

University of Nevada, Reno

Birth Defects: Interpregnancy Interval and Spatial Epidemiology

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor
of Philosophy in Environmental Science and Health

by

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Abstract

Birth defects are an important public health issue because they are the leading cause of infant mortality, causing one in every five infant deaths. Multiple factors cause some birth defects, however, the etiology of nearly half of all birth defects is unknown. Several factors affect birth defects surveillance in the United States (US) such as birth defects case ascertainment methods, pregnancy outcomes and the nomenclature used for coding birth defects. We reviewed literature on the challenges of birth defects surveillance in the US. Then we implemented two epidemiological studies using data from Nevada Birth Outcomes Monitoring System, a statewide population-based birth defects surveillance system and live birth certificate data for the period 2005-2011 to investigate the relationship between interpregnancy and birth defects. In addition, we examined the spatial patterns of birth defects and used a spatial scan statistic to identify spatial birth defects clusters at ZIP Code level. After adjusting for demographics and other confounders, the results showed that a long interpregnancy interval was independently associated with birth defects. Other independent risk factors for birth defects were male infants, advancing maternal age, Black women, three or more previous births, smoking, and prescription drug use. Additionally, it was clear that birth defects prevalence varies widely within Nevada counties. Furthermore, a statistically significant ($p < .0001$) cluster of birth defects was identified at ZIP Code level in Clark County. The results highlight the need for maternal and child health programs and health care providers to include interpregnancy interval in the campaign of improving birth outcomes. In addition, further investigations at neighborhood level are needed to elucidate these disparities in order to guide targeted birth defects prevention efforts.

Key words: Birth Defects, Interpregnancy Interval, Spatial Epidemiology

Dedication

To our children Katumbi, Mwiti, Mwendwa, and Mwenda
and to all the children with birth defects

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Dissertation Outline

This dissertation consists of three distinct studies which used different methodologies; therefore, the methods for each study are in the respective studies. The following chapters present the results of the epidemiological study on interpregnancy interval and birth defects; and the use of Geographical Information System (GIS) and spatial scan statistic. Chapter one provides a broad introduction to the study. Chapter two is a review of literature focusing on the challenges facing birth defects surveillance in the United States and the implications of the implementation of International Classification of Diseases, Tenth Revision, and Clinical Modification (ICD-CM-10) in October 2015. Chapter three investigates the relationship between interpregnancy interval and birth defects. Chapter four presents the study on spatial patterns and clusters of birth defects at Zone Improvement Plan (ZIP) Code level. Finally, chapter five summarizes the study findings and offers recommendations for birth defects prevention and future research.

Chapter 1: Introduction

1.1 Background

Birth defects are an important public health issue because they are the leading cause of infant mortality, causing one in every five infant deaths.¹ Morbidity and mortality among children with birth defects is high, and the emotional and health care costs associated with birth defects are enormous. In 2004, billed costs for hospitalizations for birth defects in the United States (US) was estimated to be 2.6 billion dollars.² In addition, birth defects affect the family and community, and some birth defects may lead to life-long disability. Furthermore, several factors affect birth defects surveillance in the US such as birth defects case ascertainment methods, pregnancy outcomes (live births only, live births and stillbirths, and all pregnancy outcomes), and the nomenclature used for coding birth defects.

Several studies on the etiology of birth defects suggest that multiple factors cause some birth defects.³⁻⁵ These factors include genetics,^{5,6} environmental factors,³⁻⁵ and gene-environment interactions.⁷ However, in spite of several decades of birth defects research, the etiology of nearly half of all birth defects is still unknown.⁵

Interpregnancy interval, the period between a live birth and subsequent conception, is an important risk factor for various adverse birth outcomes including birth defects. However, few studies have examined the association between interpregnancy interval and birth defects. In addition, a person's neighborhood is an important determinant of birth outcomes,^{8,9} including birth defects. Yet, few studies have conducted neighborhood investigations at the Zone Improvement Plan (ZIP) Code¹⁰ level to identify spatial pattern of birth defects and areas of increased burden.¹¹⁻¹⁴

Therefore, the purpose of this epidemiological study was to: a) investigate the relationship between interpregnancy interval and birth defects, and 2) examine the

spatial pattern of birth defects, and identify neighborhoods at ZIP Code level that may have birth defects clusters using a spatial scan statistic.¹⁵

Approval for this study was obtained from the Institutional Review Board at the University of Nevada, Reno.

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**Chapter 2: Birth Defects Surveillance in the United States:
Challenges and Implications of International Classification of
Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)
Implementation**

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2.1 Abstract

Major birth defects are an important public health issue because they are the leading cause of infant mortality. The most common birth defects are congenital heart defects, neural tube defects, and Down syndrome. Birth defects surveillance guides policy development and provides data for prevalence estimates, epidemiologic research, planning, and prevention. Several factors influence birth defects surveillance in the United States. These include case ascertainment methods, pregnancy outcomes, and nomenclature used for coding birth defects. In 2015, the nomenclature used by most birth defects surveillance programs in the US will change from ICD-9-CM to ICD-10-CM. This change will have implications on birth defects surveillance, prevalence estimates, and tracking birth defects trends.

Key words: Birth defects surveillance; ICD-10-CM; ICD-9-CM; BPA

2.2 Introduction

Birth defects are an important public health issue because they are the leading cause of infant mortality in the United States of America (USA) causing one in every five infant deaths.¹ In USA, birth defects affect about 3% of births.² Worldwide, birth defects are the fourth leading cause of neonatal deaths.³ An estimated 7.9 million children (6% of births) are born with a major birth defect every year globally.⁴ In 2010, about 9% of all neonatal deaths in 193 countries around the world were due to birth defects.³ Morbidity and mortality among children with birth defects are high and the health care costs are enormous. In 2004, billed costs for hospitalizations for birth defects in USA were estimated to be 2.6 billion dollars.⁵

The most common birth defects are congenital heart defects,^{3,6,7} neural tube defects, and Down syndrome.³ Several studies on the etiology of birth defects suggest that multiple factors cause some birth defects.^{8,9} These factors include genetics,¹⁰ environmental factors,^{8,9} and gene-environment interactions.¹¹ Despite several decades of birth defects research, the causes of nearly half of all birth defects are still unknown.³

Birth defects surveillance provides data for prevalence estimates, epidemiologic research, planning, and prevention and it guides policy development.¹² However, birth defects surveillance faces several challenges that make it complex to estimate national and international prevalence. These include case ascertainment methods, pregnancy outcomes, and nomenclature used by various birth defects surveillance programs.

2.3 Birth Defects Surveillance

Public health surveillance is the systematic and continuous collection, management, analysis, and interpretation of data which is disseminated in a timely manner to individuals working in public health.¹³ Interest in birth defects surveillance was sparked by the thalidomide tragedy of the 1960s when an increased number of children

with limb deformities were born in Germany and other parts of the world where thalidomide was used for treating nausea and morning sickness among pregnant women.¹⁴

Following the thalidomide tragedy, the Metropolitan Atlanta Congenital Defects Program (MACDP),¹⁵ the first population-based birth defects surveillance program in USA, was established by Centers for Disease Control and Prevention (CDC) in 1967¹⁵ to conduct birth defects surveillance. The Birth Defects Prevention Act of 1998 helped accelerate the establishment of birth defects surveillance programs in other states. Presently, most states have an established birth defects surveillance program, even though a few states are yet to implement such a program.¹⁶

The National Birth Defects Prevention Network (NBDPN),¹⁷ a volunteer-based organization which works in collaboration with CDC, was established in 1997. NBDPN's goals are to maintain a national network of state and population-based birth defects surveillance programs and to be involved in birth defects research and prevention. The NBDPN has done a tremendous job of improving the uniformity of birth defects surveillance in USA and also provides technical assistance to states whenever needed. In 2004, NBDPN published guidelines for conducting birth defects surveillance.¹⁸

In 2013, there were 43 population-based birth defects surveillance programs in USA and 41 of these programs reported data on select birth defects to NBDPN.^{16,19} This is almost two-thirds the number of programs that reported select birth defects data to NBDPN in 2000.¹² CDC's National Center on Birth Defects and Developmental Disabilities funds 14 of these state-based birth defects surveillance programs. In addition, CDC also funds the Centers for Birth Defects Research and Prevention which is involved in large birth defects studies, such as the multi-state National Birth Defects Prevention Study (NBDPS) conducted from 1997 to 2013. The Birth Defects Study to

Evaluate Pregnancy Outcomes, a multi-state birth defect study, will build on NBDPS. It started data collection in January 2014.

Global birth defects surveillance and research are conducted by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), a voluntary nonprofit organization affiliated with World Health Organization (WHO) that was established in 1974.²⁰ Currently, there are 45 birth defects surveillance programs worldwide that are members of ICBDSR, and membership is by program and not country. Countries with more than one birth defect surveillance program can have several programs as members of ICBDSR. The majority of the member programs are from Europe (15 countries), Asia (5 countries), North America (3 countries), South America (3 countries), and Australia (2 countries).²¹ USA has six birth defects surveillance programs that are members of ICBDSR. These include Arkansas, Atlanta, California, Iowa, Texas, and Utah. African countries are yet to have birth defects surveillance programs join ICBDSR.

2.3.1 Case ascertainment. Physical examination of infants provides the best assessment of birth defects; however, this is very expensive and most birth defects surveillance programs cannot afford this resource intensive method. Conversely, birth defects are underreported in birth certificates; therefore this method of surveillance does not capture all cases of birth defects in a given population.¹⁸ Consequently, states use various case ascertainment methods for birth defects surveillance in order to capture all potential birth defects cases in their population of interest. The method used by each state depends on the program's purpose, the state's birth defects legislation, resources available, collaboration with the community, and partners involved in birth defects surveillance.¹⁶

Birth defects data can be obtained from multiple sources which provide the necessary information for each case. Birth and pediatric hospitals can be used to obtain a majority of the cases. However, other data sources, such as laboratories and outpatient clinics, may provide birth defects data. Case ascertainment methods used by birth defects programs include active, passive, and active-passive (hybrid).

Active case ascertainment is the preferred method for birth defects surveillance because program staff go out to find birth defects cases from hospitals, clinics, and other health care facilities.¹⁸ This method is resource-intensive but provides the most accurate information in a timely manner.²² In addition, programs that use active surveillance generally provide the highest birth defects prevalence estimates because they are more comprehensive in capturing all possible birth defects cases.¹² Often, birth defects that are ascertained actively are usually confirmed and not probable.²³

In passive case ascertainment, the birth defects surveillance program receives reports of cases of infants with birth defects from different data sources such as hospitals, clinics, and other sources. These sources may be voluntary or are mandated by law.¹⁴ The completeness and accuracy of data may be varied for programs that use this method because the quality of data is dependent on the data source.¹⁸ This method is inexpensive because program staff do not have to make contacts with hospitals or other birth defects reporting sources. However, since different institutions report data, data quality and timeliness may be an issue.²² In addition, since verification of reported cases is not done, some of the birth defects may be probable and not confirmed.²³

Some birth defects surveillance programs use active-passive case ascertainment, a hybrid approach, whereby birth defects cases are reported to them by hospitals and other reporting facilities just as in passive surveillance. However, program staff uses various methods to ascertain the cases from these sources.¹⁸ For example, a

certain percentage of all reported birth defects cases or some specific birth defects can be actively ascertained.²⁴ This method improves the data quality because false positive cases can be easily identified.

