sensitivity analyses of adjusted mixed effect regression models of the relationship of selected birth defects and first trimester exposure to antiepileptic drugs among live births, live births and stillbirths, and all outcomes.

		Included Outcomes					
		Live Births Only		Live Births and Stillbirths Only		Live Births, Stillbirths, and Terminations	
Defect	Sample	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)
Neural tube defects	Overall	28	4.42 (2.79, 7.03)	28	NC	36	4.02 (2.62, 6.18)
	Isolated Defect	22	3.99 (2.42, 6.60)	22	NC	28	3.59 (2.25, 5.71)
	Singeltons	28	4.66 (2.92, 7.41)	28	NC	36	4.19 (2.72, 6.45)
	All Outcomes Sample	24	4.56 (2.75, 7.58)	24	4.01 (2.41, 6.65)	32	NC
Anencephaly	Overall	2	NE	2	NE	6	NE
	Isolated Defect	2	NE	2	NE	6	NE
	Singeltons	2	NE	2	NE	6	NE
	All Outcomes Sample	2	NE	2	NE	6	NE
Spina bifida	Overall	26	5.52 (3.43, 8.89)	26	NC	29	5.37 (3.39, 8.51)
	Isolated Defect	20	4.80 (2.85, 8.08)	20	NC	21	4.39 (2.63, 7.33)
	Singeltons	26	NC	26	NC	29	5.52 (3.48, 8.76)
	All Outcomes Sample	22	5.62 (3.33, 9.49)	22	5.41 (3.21, 9.13)	25	5.43 (3.29, 8.96)
Encephalocele	Overall	0	NE	0	NE	1	NE
	Isolated Defect	0	NE	0	NE	1	NE
	Singeltons	0	NE	0	NE	1	NE
	All Outcomes Sample	0	NE	0	NE	1	NE
Cleft palate	Overall	24	3.03 (1.87, 4.93)	24	3.00 (1.85, 4.88)	24	2.99 (1.84, 4.86)
	Isolated Defect	18	2.75 (1.61, 4.73)	18	2.75 (1.60, 4.72)	18	2.75 (1.6, 4.72)
	Singeltons	21	2.70 (1.62, 4.51)	21	2.68 (1.61, 4.46)	21	2.66 (1.6, 4.44)
	All Outcomes Sample	15	2.59 (1.43, 4.71)	15	2.57 (1.41, 4.65)	15	2.55 (1.41, 4.62)
Omphalocele	Overall	2	NE	2	NE	2	NE
	Isolated Defect	1	NE	1	NE	1	NE
	Singeltons	1	NE	1	NE	1	NE
	All Outcomes Sample	0	NE	0	NE	0	NE

a Mixed effect regression models and 95% confidence intervals with a random intercept for study center adjusted for fixed effects of maternal age category, race/ethnicity, and pre-pregnancy exposure to folic acid. Overall sample includes all eligible cases and controls. Isolated Defect sample is restricted to cases with isolated birth defects and all controls. All Outcome Sample excludes cases and controls from sites during times when all outcomes (live births, stillbirths, and terminations) were collected. If multiple fetuses in a multiple gestation pregnancy had eligible defects the oldest fetus was selected for inclusion. NC = no convergence. NE = Not Estimated

Supplemental Table 3.7 Results of main and sensitivity analyses of adjusted mixed effect regression models of the relationship of selected birth defects and first trimester maternal smoking among live births, live births and stillbirths, and all outcomes.