In 2013, 43 population-based birth defects surveillance programs reported data to NBDPN; of these, 17 (40%), 13 (30%) and 13 (30%) used active case finding, passive case finding, and passive case finding with active case ascertainment, respectively.²⁵

Data from the three case ascertainment methods may be comparable; however, birth defects surveillance programs that use passive case ascertainment need to incorporate various measures to ensure that the birth defects reports they receive are an accurate representation of birth defects in their targeted population.¹⁸ This may be achieved by linking data for reported cases to hospital discharge data to capture infants with birth defects discharged from hospitals. Hospital discharge data has been shown to be a valuable source of birth defects cases even though it does not identify all infants with birth defects.^{23,26} It may be difficult to capture infants born at home, especially if they do not seek medical care or if they seek medical care outside the birth defects program catchment area or in another state. It would be ideal for states to have data sharing agreements for birth defects surveillance such that, irrespective of where a child with a birth defect seeks treatment, the information will be passed on to the child's resident state's birth defects surveillance program. Most states already have data sharing agreements for cancer and new birth cases and the same idea could easily be done for surveillance of birth defects. However, it is unclear how many states or birth defects surveillance programs have data sharing agreements in place. NBDPN mainly facilitates most of the multistate collaborative birth defects research projects.

Researchers linked data for select birth defects from two independent birth defects surveillance programs in Florida that used active and passive case

ascertainment methods respectively.²³ The geographic area for the two surveillance systems overlapped, and the goal was to evaluate the sensitivity and completeness of the active and passive case ascertainment. They reported that the ability of the passive birth defects surveillance was limited and dependent on the birth defects codes. For example, the ability to identify cases of anencephaly was a challenge because most infants with the defect are stillborn or die shortly after birth; thus the hospital rarely created a record for such a case. In addition, they reported that the enhanced system that used case ascertainment was able to rule out false positives in the passive surveillance after medical records review. Thus, passive surveillance had a reduced positive value.

Another study used 2006-2010 nationwide Down Syndrome data reported to NBDPN by 41 population-based birth defects surveillance programs.¹⁶ The prevalence estimates ranged from 10.2 to 20.0 per 10,000 births and 6.9 to 20.6 per 10,000 births for programs that used active and passive case ascertainment methods, respectively (table 1).

2.3.2 Pregnancy outcomes. Population-based birth defects surveillance programs include live births only, live births and stillbirths only, and live births, stillbirths, and elective terminations (all pregnancy outcomes) in their birth defects case definition. The pregnancy outcome included by a birth defects surveillance program depends on the purpose, resources available, and access to the pregnancy outcome information.¹⁸ Birth defects programs that include all pregnancy outcomes provide the most accurate prevalence estimates. Of the 41 birth defects surveillance programs in USA that reported data to NBDPN in 2013, 29% reported data from live births only, 42% reported data from live births and stillbirths, and 29% reported data from all pregnancy outcomes.¹⁶

Ethen and Canfield compared birth defects prevalence rates for elective terminations of any gestation and elective terminations of at least 20-week gestation or 500-gram birth weight.²⁷ They reported an increase of 5% or more for the following birth defects: anencephaly, spina bifida without anencephaly, encephalocele, Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18), Down syndrome (trisomy 21), omphalocele, gastroschisis, and anophthalmia.²⁷ A recent study using birth defects data from MACDP reported Down syndrome prevalence of 16.3 per 10,000 live births among all pregnancy outcomes and 11.5 per 10,000 lives among live births only.²⁸ In addition, another study also using birth defects data from MACDP reported a prevalence of Patau syndrome (trisomy 13) of 0.63 per 10,000 live births among live births only and 1.57 per 10,000 live births among all pregnancy outcomes.²⁹ Furthermore, they also reported a prevalence of Edwards syndrome (trisomy 18) of 1.16 per 10,000 live births among live births only and 4.01 per 10,000 live births among all pregnancy outcomes. Researchers using data from 41 population-based surveillance programs that reported data to NBDPN in 2013 found a higher prevalence of Down syndrome when all pregnancy outcomes were included compared to prevalence estimates from live births only¹⁶ (table 2).

It is imperative that prevalence estimates that use data from live births only be interpreted cautiously because the above studies clearly demonstrate that including all pregnancy outcomes provides the most accurate birth defects prevalence estimates. In addition, elective terminations should include cases of any gestation and not be limited to those equal to or greater than 20-week gestation. Moreover, there is need for a general consensus on whether elective terminations will include all cases irrespective of gestation age and birth weight or include elective terminations of at least 20 weeks gestation and birth weight of 500 grams.^{12,27} This may be a challenge for some birth

defects surveillance programs because including still births and elective terminations may involve active case ascertainment which is resource intensive and it engages more partners in birth defects surveillance, such as clinics that conduct elective terminations. Additionally, the added dimension of including all birth outcomes in the birth defects surveillance may not align with the purpose of some birth defects surveillance programs.

Medical advances have made it possible for prenatal screening and detection of birth defects during pregnancy. Most prenatal procedures occur in outpatient settings and active surveillance would be the best method for prenatally diagnosed birth defects because of the follow up needed with the outpatient clinics to abstract cases of birth defects. Birth defects surveillance programs that use passive surveillance and rely on hospitals and other reporting facilities would be faced with the challenge of receiving reports of prenatally diagnosed birth defects. Cragan and Gilboa conducted a study using data from outpatient prenatal diagnostic clinics to estimate birth defects prevalence.³⁰ They noted an increase in the prevalence of specific birth defects even though the increase in prevalence of all birth defects was small. They also reported that the prenatal diagnosis records had birth defects categorized as definite or possible which posed a challenge on whether to include either definite or possible cases in the prevalence estimates. They reported separate prevalence estimates with and without possible cases. Prenatally diagnosed birth defects in population-based birth defects surveillance is an evolving field where guidelines are needed.

2.3.3 Nomenclature/Disease classification systems. The International Classification of Diseases (ICD) is the standard method for coding morbidity and mortality data to monitor disease incidence, prevalence, and other health conditions.³¹ ICD-10 is the most current version used worldwide, except in the USA, and it was implemented by the majority of WHO member states in 1994. WHO has scheduled to release ICD-11 in

2017. In the USA, the ICD-9-CM, a modified version of ICD-9, was implemented in 1979 after WHO implemented the ICD-9 in 1975. ICD-10-CM, a modified USA version of ICD-10, is scheduled to be implemented in the USA in October 2015.³²

2.3.3.1 International Classification of Diseases, Tenth Revision, Clinical

Modification, (ICD-10-CM). In 1990, WHO published ICD-10 in a continued effort for detailed descriptions of diseases and health conditions in the ever changing medical field, with new diseases and health conditions being added frequently. Most countries around the world use this coding scheme for both morbidity and mortality.³¹ However, in the USA, ICD-10 has been used for mortality coding only since 1999. Nonetheless, USA has been working on the ICD-10-CM, the USA clinical modification of the ICD-10, which is comparable to ICD-10, for morbidity coding. ICD-10-CM was initially scheduled to be implemented in October 2013, but this implementation date was rescheduled for 2014. Unfortunately, the implementation date was rescheduled again to October 2015.³² The ICD-10-CM has over 60,000 alphanumeric diagnoses codes which use five to seven characters that allow more specific reporting of diseases and new health conditions. In addition, the sixth digit captures clinical details and the added codes now show laterality.³² ICD-10-CM birth defects codes range from Q00 to Q99. ICD-10-CM is much improved compared to ICD-9-CM. For example, in ICD-9-CM coding scheme, a single code, 756.79, was assigned for both omphalocele and gastroschisis. But now, ICD-10-CM has two distinct codes: omphalocele (Q79.2) and gastroschisis (Q79.3).

NBDPN has already translated ICD-9-CM birth defects codes to ICD-10-CM (table 3). However, caution must be exercised because back translation of ICD-10-CM to ICD-9-CM cannot be done since there are many more ICD-10-CM birth defects codes that may not be translated to ICD-9-CM. NBDPN has developed a separate guidance on how to translate ICD-10-CM back to ICD-9-CM. The transition to ICD-10-CM while being

very beneficial and long overdue may pose some challenges for birth defects surveillance. For instance, nine months of data for calendar year 2015 will be coded using ICD-9-CM codes and three months of data for the same calendar year will be coded in ICD-10-CM. Additionally, it may be misleading to compare some birth defects prevalence data before and after the ICD-10-CM transition because of increased specificity of the ICD-10-CM coding scheme.

Some shortcomings for ICD-10-CM include a lack of distinction between birth defects among premature and mature infants such as patent ductus arteriosus. In addition, polydactyly, although not a major birth defect, does not have a code to indicate the position of the extra digit.³³

Researchers used Alberta Congenital Anomalies Surveillance System (ACASS) data to compare an adaptation of the ICD-10, the Royal College of Paediatrics and Child Health (ICD-10-RCPCH) coding with ICD-9-British Paediatric Association (ICD-9-BPA).³⁴ ACASS transitioned from ICD-9-BPA to ICD-10-RCPCH in 2000. It was found that some birth defects codes in ICD-10-RCPCH had moved to different sections or organ systems, there were more individual and detailed codes for congenital syndromes, and it required more detailed codes or less detailed codes for some anomalies such that ACASS had to create their own codes for Tetralogy of Fallot for more specificity. Moreover, the registry noted a significant difference for congenital hip dislocation prevalence estimates using ICD-10 coding because ICD-10 has more codes compared to ICD-9. Besides, ACASS has continued to use both ICD-10 RCPCH and ICD-9-BPA for data requests because some birth defects cannot be collapsed into one major group. For instance, Tetralogy of Fallot can be easily collapsed to one group using ICD-9-BPA. However, this is not the case in ICD-10-RCPCH because one of the defects that make up Tetralogy of Fallot has been moved to another grouping of heart defects.

Moczygamba and Fenton conducted a pilot study to evaluate the use of ICD-10-CM for diabetes, heart disease, and pneumonia.³⁵ The researchers found several validity-type errors such as incorrect assignment of the seventh-character extension, failure to use placeholders, and incomplete ICD-10-CM codes. It was concluded that although the ICD-10-CM is more robust, the increased specificity of health conditions may be challenging to find the specific code needed and that there is a varying degree of proficiency among coders depending on education level, clinical background, and training which may lead to inconsistent code assignment.

The full impact of the implementation of ICD-10-CM will be best evaluated after all the healthcare facilities transition to the new system. However, birth defects surveillance should be aware of some of the anticipated issues and address them accordingly. In addition, WHO will release the ICD-11 in 2017, two years after the proposed implementation of ICD-10-CM in the USA. It is questionable whether the USA will be ready to implement the ICD-11 soon after its release in order to allow comparison of morbidity and mortality data with the rest of the world.

2.3.3.2 International Classification of Diseases, Ninth Revision, Clinical

Modification, (ICD-9-CM). ICD-9-CM is the coding scheme that has been used in the USA for over 30 years to code diagnoses and procedures during a hospital encounter. It is also used for research, hospitalization rates, and estimation of healthcare costs. ICD-9-CM is based on 1978 WHO's ICD-9 and was modified to meet statistical needs in the USA and implemented in 1979.³⁶ The ICD-9-CM includes more than 13,000 diagnoses codes and uses more digits in the codes than WHO's ICD-9, thus diseases are described more specifically.³⁷ It uses three to five numeric codes and at least two codes are needed to code etiology and manifestation. The ICD-9-CM is updated every October in order to be current with the ever changing medical field. However, in as much as the

ICD-9-CM was intended to be more accurate, the coding scheme has outlived its usefulness and does not adequately capture all the current medical conditions, resulting in inaccuracies in reporting health conditions. ICD-9-CM birth defects codes range from 740.0 to 759.9.

Over half of the 43 USA population-based birth defects surveillance programs that report data to NBDPN use ICD-9-CM to code birth defects.²⁵ This has had an impact on birth defects surveillance in the USA because the coding scheme has not kept up with the changes in the medical field. For instance, gastroschisis and omphalocele both have the same ICD-9-CM code of 756.79 and yet they are distinct birth defects. In 2009, NBDPN introduced separate codes for these two birth defects in order to make a distinction.³³

2.3.3.3 Centers for Disease Control and Prevention/British Paediatric Association

Classification. The British Paediatric Association (BPA) modified the ICD-9 in 1979 to be used for pediatric and neonatal cases. The codes range from 740.000 to 759.999 in order to be similar to ICD-9 codes. The first four digits match the ICD-9; however, the fifth digit is specific to children. In 1983, the staff of CDC's Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities modified the BPA coding system and created a 6-digit code for the birth defects classification system to provide more details of a birth defect.¹⁸ In addition, the sixth digits '5', '6', and '7' are used for instances when a more detailed description is needed, which cannot be captured by the first five digits.³⁸ For example, more specificity for spina bifida is demonstrated in the following codes:

741.085 Spina bifida, meningocele, cervicothoracic, with hydrocephalus

741.086 Spina bifida, meningocele thoracolumbar, with hydrocephalus

741.087 Spina bifida, meningocele, lumbosacral with hydrocephalus.¹⁸

The CDC/BPA coding scheme while being very detailed has some shortcomings. These include being complicated to use, comprehensive coding instructions for some birth defects are not provided, it is over 30 years old and the birth defects field has evolved in this time period making some codes outdated, and individuals using the coding scheme need to be familiar with medical terminology, human anatomy, and birth defects.³⁹

Like the ICD-10-CM coding system, the 6-digit CDC-modified BPA system allows a more robust system that provides greater specificity of birth defects, laterality of the defect, and whether a defect is possible or probable or diagnosed only prenatally, and related conditions. For example, omphalocele is coded as 756.700 and gastroschisis is coded as 756.710. In addition, the CDC/BPA coding scheme is even more detailed than the ICD-10-CM for some birth defects such as spina bifida without anencephalus in which CDC/BPA has 21 codes compared to 10 and 2 codes for ICD-10-CM and ICD-9-CM respectively.

2.4 Future Directions

Birth defects surveillance in USA faces some challenges and a more standardized surveillance method used by all birth defects programs is needed. Cancer surveillance and the behavioral risk factor surveillance system (BRFSS) core questions have standardized surveillance procedures. Furthermore, the aforementioned surveillance systems are federally funded in all 50 states, District of Columbia (DC), and USA territories. Yet, only one third of state-based birth defects surveillance programs receive federal funding.³⁸ With reduced funding in most public health programs, federal funding for birth defects surveillance in all 50 states may not be feasible soon. In addition, some states do not even have a birth defects surveillance system yet; although it is 16 years after the Birth Defects Prevention Act of 1998. With the implementation of ICD-10-CM in 2015, it may be misleading to compare birth defects prevalence estimates

using ICD-10-CM and ICD-9-CM because in general, ICD-10-CM has more codes. However, for some birth defects such as congenital cataract, ICD-9-CM has more codes than ICD-10-CM and CDC/BPA coding schemes respectively. Additionally, NBDPN is yet to translate CDC/BPA to ICD-10-CM even though some birth defects surveillance programs are ready for the implementation of ICD-10-CM.²⁵ It may be beneficial for birth defects surveillance to apply partly the BRFSS model. BRFSS is a state-based telephone health survey that collects health-related risk behaviors, chronic health conditions, and use of preventive services data yearly from all 50 states, DC, Puerto Rico, the USA Virgin Islands, Guam, American Samoa, and Palau among non-institutionalized adults aged 18 years and over. BRFSS has three sets of questions: the core (fixed) questionnaire which is asked every year by all states, the rotating core which has questions that are asked every other year, optional modules, and the state-added questions which give states the autonomy to ask questions that are specific to each state's individual needs⁴⁰. In 2011, BRFSS methodology changed to include cell phones and the weighting methodology changed. Therefore, data from years prior to 2011 may not be comparable to data after the methodological change.

BRFSS and birth defects surveillance are inherently very different; however, some guidelines from BRFSS such as having core, rotating, optional, and state-added modules or questions may be applicable to birth defects surveillance. Categorization of birth defects reported to NBDPN for instance, core and optional, may be very useful especially after October 2015 once the ICD-10-CM is implemented. NBDPN recently revised the birth defects list which will be implemented soon by birth defects surveillance programs. The revised birth defects list has now categorized birth defects as core, recommended, and extended (Cara Mai, MPH, e-mail communication, July 14, 2014). The revision of the birth defects list will potentially increase reporting of all core birth

defects to NBDPN by most birth defects surveillance programs. Currently, NBDPN has a list of 45 birth defects⁴¹ that are not categorized and it may be daunting for some programs that have limited resources to report all or some of the 45 birth defects on the list (table 3). The revision of the NBDPN birth defects list is very timely, especially after the ICD-10-CM is implemented in 2015. Birth defects surveillance programs will still be at liberty to use other coding schemes such as the CDC/BPA if they so wish and will also be able to track other birth defects that may be of interest to them. This approach will ensure a standard coding scheme of reporting core birth defects and will allow comparison across all birth defects surveillance programs in the USA. Of course the issues of case ascertainment methods and pregnancy outcomes included by birth defects surveillance programs would persist, but at least the nomenclature used by birth defects surveillance programs would be uniform.

2.5 Conclusion

Birth defects surveillance programs in the USA use various case ascertainment methods (passive versus active surveillance), include various pregnancy outcomes (live births only, live births and stillbirths, and all pregnancy outcomes), and use different nomenclature (ICD-9-CM and CDC/BPA) in their surveillance efforts. The change in nomenclature from ICD-9-CM to the more comprehensive ICD-10-CM in 2015 will have an impact on birth defects surveillance, especially the comparison of data in the two coding systems. Individual state's birth defects surveillance legislation and resources available greatly determine the scope of birth defects surveillance efforts of state programs. However, the effects of this nomenclature change can only be fully assessed once the implementation of ICD-10-CM has occurred.

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Table 2.1 Down Syndrome Prevalence from Population-based Birth Defects Surveillance Programs by Case Ascertainment Methods, All Ages, United States, 2006-2010¹⁶

Case Ascertainment Method	Prevalence per 10, 000 births
Active case finding (n=15)	10.2 - 20.0
Passive case finding* (n=26)	6.9 - 20.6

* With or without case ascertainment

Table 2.2 Down Syndrome Prevalence from Population-based Surveillance Programs by Pregnancy Outcome, All Ages, United States 2006-2010¹⁶

Pregnancy outcome	Prevalence per 10, 000 births
Live births (n=12)	6.9 - 15.6
Live births and stillbirths (n=17)	8.8 - 17.0
All pregnancy outcomes (n=12)	10.2 - 20.6

Table 2.3 Birth Defects List with ICD-9-CM, ICD-10-CM, and CDC/BPA Codes, National Birth Defects Prevention Network⁴¹

Birth Defects	ICD-9-CM Codes	CDC/BPA Codes	ICD-10-CM Codes
Central Nervous System			
Anencephalus	740.0 - 740.1	740.00 - 740.10	Q00.0 - Q00.1
Spina bifida without Anencephalus	741.0, 741.9 without 740.0 - 740.10	741.00 - 741.99 without 740.0 - 740.10	Q05.0 - Q05.9, Q07.01, Q07.03 without Q00.0 - Q00.1
Hydrocephalus without spina bifida	742.3 without 741.0, 741.9	742.30 - 742.39 without 741.00 - 741.99	Q03.0 - Q03.9
Encephalocele	742.0	742.00 - 742.09	Q01.0 - Q01.9
Microcephalus	742.1	742.10	Q02
Eye			
Anophthalmia/ Microphthalmia	743.0, 743.1	743.00 - 743.10	Q11.0 - Q11.2
Congenital cataract	743.30 - 743.34	743.32	Q12.0
Aniridia	743.45	743.42	Q13.1
Ear			
Anotia/microtia	744.01, 744.23	744.01, 744.21	Q16.0, Q16.1
Cardiovascular			
Common truncus	745.0	745.00	Q20.0
Transposition of great arteries	745.10, 745.11, 745.12, 745.19	745.10 - 745.19 (exclude 745.13, 745.15, 745.18)	Q20.1, Q20.3, Q20.5
Tetralogy of Fallot	745.2	745.20 - 745.21, 747.31	Q21.3

Table 2.3: Birth Defects List with ICD-9-CM, ICD-10-CM, and CDC/BPA Codes, National Birth Defects Prevention Network⁴¹ (*continued*)

Birth Defects	ICD-9-CM Codes	CDC/BPA Codes	ICD-10-CM Codes
Ventricular septal defect	745.4	745.40 - 745.49 (exclude 745.487, 745.498)	Q21.0
Atrial septal defect	745.5	745.51 - 745.59	Q21.1
Atrioventricular septal defect (endocardial cushion defect)	745.60, 745.61, 745.69	745.60 - 745.69, 745.487	Q21.2
Pulmonary valve atresia and stenosis	746.01, 746.02	746.00 - 746.01	Q22.0, Q22.1
Tricuspid valve atresia and stenosis	746.1	746.10 (exclude 746.105)	Q22.4
Ebstein's anomaly	746.2	746.20	Q22.5
Aortic valve stenosis	746.3	746.30	Q23.0
Hypoplastic left heart syndrome	746.7	746.70	Q23.4
Patent ductus arteriosus	747.0	747.00	Q25.0
Coarctation of aorta	747.10	747.10 - 747.19	Q25.1
Total anomalous pulmonary venous return (TAPVR)	747.41	747.42	Q26.2
Orofacial			
Cleft palate without cleft lip	749.0	749.00 - 749.09	Q35.0 - Q35.9
Cleft lip with and without cleft palate	749.1, 749.2	749.10 - 749.29	Q36.0 - Q36.9, Q37.0 - Q37.9
Choanal atresia	748.0	748.0	Q30.0

Table 2.3 Birth Defects List with ICD-9-CM, ICD-10-CM, and CDC/BPA Codes, National Birth Defects Prevention Network ⁴¹ (continued)

Birth Defects	ICD-9-CM Codes	CDC/BPA Codes	ICD-10-CM Codes
Omphalocele**	756.79	756.70	Q79.2
Congenital hip dislocation	754.30, 754.31, 754.35	754.30	Q65.0 – Q65.2
Diaphragmatic hernia	756.6	756.61	Q79.0 – Q79.1
Chromosomal			
Patau syndrome	758.1	758.10 - 758.19	Q91.4 - Q91.7
Down syndrome	758.0	758.00 - 758.09	Q90.0 - Q90.9
Edwards syndrome	758.2	758.20 - 758.29	Q91.0 - Q91.3
Other			
Fetus or newborn affected by maternal alcohol use	760.71	760.71	Q86.0
Amniotic bands	No code	658.80	No code

Note.

ICD-9-CM: International Classification of Diseases, Ninth Edition, Clinical Modification.

ICD-10-CM: International Classification of Diseases, Tenth Edition, Clinical Modification.

CDC/BPA Codes: Centers of Disease Control and Prevention/British Paediatric Association.

*756.79 started being coded as 756.73 as of 10/1/2009

**756.79 started being coded as 756.72 as of 10/1/2009

Chapter 3: Interpregnancy Interval and Birth Defects

3.1 Abstract

Background: Interpregnancy interval is a risk factor for various adverse birth outcomes including birth defects. We investigated the relationship between interpregnancy interval and birth defects.

Methods: We conducted a retrospective cohort study using linked data from Nevada Birth Outcomes Monitoring System and birth certificate data for 124,341 singleton live births, of which 4,641 infants had 7,192 birth defects, among Nevada resident women between 2006 and 2011. We used logistic regression to assess factors independently associated with birth defects.