		Included Outcomes					
		Live Births Only		Live Births and Stillbirths Only		Live Births, Stillbirths, and Terminations	
Defect	Sample	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)	N Exposed	OR (95% CI)
Neural tube defects	Overall	245	0.97 (0.83, 1.12)	276	NC	335	0.93 (0.82, 1.07)
	Isolated Defect	210	0.94 (0.80, 1.10)	235	NC	283	0.89 (0.77, 1.03)
	Singeltons	238	NC	266	NC	323	NC
	All Outcomes Sample	203	0.93 (0.79, 1.1)	234	0.94 (0.80, 1.10)	292	NC
Anencephaly	Overall	18	0.47 (0.29, 0.77)	40	NC	76	0.69 (0.53, 0.88)
	Isolated Defect	16	NC	35	0.59 (0.41, 0.85)	66	0.65 (0.50, 0.86)
	Singeltons	15	NC	34	NC	69	NC
	All Outcomes Sample	16	0.51 (0.3, 0.87)	38	0.67 (0.47, 0.96)	74	0.72 (0.56, 0.94)
Spina bifida	Overall	193	NC	200	NC	218	1.03 (0.88, 1.21)
	Isolated Defect	169	1.01 (0.84, 1.21)	173	NC	186	0.98 (0.82, 1.16)
	Singeltons	189	NC	196	NC	214	NC
	All Outcomes Sample	157	0.97 (0.81, 1.18)	164	0.99 (0.83, 1.19)	181	0.97 (0.81, 1.15)
Encephalocele	Overall	34	1.12 (0.76, 1.66)	36	1.11 (0.76, 1.62)	41	1.11 (0.78, 1.58)
	Isolated Defect	25	1.16 (0.74, 1.82)	27	1.17 (0.76, 1.81)	31	1.12 (0.75, 1.68)
	Singeltons	34	1.22 (0.82, 1.81)	36	NC	40	NC
	All Outcomes Sample	30	1.18 (0.78, 1.79)	32	1.16 (0.78, 1.74)	37	1.15 (0.79, 1.67)
Cleft palate	Overall	343	1.28 (1.11, 1.46)	344	1.27 (1.11, 1.45)	346	1.27 (1.11, 1.45)
	Isolated Defect	281	1.27 (1.10, 1.48)	281	1.27 (1.10, 1.47)	281	1.27 (1.10, 1.47)
	Singeltons	331	1.28 (1.12, 1.47)	332	NC	334	NC
	All Outcomes Sample	256	1.26 (1.08, 1.47)	257	1.25 (1.07, 1.46)	259	1.25 (1.07, 1.46)
Omphalocele	Overall	86	1.38 (1.07, 1.78)	91	1.33 (1.04, 1.70)	93	1.28 (1.00, 1.63)
	Isolated Defect	45	1.13 (0.80, 1.59)	48	1.09 (0.79, 1.52)	49	1.07 (0.77, 1.49)
	Singeltons	75	1.35 (1.03, 1.78)	79	NC	81	NC
	All Outcomes Sample	70	1.45 (1.09, 1.93)	75	1.4 (1.06, 1.84)	77	1.33 (1.02, 1.74)

Mixed effect regression models and 95% confidence intervals with a random intercept for study center adjusted for fixed effects of maternal age category, race/ethnicity, and pre-pregnancy exposure to folic acid. Overall sample includes all eligible cases and controls. Isolated Defect sample is restricted to cases with isolated birth defects and all controls. All Outcome Sample excludes cases and controls from sites during times when all outcomes (live births, stillbirths, and terminations) were collected. If multiple fetuses in a multiple gestation pregnancy had eligible defects the oldest fetus was selected for inclusion. NC = no convergence. NE = Not Estimated

Conclusions

Although the potential for competing risks to bias studies of perinatal mortality and birth defects has been previously noted, few studies have examined the full range of possible competing events or the impact of competing risks in real world data. We found that competing risks result in varied levels of bias in studies of perinatal mortality and birth defects, depending on the specific situation of interest. Here for each chapter we review the main findings, the implication our results, and future research to build off of these results.

Chapter 1

The results of chapter 1 highlight the heterogeneity hiding in standard definitions of perinatal and neonatal mortality. We first quantified the degree to which the risk of mortality is higher on the day of birth than at any other point in the first week of life, independent of gestational age at birth. Second, we found that although demographic characteristics of mothers did not vary by timing of perinatal mortality, delivery route and multiple gestation pregnancies demonstrated different risk patterns than other possible predictors. Finally, we found that the major underlying causes of death differed substantially by age at perinatal death, especially during the neonatal period.

Taken together, our results suggest that standard definitions of perinatal and neonatal mortality obscure the differences within these categories, in particular that first day neonatal deaths differ from later neonatal deaths. The deviation in age at perinatal mortality risk patterns for multiple gestation pregnancies and by delivery route suggests that medical interventions may act as a competing risk for stillbirth. However, we were unable to examine this directly due to the limitations of vital statistics data. Further, the substantial etiologic

heterogeneity in cause of death by age at perinatal death identified suggests that the current categorizes used to report and study mortality in this age group may mask important risk factors because the causes of death for the group as a whole are not representative of the individual groups comprising the combined categories of perinatal death and neonatal death.

While some of the results of our study are consistent with previous analyses, as this is the first study to examine etiology of first day neonatal deaths in a high-income country, further research is needed to determine if our findings on cause of death by age at perinatal death are replicated in other countries and in data sources with more detailed information on cause of death. If they are replicated, changes to official definitions of perinatal mortality and research guidelines should be considered. Nonetheless, we suggest that researchers consider reporting and examining first day neonatal deaths separately from later neonatal deaths in addition to reporting conventional definitions of neonatal mortality and avoid use of perinatal death as the only outcome in etiological studies. Future studies should explore differences in characteristics and etiology by timing of perinatal death in both developed and developing countries and directly explore when medical interventions act as a competing risk for stillbirth.