Results: Women who had an interpregnancy interval of 36 months or more, adjusted odds ratio (AOR) = 1.16, 95% CI (1.01-1.33), were more likely to have an infant with a birth defect compared with women with an interpregnancy interval of 18-23 months. Other independent risk factors for birth defects included male infants, AOR = 1.34, 95% CI (1.26-1.42); maternal age (30-34 years) and advanced maternal age (35 years and older), AOR = 1.10, 95% CI (1.01-1.19) and AOR = 1.29, 95% CI (1.18-1.42) respectively; being a Black woman, AOR = 1.46, 95% CI (1.32-1.61); three and four or more previous births, AOR = 1.12, 95% CI (1.02-1.23) and AOR = 1.24, 95% CI (1.11-1.38) respectively; smoking, AOR = 1.23, 95% CI (1.10-1.38); and prescription drug use, AOR = 1.14, 95% CI (1.07-1.21).

Conclusion: A long interpregnancy interval is an independent risk factor for birth defects. It may be helpful for maternal and child health programs and health care providers to highlight the deleterious effects of a long interpregnancy interval.

Key words: Birth defects, interpregnancy interval, pregnancy spacing

3.2 Introduction

Birth defects are an important public health issue because they are the leading cause of infant mortality, causing one in every five infant deaths.¹ Morbidity and mortality among children with birth defects is high, and the emotional and health care costs associated with birth defects are enormous. In 2004, billed costs for hospitalizations for birth defects in the United States was estimated to be 2.6 billion dollars.² In addition, birth defects affect the family and community, and some birth defects may lead to life-long disability.

Birth defects are structural or functional anomalies, including metabolic disorders, which are present at birth.³ The most common birth defects that have serious health implications are congenital heart defects, neural tube defects, and Down syndrome.³⁻⁵ Several studies on the etiology of birth defects suggest that multiple factors cause some birth defects.^{3,6,7} These factors include genetics,^{3,8} environmental factors,^{3,6,7} and gene-environment interactions.⁹ However, in spite of several decades of birth defects research, the etiology of nearly half of all birth defects is still unknown.³

Interpregnancy interval, the period between a live birth and subsequent conception, is an important risk factor for various adverse birth outcomes including birth defects. However, few studies have examined the association between interpregnancy interval and birth defects. A recent population-based Canadian study investigated the relationship between interpregnancy interval and birth defects.¹⁰ The researchers categorized interpregnancy intervals as follows (months): 0-5, 6-11, 12-17, 18-23, 24-35, and 36 or more. In addition, they used a referent group of 12-17 months. They found that short (0-5 months) and long (24-35 months) interpregnancy intervals were risk factors for birth defects. Kwon, Lazo-Escalante, Villaran & Li¹¹ conducted a population-based case-control study to investigate the association between interpregnancy interval and birth

defects in Washington state. They categorized interpregnancy interval as follows (months): 0-5, 6-11, 12-17, 18-23, 24-59, and 60 or more. Their referent group was 18-23 months. They found that interpregnancy intervals of less than six months, 6-11 months, 24-59 months, and 60 months or more were risk factors for birth defects. An Israeli nationwide population-based cohort study¹² examined the relationship between interpregnancy interval and major birth defects. Interpregnancy intervals were categorized as follows (months): 0-5, 6-11, 12-23, 24-59, and 60 or more. The researchers used a referent group of 12-23 months. They found that a short interpregnancy interval of less than 6 months increased the risk of major birth defects.

Other studies have investigated the relationship between interpregnancy interval and specific birth defects with mixed findings. Getz, Anderka, Werler & Case¹³ investigated the effect of short interpregnancy interval on gastroschisis risk among women who had an interpregnancy interval of less than 24 months. They reported that an interpregnancy interval of less than 12 months increased the risk of gastroschisis compared to an interpregnancy interval of 18 to 23 months. A Brazilian study¹⁴ did not find any association between interpregnancy interval and cleft palate. Another study using data from Sweden found an increased risk for isolated cleft palate for interpregnancy intervals of 36-47 months and 48 months or more.¹⁵ In addition, they found an increased risk for all cleft palate for an interpregnancy interval of 48 months or more. Todoroff and Shaw¹⁶ reported no association between interpregnancy interval and neural tube defects among all pregnancy outcomes. However, they found an increased neural tube defects risk associated with a short interpregnancy interval of 0-6 months among live births.

Even though previous studies have found that a short or long interpregnancy interval increased the risk of birth defects in general and for some specific birth defects,

they all used different interpregnancy interval categories and referent groups. In addition, only one study that investigated the relationship of all birth defects and interpregnancy interval used data with active case ascertainment of birth defects.¹⁰ We used a retrospective cohort study with active case ascertainment of birth defects (based on passive surveillance) to investigate the association between interpregnancy interval and all birth defects.

3.3 Methods

3.3.1 Data collection and Participants

We conducted a retrospective cohort study using data from Nevada Birth Outcomes Monitoring System (NBOMS), a statewide population-based surveillance system that monitors and collects birth defects data in Nevada. NBOMS was established in 2005 and uses passive surveillance with active case ascertainment. Hospitals send a list of records of infants with birth defects to NBOMS. Staff from NBOMS then visit the hospitals, review medical records, and gather birth defects data. NBOMS collects birth defects data from live births only using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We linked NBOMS data with live birth certificate data in order to obtain maternal and perinatal variables.

The study included all live-born singleton births among Nevada resident women of child-bearing age (15-49 years)¹⁷ from January 1, 2006 to December 31, 2011. A total of 229,005 live births were reported among Nevada resident women between January 1, 2006 and December 31, 2011. The study excluded records with multiple births and no previous birth; records with missing values for gestation age, last live birth date, and records with implausible (negative) values for interpregnancy interval. After these exclusions, the final study cohort consisted of 124,341 records (Figure 1) of which 4,641 infants had 7,192 birth defects.

3.3.2 Measures

Interpregnancy interval was calculated as the time period between two consecutive deliveries (the index delivery and the most recent delivery preceding the index delivery) and subtracting the gestation age of the second infant. Interpregnancy interval was first calculated in weeks and then converted back to months. Similar to a previous study, interpregnancy intervals were categorized as follows (months): 0-5, 6-11, 12-17, 18-23, 24-35, and 36 or more.¹⁰ Maternal variables included age (in years) at delivery (less than 20, 20-24, 25-29, 30-34, and 35 or older) race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic other), education (less than 12 years, 12 years, and more than 12 years), sex of index infant (male, female), number of previous live births (1, 2, 3, and 4 or more), cigarette smoking (yes, no), alcohol consumption (yes, no), illicit drug use (yes, no), prescription drug use (yes, no), and over-the-counter drug use (yes, no). Birth defects were identified from NBOMS using ICD-9-CM diagnosis codes in the 740 to 759 range. NBOMS does not include isolated birth defects for patent ductus arteriosus, patent foramen ovale, and atrial septal if they are less than 40 weeks gestation and/or birth weight less than 2500 grams. In addition, ventricular septal birth defects are excluded if the birth weight is less than 2500 grams and/or less than 36 weeks gestation.

3.4 Data analysis

We used descriptive statistics to describe the study population and we conducted chi-square analyses to assess factors associated with birth defects. We also conducted univariate analyses for specific birth defects that had adequate counts (≥ 100). In addition, we used logistic regression to assess factors independently associated with birth defects. Maternal age, race/ethnicity, and other factors significantly associated with birth defects in the bivariate analyses ($p \leq .05$) were entered in the logistic regression

model using simultaneous entry. We used “collin”, a SAS macro to assess collinearity (D. Kleinbaum, PhD, personal communication, May 30, 2014). All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

3.5 Results

Characteristics of the study population and factors associated with birth defects in the bivariate analyses are presented in Table 1. Over half (54.6%) of the women had an interpregnancy interval of between zero and 11 months and over half (51.2%) of the infants were male. Over three-quarters (79.5%) of the women were aged 20-34 years at birth of the index infant and over half (51.3%) had a high school education. The race/ethnicity groups of the women were as follows: Hispanic (42.3%), non-Hispanic White (40.1%), non-Hispanic Black (9.0%), and non-Hispanic other (8.6%). Nearly half (48.5%) of the women had one previous birth. Risk behaviors during index pregnancy associated with birth defects included smoking (7.2%), illicit drug use (34.9%), prescription drug use (29.0%), over-the-counter drug use (8.2%), and less than 1% (0.7%) used alcohol during the index pregnancy.

An interpregnancy interval of 36 months or more ($p < .0001$) was associated with birth defects. Other factors associated with birth defects included male infants ($p < .0001$), advanced maternal age ($p < .0001$), Black women ($p < .0001$), and women who had less than high school education ($p = 0.02$). In addition, birth defects were associated with women who had three or more previous births ($p < .0001$), smoking ($p < .0001$), alcohol use ($p = 0.03$), illicit drug use ($p < .0001$), over-the-counter drug use ($p = 0.02$), and prescription drug use ($p < .0001$). Univariate analyses of interpregnancy interval and specific birth defects are shown in Table 2. An interpregnancy interval of 35 months or more was associated with Down syndrome, OR = 3.08, 95% CI (1.49-6.36).

The logistic regression model assessed the independent effect of interpregnancy interval on birth defects while simultaneously controlling for maternal age, race/ethnicity, and other significant risk factors (Table 3). Women who had an interpregnancy interval of 36 months or more, adjusted odds ratio (AOR) = 1.16, 95% CI (1.01-1.33), were more likely to have infants with birth defects compared with women who had an interpregnancy interval of 18-23 months. Other independent risk factors for birth defects included male infants, AOR = 1.34, 95% CI (1.26-1.42); maternal age (30-34 years) and advanced maternal age (35 years and older), AOR = 1.10, 95% CI (1.01-1.19) and AOR = 1.29, 95% CI (1.18-1.42) respectively; being a non-Hispanic Black woman, AOR = 1.46, 95% CI (1.32-1.61); three and four or more previous births, AOR = 1.12, 95% CI (1.02-1.23) and AOR = 1.24, 95% CI (1.11-1.38) respectively; smoking, AOR = 1.23, 95% CI (1.10-1.38); both smoking and alcohol (combined) AOR = 1.69, 95% CI (1.13-2.55); and prescription drug use AOR = 1.14, 95% CI (1.07-1.21).

We ran a model with 12-17 months as the referent group and the results were similar to the model with 18-23 months as the referent group. Illicit drug use and prescription drugs were highly correlated; therefore, the two covariates could not be assessed in the same model. In addition, we ran a different model excluding hypospadias, which affects male infants only, and male infants were still at an increased risk of having birth defects compared with female infants. We also ran a model to evaluate if interpregnancy interval was an independent risk factor for congenital heart defects, but we did not observe any statistical significance (results not shown).

3.6 Discussion

Our study is among the few studies using active case ascertainment of birth defects (even if based on passive surveillance) to investigate the association between interpregnancy interval and birth defects. We found that women with an interpregnancy

interval of 36 months or more were 1.16 times more likely to have infants with birth defects compared with women with an interpregnancy interval of 18-23 months. Previous studies have found an interpregnancy interval of 24-35 months¹⁰ and 24 months or more¹¹ to be independent risk factors for birth defects. In addition, we found that an interpregnancy interval of 36 months or more was associated with Down syndrome which was similar to a previous study,¹¹ although the researchers included all chromosomal defects while our study investigated Down syndrome only. Additionally, the study categorized long interpregnancy interval as 24-59 months and 60 or more months. Previous studies have used different interpregnancy interval categories and referent groups. For instance, one study¹⁰ used interpregnancy interval categories similar to the current study (months): (0-5, 6-11, 12-17, 18-23, 24-35, and 36 or more), however, their referent group was 12-17 months. The current study did not find a short interpregnancy interval of less than six months statistically significant unlike previous studies.¹⁰⁻¹² We used an interpregnancy interval of 18-24 months as the referent group because this interpregnancy interval range has been suggested to be the most favorable with the lowest risk for birth defects.¹⁸⁻²⁰

It is unclear why a long interpregnancy interval is associated with birth defects and other adverse birth outcomes. However, it has been hypothesized that “physiological regression” may explain the adverse birth outcomes after a long interpregnancy interval.^{18,20} During pregnancy, a woman’s body undergoes physiologic changes that are conducive for the optimal growth of the fetus. After birth, the body slowly returns to near normal and if conception does not occur soon enough, the physiologic characteristics may become similar to those of a primigravid and thus adverse birth outcomes.