Chapter 2

The results of our analysis detailed in Chapter 2 identified that fetuses with major, non-syndromic birth defects have an elevated risk of stillbirth compared to the general US population and further found that stillbirth the major form of near delivery perinatal mortality for many fetuses with these birth defects. Analyses stratified by birth defect pattern and most severe defect found that the risk of stillbirth and termination of pregnancy increased with the presence of multiple birth defects and increasing severity, suggesting that termination of

fetuses with birth defects selectively removes high risk fetuses from the pool at risk of stillbirth, thus leading to the “depletion of succeptibles”. Termination-corrected minimum and maximum risk estimates suggest that the observed risk of stillbirth in the presence of terminations is more likely to be underestimated than overestimated. We further observed that the difference in observed estimates compared to the termination-corrected estimates was unrelated to the magnitude of the observed stillbirth risk. Thus, some estimates with the lowest observed risks of stillbirth had some of the highest maximum termination-corrected risks of stillbirth, demonstrating the importance of considering potential bias introduced by the competing event of termination of pregnancy when studying risks of perinatal mortality, particularly in the setting of major birth defects.

Our study represents the largest study to date on the risk of stillbirth among fetuses with specific non-syndromic birth defects, with over 10,000 more cases than the largest previously published study. As a result, our study provides the most stable estimates published to date and is the only study to provide estimates of stillbirth risk for fetuses with multiple birth defects by their most severe defect and various phenotypes of specific birth defects; to examine combined mortality due to termination, stillbirth, and neonatal death on the day of birth; and to estimate minimum and maximum termination-corrected stillbirth risk estimates. Additionally, our study advances the methods for studying stillbirth and other forms of perinatal mortality among infants with major birth defects through the multiple birth defect analyses, combined mortality analyses, and termination-corrected risk estimates. In particular,

combined mortality estimates and termination-corrected estimates may be useful for studying risks of perinatal mortality even in the context of fetuses without birth defects.

Thus, chapter 2 provides estimates that are of immediate assistance to physicians caring for patients with prenatally diagnosed birth defects as a basis for providing evidence-based counseling on the mortality risks during pregnancy and immediately after delivery. This work also has important implications for policy makers and researchers as it highlights the burden of stillbirth among fetuses with birth defects and the need for further research into modifiable risk factors for stillbirth in this population. Given that approximately 15 to 20% of stillborn fetuses have major birth defects, efforts to reduce risks in this population are needed to decrease the overall rate of stillbirth. Finally, this work introduces a simple method for estimating the boundaries of possible perinatal mortality risks after accounting for terminations of pregnancy which can improve interpretation and comparability of studies, as well as provide more accurate estimates of risks for counseling parents.

Chapter 3

In Chapter 3 we evaluated selection bias in studies of risk factors for birth defects which are conducted among live births only. Using a set of birth defects with a range of risk for prenatal loss (stillbirth and termination) and a set of established risk factors with a range of strength of association with both birth defects and risk of prenatal loss, we examine most of the possible combinations of associations (e.g., high mortality defect, strong association with risk factor, low association of risk factor with prenatal loss) likely to be found in birth defects research. Our analyses found little evidence for substantial selection bias in risk factor studies of birth defects, even for most analyses of defects with a high risk of prenatal loss. However, when both the

exposure and the birth defect were very strongly associated with prenatal loss the magnitude of the association was substantially biased away from the null when evaluated among live births only. Yet, even in this situation the conclusion that an association exists between the exposure and the outcome would have been correct. Thus, we conclude that most risk factor studies for birth defects conducted only among live births will not suffer from selection bias sufficient to alter the interpretation of the results. Nonetheless, when possible cases ending in termination or stillbirth should be included. This is particularly important for defects with a very high risk of prenatal loss in order to ensure enough observations to generate statistically stable estimates.

These results offer important reassurance that the results of risk factor studies for specific birth defects conducted among live births only are unlikely to suffer from selection bias that is strong enough to change the overall interpretation of the magnitude and direction of risk. Further, that results among National Birth Defects Prevention Study centers that collected all pregnancy outcomes did not differ from results among all centers, some of which did not collect terminated or stillborn cases, provides assurance that results from this important study are robust. Thus, these results aid researchers in the interpretation of previously conducted studies and in the design of new studies. Research into the associations of risk factors of interest with risk of termination and stillbirth among fetuses with birth defects would further aid researchers in understanding when significant selection bias may occur.

Conclusion

Thus, in conclusion, we found: first, that the risk of stillbirth and first day mortality were higher than later neonatal deaths at all gestational ages and that there is substantial heterogeneity in

the causes of perinatal deaths by age at death; second, that fetuses with non-syndromic major birth defects have elevated risks of stillbirth and that simple analyses can quantify bias due to termination of pregnancy; finally, we found that studies conducted among live births only were not meaningfully biased in most situations. The results of each of these analyses have important implications for research, policy, and clinical practice.

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