Health care providers need to discuss the adverse effects of interpregnancy interval with women of child bearing age so that they can make informed decisions regarding interpregnancy interval especially if they plan to have multiple children. Most maternal child health programs focus on addressing low birth weight and preterm births. However, a long interpregnancy interval is a risk factor for birth defects and deserves attention in order to prevent some birth defects. Additionally, there is need for researchers to standardize interpregnancy interval categories and the referent group in order to make interpregnancy interval studies comparable.

We also found that non-Hispanic Black women were more likely to have infants with birth defects compared with non-Hispanic White women. Researchers²¹ investigated racial/ethnic variations in the prevalence of birth defects in Metropolitan Atlanta and found that the prevalence of all birth defects among Blacks was much lower than that of Whites and Hispanics. However, the prevalence of specific heart defects such as Tetralogy of Fallot, atrioventricular septal defects, and limb deficiencies have been found to be higher among Blacks compared to Whites.²² Certain birth defects may be more prevalent among different race/ethnic groups and prevention efforts need to be targeted to respective race/ethnic groups accordingly.

Consistent with previous studies,²³⁻²⁵ we found that smoking was a risk factor for birth defects even though another study¹⁰ reported that smoking was not a significant risk factor. Smoking is a known risk factor for birth defects.^{26,27} In addition, health care providers should offer tobacco cessation options to women of childbearing age and to those who present themselves for prenatal care and report that they are current smokers.

Our study found that prescription drug use was an independent risk factor for birth defects. Medication use during pregnancy is common with prevalence estimates

ranging from 27% to 99%.²⁸ However, little is known about the safety of most Food and Drug Administration approved medications because pregnant women are not included in clinical trials.²⁹ More research is needed to provide a better understanding of the various classes of prescription medications and their teratogenic effect. Moreover, there is need for a standard guidance for medications that may be safe to use during pregnancy.³⁰

It is well established that advancing maternal age is a risk factor for birth defects^{10,26} and this was confirmed in our study. Public health messages and health care providers need to reiterate the importance of bearing children at a younger age, whenever possible, to prevent adverse birth outcomes such as birth defects.

Confirming previous studies,^{10,31,32} we found that male infants were at increased risk of having birth defects compared to female infants. More research is needed to elucidate these sex differences, which might continue even in adulthood.

Our study should be interpreted in light of some potential limitations. First, NBOMS includes birth defects from live births only and not other pregnancy outcomes (still births and terminations), and yet birth defects from these important sources may have unique characteristics. Therefore, if there was a still birth or termination preceding the index pregnancy, the data was unavailable to be used in the calculation of the interpregnancy interval. Thus, the interpregnancy interval was the period between a live birth and subsequent conception. Also, the study might have underestimated the prevalence of birth defects by not having data from still births and terminations. Second, NBOMS uses ICD-9-CM codes for diagnosis of birth defects and yet ICD-9-CM codes have been shown not to be specific enough to distinguish significant birth defects from minor conditions and may lead to misclassification for some conditions.^{33,34} Third, maternal demographic and substance use measures were self-reported and some measures such as substance use may not have been sensitive enough since the

responses to these questions were dichotomous (yes or no). For instance, it was not possible to specify the kinds of prescription medications used. In addition, substance use maternal risk factors (for example, smoking and alcohol use) are under-reported on birth certificates.^{35,36} The percent of women reporting smoking and alcohol use in our study was 7.2% and 0.7% respectively. However, smoking prevalence among women of childbearing age has been estimated to be 22.4%³⁷ and alcohol use in the past 30 days was estimated at 7.6% and 51.5% among pregnant and nonpregnant women respectively.³⁸ Fourth, birth certificate data does not include other important risk factors for birth defects such as family history, lifestyle, and environmental exposure to pollutants (potential confounders), which would be adjusted for in the analyses. Fifth, NBOMS collects data from cases of infants mainly during the first year of life and does not capture infants who died shortly after birth or were diagnosed later in their childhood. Finally, since our study used data from one state, caution should be exercised when making generalizations.

Despite the aforementioned limitations, we present one of the few studies using active case ascertainment of birth defects (even if based on passive surveillance) that assessed the independent risk factor of interpregnancy interval on birth defects. Our findings can be used to inform maternal child health programs and health care providers on the need to enlighten women of childbearing age that a long interpregnancy interval is a risk factor for birth defects, although half of all pregnancies in the United States are unplanned.³⁹ This will empower women to make informed decisions on the most favorable interpregnancy interval if they plan to have multiple children. Traditionally, most maternal child health programs and health care providers have focused on adverse pregnancy outcomes, such as preterm births and low birth weight, which are risk factors for infant mortality. However, it may help to include interpregnancy interval on the

campaign of reducing infant mortality because birth defects are the leading cause of infant deaths.

3.7 References

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Table 3.1 Bivariate Analysis: Factors Associated with Birth Defects

Characteristic	Total n (%)	No birth defects n (%)	Birth defects n (%)	p-value
	124,341 (100)	119,700 (100)	4,641 (100)	
Interpregnancy interval, months				
0-5	32,962 (26.5)	31,722 (26.5)	1,240 (26.7)	
6-11	34,886 (28.1)	33,680 (28.1)	1,206 (26.0)	
12-17	19,824 (15.9)	19,111 (16.0)	713 (15.4)	
18-23	12,319 (9.9)	11,864 (9.9)	455 (9.8)	
24-35	13,431 (10.8)	12,912 (10.8)	519 (11.2)	
36+	10,919 (8.8)	10,411 (8.7)	508 (11.0)	<.0001
Infant sex				
Male	63,605 (51.2)	60,921 (50.9)	2,684 (57.8)	
Female	60,736 (48.9)	58,779 (49.1)	1,957 (42.2)	<.0001
Maternal age, years				
<20	4,229 (3.4)	4,110 (3.4)	119 (2.6)	
20-24	26,729 (21.5)	25,835 (21.6)	894 (19.3)	
25-29	39,604 (31.9)	38,213 (31.9)	1,391 (30.0)	
30-34	32,504 (26.1)	31,246 (26.1)	1,258 (27.1)	
≥35	21,275 (17.1)	20,296 (17.0)	979 (21.1)	<.0001
Maternal race/ethnicity				
White non-Hispanic	49,331 (40.1)	47,498 (40.1)	1,833 (39.9)	
Black non-Hispanic	11,130 (9.0)	10,525 (8.9)	605 (13.2)	
Hispanic	52,086 (42.3)	50,294 (42.4)	1,792 (39.0)	
Other non-Hispanic	10,623 (8.6)	10,256 (8.7)	367 (8.0)	<.0001
Maternal education				
Less than high school	10,785 (8.9)	10,435 (8.9)	350 (7.7)	
High school	62,541 (51.3)	60,162 (51.3)	2,379 (52.3)	
More than high school	48,594 (39.9)	46,778 (39.9)	1,816 (40.0)	0.02
Previous births				
1	60,264 (48.5)	58,140 (48.6)	2,124 (45.8)	
2	36,004 (29.0)	34,728 (29.0)	1,276 (27.5)	
3	16,786 (13.5)	16,102 (13.5)	684 (14.7)	
≥4	11,287 (9.1)	10,730 (9.0)	557 (12.0)	<.0001
Smoking				
Yes	8,825 (7.2)	8,398 (7.1)	427 (9.3)	
No	114,010 (92.8)	109,843 (92.9)	4,167 (90.7)	<.0001
Alcohol use				
Yes	847 (0.7)	803 (0.7)	44 (1.0)	
No	121,247 (99.3)	116,699 (99.3)	4,548 (99.0)	0.03

Table 3.1 Bivariate Analysis: Factors Associated with Birth Defects (continued)

Characteristic	Total n (%)	No birth defects n (%)	Birth defects n (%)	p-value
	124,341 (100)	119,700 (100)	4,641 (100)	
Smoking and alcohol use (combined)				
None	112,755 (92.5)	108,610 (92.6)	4,145 (90.4)	
Smoking only	8,266 (6.8)	7,869 (6.7)	397 (8.7)	
Alcohol only	445 (0.4)	429 (0.4)	16 (0.4)	
Both smoking and alcohol	391 (0.3)	365 (0.3)	26 (0.6)	<.0001
Over-the-counter drug use				
Yes	10,068 (8.2)	9,734 (8.2)	334 (7.3)	
No	112,611 (91.8)	108,351 (91.8)	4,260 (92.7)	0.02
Prescription drug use				
Yes	35,597 (29.0)	34,138 (28.9)	1,459 (31.8)	
No	87,082 (71.0)	83,947 (71.1)	3,135 (68.2)	<.0001
Illicit drug use				
Yes	42,351 (34.9)	40,575 (34.7)	1,776 (38.8)	
No	79,030 (65.1)	76,225 (65.3)	2,805 (61.2)	<.0001

Note: other race non-Hispanic = Asian, Native Hawaiian or other Pacific Islander

Table 3.2 Association of Interpregnancy Interval with Specific Birth Defects

Birth Defects	Number (% of total birth defects) ^a	Interpregnancy interval, months					
		0-5	6-11	12-17	18-23	24-35	36+
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR	OR (95% CI)	OR (95% CI)
Ventricular septal defect	502 (7.0%)	0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.8 (0.6-1.2)	1.0	0.7 (0.5-1.1)	1.2 (0.9-1.8)
Atrial septal defect	1,190 (16.5%)	0.9 (0.7-1.2)	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1.0	1.1 (0.8-1.6)	1.1 (0.8-1.6)
Pulmonary valve artresia and stenosis	102 (1.4%)	2.9 (0.9-9.5)	2.1 (0.6-7.2)	1.9 (0.5-6.9)	1.0	2.8 (0.7-10.2)	3.4 (0.9-12.6)
Cleft lip with and without cleft palate	102 (1.4%)	0.9 (0.4-2.0)	1.2 (0.5-2.6)	0.9 (0.3-2.1)	1.0	0.7 (0.2-2.0)	0.9 (0.3-2.5)
Pyloric stenosis	133 (1.8%)	1.5 (0.7-3.1)	1.3 (0.6-2.6)	1.4 (0.6-3.0)	1.0	1.9 (0.9-4.3)	1.5 (0.6-3.6)
Hypospadias	167 (2.3%)	2.1 (1.0-4.4)	1.5 (0.7-3.2)	2.2 (1.0-4.8)	1.0	2.3 (1.0-5.2)	1.9 (0.8-4.5)
Obstructive genitourinary	334 (4.6%)	0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.7 (0.5-1.2)	1.0	0.5 (0.3-0.9)	0.7 (0.4-1.1)
Down Syndrome	152 (2.1%)	1.0 (0.5-2.2)	0.9 (0.4-1.9)	0.7 (0.3-1.6)	1.0	1.7 (0.8-3.6)	3.1 (1.5-6.4)*

Note: OR = odds ratio (unadjusted); CI = confidence interval

* $p < .05$

^a The total birth defects were 7,192 among 4,641 infants who had at least one birth defect. The total birth defects were used as the denominator in the calculation of the percent of birth defects.

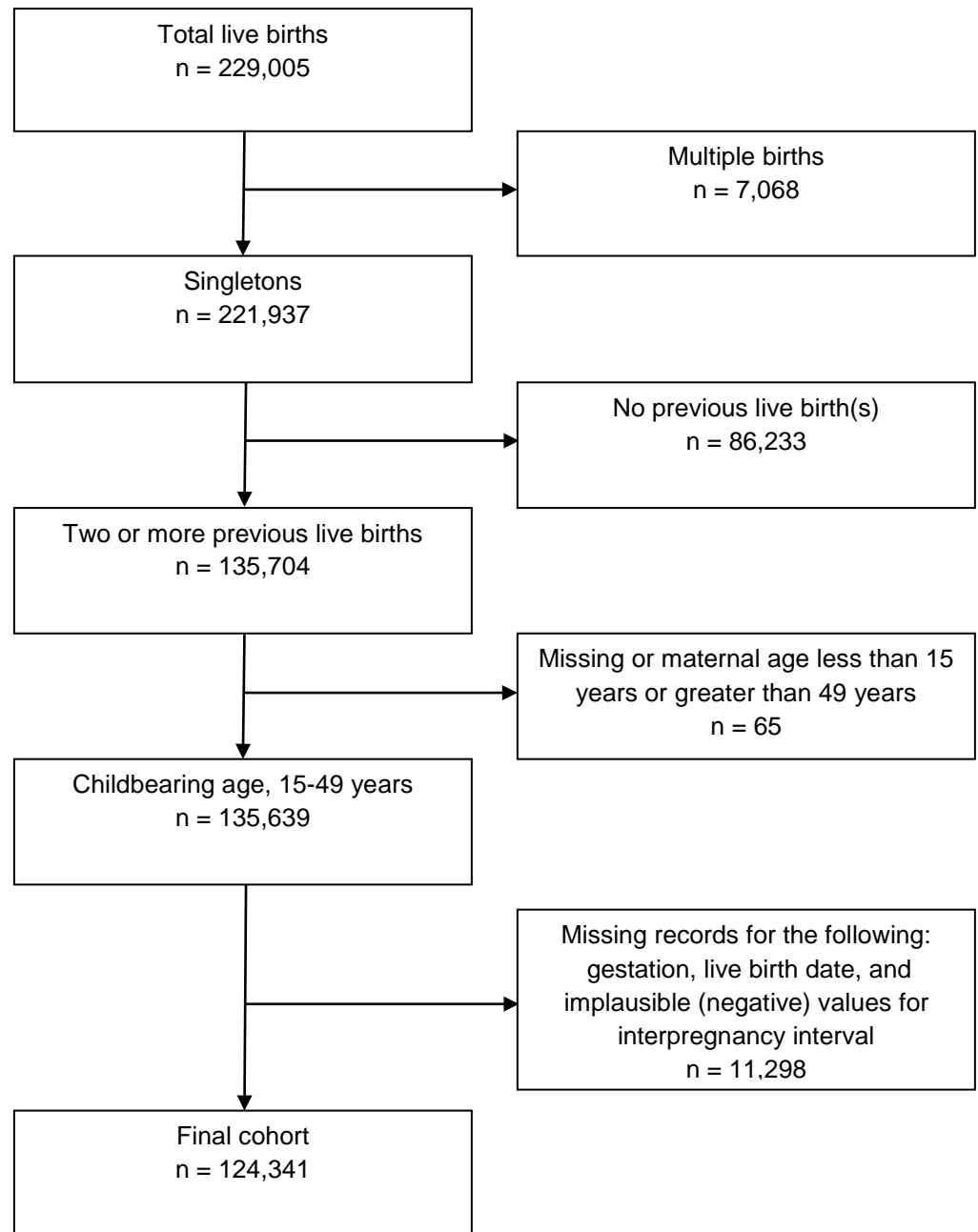
Table 3.3 Factors Independently Associated with Birth Defects

Characteristic	AOR (95% CI)	p-value
Interpregnancy interval, months		
0-5	1.04 (0.93-1.16)	
6-11	0.97 (0.86-1.08)	
12-17	1.00 (0.89-1.13)	
18-23	Referent	
24-35	1.04 (0.91-1.18)	
36+	1.16 (1.01-1.33)*	0.06
Infant sex		
Male	1.34 (1.26-1.42)**	
Female	Referent	<.0001
Maternal age, years		
<20	0.83 (0.68-1.01)	
20-24	1.00 (0.88-1.06)	
25-29	Referent	
30-34	1.10 (1.01-1.19)*	
≥35	1.29 (1.18-1.42)**	<.0001
Maternal race/ethnicity		
White non-Hispanic	Referent	
Black non-Hispanic	1.46 (1.32-1.61)**	
Hispanic	0.94 (0.87-1.01)	
Other race, non-Hispanic	0.93 (0.83-1.04)	<.0001
Maternal education		
Less than high school	0.88 (0.77-1.00)	
High school	1.04 (0.97-1.12)	
More than high school	Referent	0.02
Previous births		
1	Referent	
2	0.98 (0.91-1.05)	
3	1.12 (1.02-1.23)*	
≥4	1.24 (1.11-1.38)*	<.0001
Smoking and alcohol use (combined)		
None	Referent	
Yes, smoking only	1.23 (1.10-1.38)*	
Yes, alcohol only	0.89 (0.53-1.50)	
Both smoking and alcohol	1.69 (1.13-2.55)*	0.0002
Prescription drug use		
Yes	1.14 (1.07-1.21)*	
No	Referent	0.0001

Note: AOR = adjusted odds ratio; CI = confidence interval; other race, non-Hispanic = Asian, Native Hawaiian or other Pacific Islander

* p < .05; **p < .0001

Figure 3.1 Exclusions Applied to the Study Population, Nevada Residents, 2006-2011



Chapter 4: Spatial Epidemiology of Birth Defects: A Geographic Information System and Spatial Scan Statistic Approach

4.1 Abstract

Background: Birth defects are an important public health issue because they are the leading cause of infant mortality causing one in every five infant deaths. Most epidemiological studies have used personal level data to investigate the etiology of birth defects and yet a person's neighborhood is an important determinant of birth outcomes, including birth defects. The objective of the study was to investigate spatial patterns of birth defects in Nevada from 2005 to 2011 and identify areas that may have high birth defects clusters using a spatial scan statistic.

Methods: Data from Nevada Birth Outcomes Monitoring System (NBOMS) and Nevada live birth certificate for the period 2005-2011, aggregated at ZIP Code level were used for the study. Birth defects rates were smoothed using Spatial Empirical Bayesian technique. This technique adjusts for spatial autocorrelation, population heterogeneity and unstable rates. Birth defects spatial clusters were identified using a spatial scan statistic using a Poisson model. Monte Carlo hypothesis testing was used to assess significance.

Results: For the period 2011-2011, there were 11,405 infants with 17,626 birth defects reported in NBOMS and 266,357 live births among Nevada residents. ZIP Codes with high birth defects rates were identified. The state birth defects raw rates for the study period ranged from 0-10,000 per 10,000 live births, with 47% of the ZIP Codes exceeding the state's birth defects rate. One significant ($p < .0001$) spatial cluster of birth defects was identified.

Conclusion: The spatial analyses methods identified disparities of birth defects rates at ZIP Code level. Prevention efforts of birth defects, should target populations at ZIP Code level in order to improve birth outcomes of target populations.

Key words: Birth Defects, Geographic Information System, Spatial Analysis

4.2 Introduction

Birth defects are an important public health issue because they are the leading cause of infant mortality causing one in every five infant deaths.¹ Morbidity and mortality among children with birth defects is high and the emotional and health care costs associated with birth defects are enormous.² In addition, birth defects can lead to life-long disability which can put strain on the family, society, and the health care system. In 2004, billed costs for hospitalizations for birth defects in the United States was estimated to be 2.6 billion dollars.³

Most epidemiological studies on the etiology of birth defects have used personal level data which suggest that multiple factors cause some birth defects.^{2,4,5} These factors include genetics,^{2,6} environmental factors,^{2,4,5} and gene-environment interactions.⁷ However, in spite of several decades of birth defects research, the cause of nearly half of all birth defects is still unknown.²

Geographical Information System (GIS) and spatial statistics have been used increasingly in public health surveillance in recent years. Spatial analyses is very useful in identifying spatial pattern of health conditions, areas of increased burden of the disease, and investigating if there is an association between the incidence or prevalence of disease and potential risk factors that may contribute to the spatial variation of risk factors.⁸⁻¹¹

A person's neighborhood is an important determinant of birth outcomes,^{12,13} including birth defects. Spatial patterns and clustering of areas of high birth defects cases with the neighborhood as the unit of analysis, helps in identifying communities at high risk which allow for targeted intervention, thus, improving the population's health at the local level.

Other studies have used spatial analyses to investigate specific birth defects. Cech, Burau & Walston¹⁴ used SaTScan to examine the spatial distribution of orofacial cleft defects in Harris County, Texas for the period 1990-1994 using Texas birth certificates as the source of cases. Data were aggregated by Zone Improvement Plan (ZIP) Codes for Harris County. They found a cluster of oral cleft defects where the presence of elevated levels of radium and radon in tap water has been known since the 1990s. Gebreab⁸ conducted a spatial cluster analyses using the spatial scan statistic for Utah Birth Defects Network, a state-wide birth defects program for the period 1995-2005. A cluster in the Tri-County Health District was detected but no evidence was found to suggest a single point source of environmental exposure that may cause oral clefts. Root, Meyer & Emch¹⁵ used SaTScan's spatial scan statistic to investigate clusters of gastroschisis in North Carolina. Data on cases of gastroschisis were obtained from the North Carolina Birth Defect Monitoring Program and control births were chosen from all resident live births without birth defects contained in the North Carolina composite linked birth files. They found a statistically significant cluster in rural Southern Piedmont. This finding confirmed anecdotal evidence from health professionals and pointed to areas of further investigation with regard to environmental factors that may contribute to the gastroschisis cluster.

The above studies demonstrate that the spatial scan statistic is very useful in identifying locations of birth defects clusters. To our knowledge, no studies have used spatial analysis to investigate birth defects clusters and spatial patterns in Nevada. The objective of this study was to investigate the spatial patterns of birth defects in Nevada and identify areas that may have high birth defects clusters using a spatial scan statistic for the period 2005 to 2011.¹⁶

4.3 Methods

4.3.1 Study area and data collection

The study area included the 156 ZIP Codes¹⁷ in the state of Nevada. We used United States Postal Service (USPS) ZIP Codes as the geographic unit of analysis. USPS uses ZIP Codes as subdivisions of counties to streamline their mail delivery system. The first digit of a ZIP Code represents a broad geographical area of the United States ranging from zero in the Northeast to nine for the far West. The next two digits represent sectional centers and the last two digits denote the post office facility, branch, or local delivery area.¹⁷

We used birth defects data for the period 2005 to 2011 from Nevada Birth Outcomes Monitoring System (NBOMS), a population-based surveillance system that collects birth defects data throughout Nevada. NBOMS was established in 2005 and uses passive surveillance with active case ascertainment. NBOMS collects birth defects data from live births only using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and birth defects codes are in the 740 to 759 range. Birth certificate data for the period 2005-2011 were used in the calculation of birth defects rates.

A Nevada shape file with ZIP Codes was obtained from Environmental Systems Research Institute (ESRI). A point-in-polygon join was used to link NBOMS birth defects and live births data to openly available ZIP code cartographic boundary files downloaded from ESRI website.¹⁸

4.4 Data analysis

4.4.1 Descriptive analyses and spatial smoothing

Investigation of disease patterns at small geographic areas such as neighborhoods has some challenges that need to be addressed. Since the populations

are heterogeneous, birth defects rates from areas with low populations will likely have higher variances and consequently, be more unstable compared to areas with high populations. This is referred to as the “small number problem”.¹⁹ Spatial smoothing of rates is one of the techniques used to reduce the “noise” from areas with low populations¹⁹ which makes the rates more stable and less variable.^{20,21}

The raw (unsmoothed) rates were expected to have high standard errors because of the small number problem since there were ZIP Codes with few or no birth defects. The raw rates for Nevada birth defects were smoothed using Spatial Empirical Bayes (SEB) smoothing using 1st order queen weights in GeoDa²² in order to address the small number issue and to adjust for spatial autocorrelation and population heterogeneity.²³ In this smoothing method, the raw rates for low population ZIP Codes without clear spatial patterns are shrunk towards the local mean. On the other hand, in ZIP Codes where spatial patterns are evident, the less reliable rates from areas with few births are adjusted towards a local mean. Hence, the SEB smoothed rates are more stable than raw (unsmoothed) rates.^{21,24} Smoothing of rates for each of the race/ethnic groups was not done because several ZIP Codes did not have any live births.

Birth defects rates were expressed as the proportion of birth defects and live births in a ZIP Code per 10,000 live births. All descriptive analyses were done in SAS[®] version 9.4 (SAS Institute, Cary, NC).

4.4.2 Detection and identification of birth defects clusters

The spatial scan statistic¹⁶ was implemented in SaTScan²⁵ which uses either a Poisson-based model or a Bernoulli model with binary event data. In the Poisson model, the number of events in an area is Poisson distributed according to a known underlying population at risk. This study used the Poisson model and the spatial scan statistic was used to detect the presence of high clusters of birth defects and identify their locations.¹⁶

The spatial scan statistic uses circular windows of variable radius that move across the study area to compare the number of birth defects in the window with what would be expected if birth defects were randomly distributed in space. The radius of the circular window varies continuously and ranges from zero up to a specified maximum, such that the window never includes more than 50% of the total population at risk. Thus, the circular window has both location and size flexibility. Clusters are identified based on a likelihood ratio test²⁶ with a p-value obtained using Monte Carlo simulation.¹⁶ The primary cluster with the highest significant likelihood is interpreted such that there is an increased number of birth defects within the window compared to outside.²⁷ Non-overlapping, spatial clusters of high birth defects cases were identified using a purely spatial, discrete Poisson model.¹⁶

4.5 Cartographic displays

ArcGIS 10.3 (ESRI, Redlands, CA) was used for all cartographic manipulations and displays. Jenk's optimization classification scheme was used for the intervals for displaying the SEB smoothed rates of birth defects in the choropleth maps. Smoothed proportions are more appropriate for mapping small areas compared to unsmoothed proportions,^{19,20} therefore, the former are presented. Significant spatial clusters were displayed in ArcGIS 10.3.²⁸

4.6 Results

4.6.1 Description of birth defects

For the period 2005 to 2011, NBOMS had a total of 17,626 birth defects cases and 266,357 live births were reported among Nevada residents. No birth defects were reported in 23 ZIP Codes. Female infants accounted for 41% birth defects. The race/ethnicity categories of the infant's mothers were 43% non-Hispanic White, 12%

non-Hispanic Black, 35% Hispanic, 6% non-Hispanic Asian, 1% non-Hispanic Native American, and 3% unknown.

4.6.2 Spatial distribution of birth defects rates

The raw unsmoothed birth defects rates for Nevada was 662 per 10,000 live births (range: 0-10,000), with 47% of the ZIP Codes exceeding the state's birth defects rates. ZIP Codes with the highest birth defects rates higher than the state rate were mainly in Clark County. Statewide smoothed birth defects rates are displayed in Figure 4.2. Raw (unsmoothed) birth defects rates by race/ethnicity showed variations at ZIP Code level (Figure 4.3).

4.6.3 Spatial clusters of birth defects

Table 1 displays the results of identified spatial birth defects clusters. The table provides the number of ZIP Codes in the cluster, total live births, observed number of birth defects in the cluster, expected number of birth defects based on the Poisson model, estimated annual number of cases per 100,000 live births, and the significance level (p-value) obtained from the likelihood ratio test with Monte Carlo permutations.¹⁶ Figure 4.1 displays the geographic distribution of spatial clusters of birth defects in Nevada for the period 2005-2011.

4.7 Discussion

To our knowledge, this is the first study to investigate the spatial patterns and clusters of birth defects in Nevada at ZIP Code level using birth defects data from a population-based surveillance system where birth defects are actively ascertained. The results of the current study show that birth defects rates vary within counties. In addition, we found racial/ethnic variations within the ZIP Codes. Therefore, analyses conducted at county level, as is the norm, does not capture disparities within the counties at ZIP Code

level. Consequently, ZIP Codes would likely be erroneously ignored by programs that target birth defects prevention. Most health data in Nevada is reported at county level and yet, as shown by these results, there are disparities at ZIP Code level. Other studies have used spatial analyses to investigate clusters of specific birth defects and identify their location. Cech, Burau & Walston¹⁴ found a cluster of cleft defects in Harris County, Texas where the presence of elevated levels of radium and radon in tap water has been known since the 1990s. Gebreab⁸ detected a cluster of oral clefts in the Tri-County Health District, Utah but did not find evidence that suggested a single point source of environmental exposure that may cause oral clefts. Root, Meyer & Emch¹⁵ found a statistically significant cluster of gastroschisis in rural Southern Piedmont, North Carolina.

The implication of our findings is that the focus of health research, planning, and prevention activities need to be at jurisdictions lower than the county level in order to address birth defects disparities within a county. In addition, these findings call for more studies to explore further the ZIP Codes with a significant birth defect cluster since this is the first spatial study of birth defects in Nevada.

Our study should be interpreted in light of some potential limitations. First, NBOMS uses ICD-9-CM Codes for diagnosis of birth defects and yet ICD-9-CM codes have been shown not to be specific enough to distinguish significant birth defects from minor conditions and may lead to misclassification for some conditions.^{29,30} Second, NBOMS includes birth defects from live births only and yet birth defects from other pregnancy outcomes (still births and terminations) are important sources that may have unique characteristics. Also, the study might have underestimated the prevalence of birth defects by not having data from still births and terminations. Third, NBOMS data does not include other important risk factors for birth defects such as family history,

lifestyle, and environmental exposure to pollutants (potential confounders) were not available to be included for in the analyses. Finally, NBOMS collects data from cases of infants mainly during the first year of life and does not capture infants who died shortly after birth or were diagnosed later in their childhood.

Analyses at ZIP Code level provides the advantage of a better understanding of health conditions, however, small area spatial analyses methods pose several challenges. These include the small number problem, visualization of raw rates from areas with few birth defects can be misleading. This study addressed this problem by using SEB smoothing of overall statewide rates which reduces “noise” associated with population heterogeneity and variance instability by borrowing strength from neighbors. While the removal of “noise” areas with few birth defects with unstable rates eases visual interpretation or presentation, it may introduce artifacts into the map,^{31,32} thus the rates should be used for visualization and not statistical analyses.³³ In addition, many smoothing techniques, including SEB used in this study, are prone to edge effects such that ZIP Codes on the edges of the study area have fewer neighbors than those in the interior therefore less information to borrow from neighbors for smoothing.¹⁹ Despite these limitations, spatial smoothing of rates minimizes erroneous visual interpretations associated with raw rates by reducing “noise”, making spatial patterns more clear, and reducing attention to outliers by focusing on the overall geographic pattern of the study area.¹⁹ In the current study, the overall statewide smoothed rates were similar to the raw rates, except that the localized patterns were made more noticeable. Therefore, it is expected that SEB will have an impact on unstable rates and little impact on stable rates.^{19,20,33} Consequently, the differences between the unsmoothed and SEB rates will be minimal.

The number and width of class intervals used to represent rates greatly affects the visual interpretation of spatial patterns.¹⁹ To address this potential bias, we used the Jenks (natural breaks) classification method where interval definitions are based on the natural distribution of breaks or groupings in the data.

Spatial scan statistic was used to identify and assess the statistical significance of areas with birth defects clusters. SaTScan²⁵ version 9.3.1 was used to run the spatial scan statistics because it corrects for multiple comparisons, adjusts for population heterogeneity in the study area, and identifies clusters without *a priori* specification of their suspected location or size overcoming pre selection bias.¹⁶ The visualization of spatial patterns of overall statewide SEB smoothed birth defects rates and the results of the spatial scan statistics in the ZIP Codes with the highest rates were consistent and easily located. Identification of spatial clusters of health conditions allows for effective identification and planning of specific health needs of the populations with the highest prevalence, incidence etc. For example, high rates in the smoothed risk maps were observed but cluster detection highlighted ZIP Codes with a statistically significant birth defects cluster in Clark County.

Despite the aforementioned limitations, we present the first study using spatial analyses of birth defects in Nevada. A spatial cluster of birth defects at ZIP Code level was identified in Clark County, Nevada. In addition, it was evident that birth defects rates vary within a county which implies that prevention efforts should be targeted at the neighborhood level so that the affected populations receive targeted intervention. Furthermore, this study demonstrated that spatial analysis, cluster detection methods, and GIS are useful tools in birth defects surveillance which identify neighborhoods (ZIP Codes) with the most need to target scarce resources appropriately.

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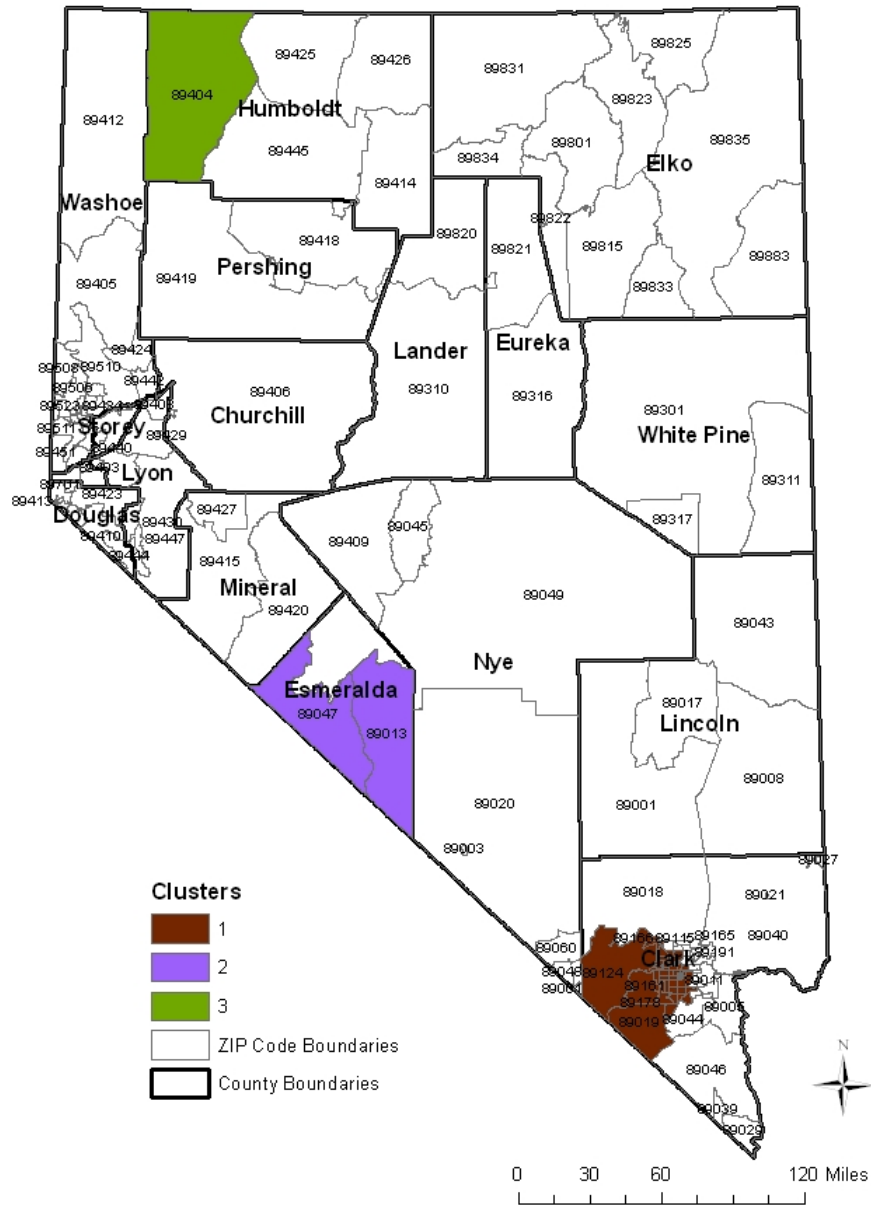
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Table 4.1 Spatial Clusters of Birth Defects among Nevada Residents, 2005-2011

Cluster	Number of ZIP Codes	Live births	Observed birth defects	Expected number of birth defects	Annual number of birth defects/100,000 live births	p-value
1	42	129,058	10,100	8518.78	7831.1	<.0001*
2	3	24	6	1.58	25016.6	0.79
3	1	2	2	0.13	100066.4	0.80

*Significant cluster

Figure 4.1 Spatial Clusters of Birth Defects among Nevada Residents, 2005-2011



Note: Cluster 1 is significant with a p-value $< .0001$. Clusters 2 and 3 are not significant with p-values 0.791 and 0.795 respectively.

Figure 4.2 Spatial Empirical Bayes Birth Defects Smoothed Rates, Nevada Residents, 2005 -2011

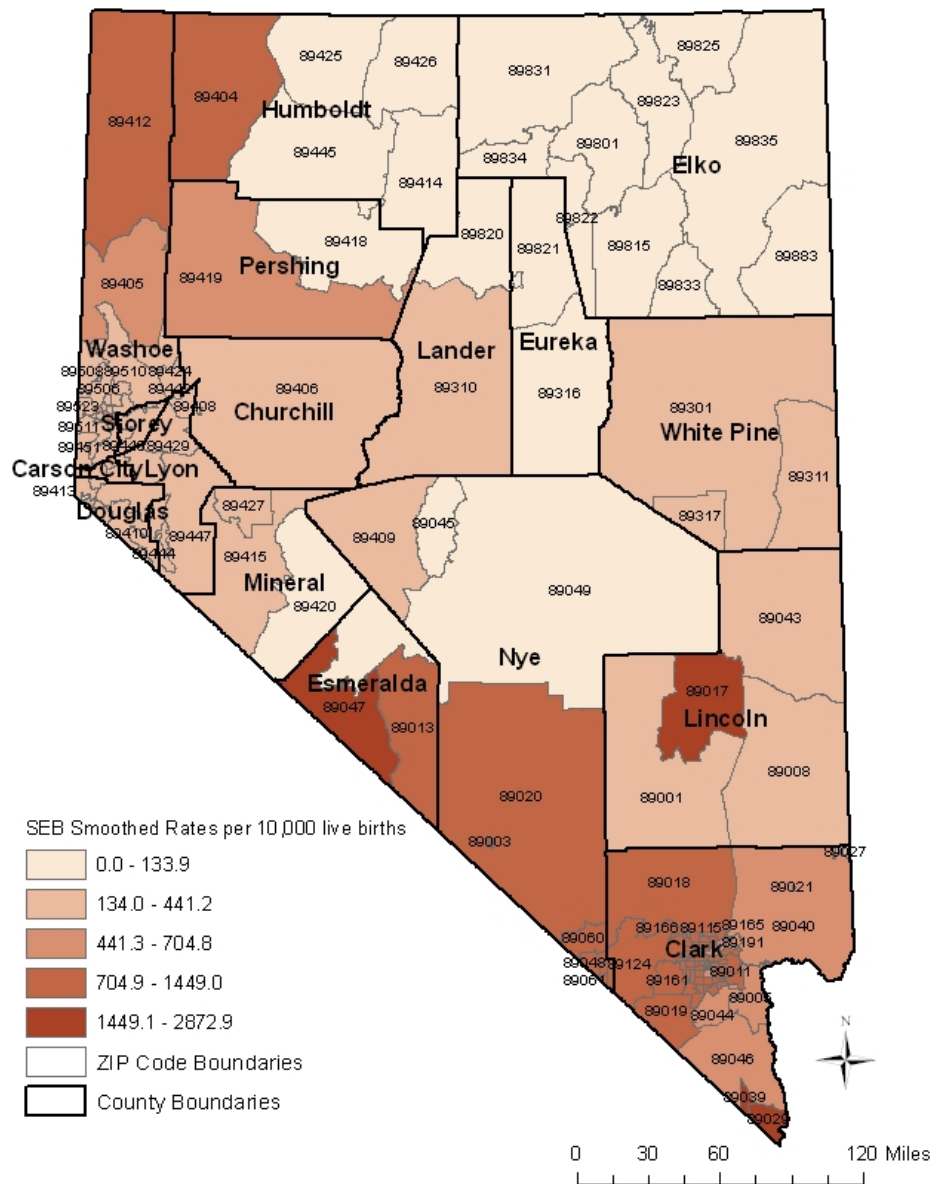
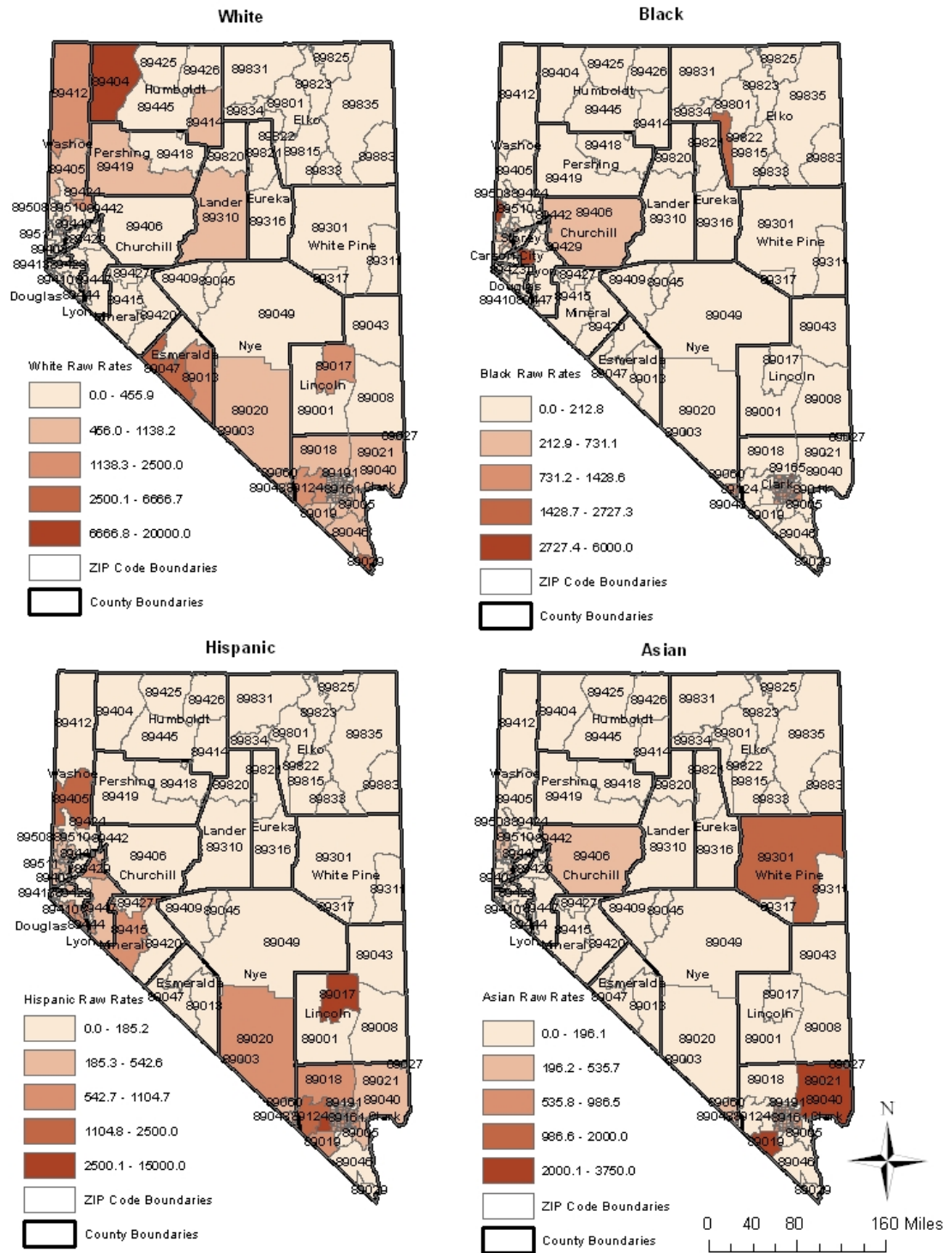


Figure 4.3 Spatial Distribution of Birth Defects Unsmoothed (Raw) Rates (per 10,000 live births) by Race/Ethnicity, Nevada Residents, 2005-2011



Chapter 5: Summary and Recommendations

Birth defects surveillance programs in the US use various case ascertainment methods (passive versus active surveillance), include various pregnancy outcomes (live births only, live births and stillbirths, and all pregnancy outcomes), and use different nomenclature (ICD-9-CM and CDC/BPA) in their surveillance efforts. The change in nomenclature from ICD-9-CM to the more comprehensive ICD-10-CM in 2015 will have an impact on birth defects surveillance, especially the comparison of data in the two coding systems. Individual state's birth defects surveillance legislation and resources available greatly determine the scope of birth defects surveillance efforts of state programs. However, the effects of this nomenclature change can only be fully assessed once the implementation of ICD-10-CM has occurred.

The interpregnancy interval and birth defects study is one of the few studies using active case ascertainment of birth defects (even if based on passive surveillance) that assessed the independent risk factor of interpregnancy interval on birth defects. Our findings can be used to inform maternal child health programs and health care providers on the need to enlighten women of childbearing age that a long interpregnancy interval is a risk factor for birth defects, although half of all pregnancies in the US are unplanned. This will empower women to make informed decisions on the most favorable interpregnancy interval if they plan to have multiple children. Traditionally, most maternal child health programs and health care providers have focused on adverse pregnancy outcomes, such as preterm births and low birth weight, which are risk factors for infant mortality. However, it may help to include interpregnancy interval on the campaign of reducing infant mortality because birth defects are the leading cause of infant deaths.

To our knowledge, the spatial analysis of birth defects at ZIP Code level is the first study to investigate birth defects in Nevada. A spatial cluster of birth defects at ZIP Code level was identified in Clark County, Nevada. In addition, it was evident that birth

defects rates vary within a county which implies that prevention efforts should be at the neighborhood level so that the affected populations receive targeted intervention.

Furthermore, this study demonstrated that spatial analysis, cluster detection methods, and GIS are useful tools in birth defects surveillance which identify neighborhoods (ZIP Codes) with the most need to target scarce resources appropriately. In addition, more research is necessary to investigate further risk factors for these birth defects clusters and for specific birth defects.