

Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

Marissa Person

Date

Risk Factors for Infectious Disease Infant Mortality in the United States, 2008-2009

By

Marissa Person
Master of Science in Public Health

Biostatistics

Vicki Stover Hertzberg, Ph.D.
(Thesis Advisor)

Robert C. Holman, M.S.
Reader

Risk Factors for Infectious Disease Infant Mortality in the United States, 2008-2009

By

Marissa Person

B.S.
University of Michigan
2010

Thesis Committee Chair: Vicki Stover Hertzberg, Ph.D.
Reader: Robert C. Holman, M.S.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Biostatistics
2013

Abstract

Risk Factors for Infectious Disease Infant Mortality in the United States, 2008-2009

By Marissa Person

PURPOSE: The objective of this study is to determine maternal and infant risk factors associated with infant deaths due to infectious diseases (IDs) in the United States and the role that birth weight and infant race have on infant ID mortality.

METHODS: A retrospective case-control study was conducted to determine infant and maternal risk factors for ID infant mortality occurring in 2008-2009 using the Period Linked Birth/Infant Death data among singleton infants born in the United States to U.S. residents. An ID death was defined when the underlying cause of death was an ID International Classification of Diseases, 10th Revision code. A 1:1 ratio of cases to controls was selected with controls defined as infants surviving to the end of their birth year. Risk factors for infant ID deaths were determined with multivariable logistic regression models stratified by birth weight [low (LBW) and normal birth-weight (NBW)] and also with continuous birth weight in spline regression. A sub-analysis of births recorded with the 2003 birth certificate was conducted to determine the role of maternal education and prenatal care in infant mortality due to IDs.

RESULTS: There were 3,798 infant deaths (2,633 LBW and 1,158 NBW) due to IDs during 2008-2009 in the United States. Male sex, younger maternal age (<25 years), a live birth order of fourth or more and low 5-minute Apgar score were associated with ID death among LBW and NBW infants. Non-Hispanic ethnicity and having an unmarried mother were both associated with increased odds of ID death among NBW infants, while for LBW infants, black race was associated with increased odds of death. Among infants with a 2003 birth certificate, less than adequate prenatal care was a risk factor for NBW infant ID deaths. American Indian/Alaska Native (AI/AN) race was a risk factor for infant mortality due to ID in the spline regression analysis.

DISCUSSION: Awareness of ID mortality risk factors should lead to improved prevention of IDs for children with ID mortality risk factors in their first year of life. Future studies should focus on eliminating disparities in infant death due to IDs.

Risk Factors for Infectious Disease Infant Mortality in the United States, 2008-2009

By

Marissa Person

B.S.
University of Michigan
2010

Thesis Committee Chair: Vicki Stover Hertzberg, Ph.D.
Reader: Robert C. Holman, M.S.

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Biostatistics
2013

ACKNOWLEDGEMENTS

I would like to thank Professor Vicki Stover Hertzberg at Emory University for her willingness to be my thesis advisor and for all of the support and feedback she gave me on my thesis. I would also like to thank Robert Holman at the Centers for Disease Control and Prevention for the idea of this thesis topic, for being my thesis reader, and for all of the support, time, and feedback he gave in helping me accomplish this project. Thanks to Laura Callinan and Jason Mehal for taking the time to read and edit sections of my thesis. Lastly, I would like to thank the Rollins School of Public Health for a great two years and for increasing my knowledge in biostatistics and the field of public health.

TABLE OF CONTENTS

	Page
List of Tables.....	i
List of Figures.....	ii
1. Introduction.....	1
1.1. Problem Statement.....	1
1.2. Purpose Statement.....	2
1.3. Significance Statement.....	2
1.4. Definition of Terms.....	3
2. Review of the Literature.....	4
2.1. Global Burden of Infectious Disease.....	4
2.2. Global Infant Mortality.....	6
2.3. Infectious Disease in the United States.....	7
2.4. Burden of Infectious Disease in Infants in the United States.....	11
3. Methodology.....	18
3.1. 2008 and 2009 Period Linked Birth/Infant Death Data Set.....	18
3.2. Study Design.....	19
3.3. Variables.....	20
3.4. Analyses.....	21
4. Results.....	25
4.1. Overall Analysis.....	25
4.2. Stratification by Birth Weight.....	26
4.2a. Low Birth Weight.....	26

4.2b.	Normal Birth Weight.....	26
4.2c.	Multivariable Logistic Regression Models.....	27
4.3.	Continuous Birth Weight.....	28
4.4.	2003 Birth Certificate Sub-Analysis.....	29
4.4a.	Low Birth Weight.....	30
4.4b.	Normal Birth Weight.....	31
4.4c.	Multivariable Logistic Regression Models.....	32
5.	Discussion.....	34
	References.....	38
	Appendix.....	41

LIST OF TABLES

- TABLE 1. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, United States, 2008-2009
- TABLE 2. Proportion of Selected Maternal and Infant Characteristics by Birth Weight, United States, 2008-2009
- TABLE 3. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, Stratified by Birth Weight, United States, 2008-2009
- TABLE 4. Odds Ratio Estimates and 95% Confidence Intervals of Selected Maternal and Infant Characteristics for the Multivariable Logistic Regression Analysis Stratified by Birth Weight, United States, 2008-2009
- TABLE 5. Multivariable Logistic Regression Spline Analysis Results, Select Maternal and Infant Characteristics, United States, 2008-2009
- TABLE 6. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, 2003 Birth Certificate Sub-Analysis, United States, 2008-2009
- TABLE 7. Proportion of Selected Maternal and Infant Characteristics by Birth Weight, 2003 Birth Certificate Sub-Analysis, United States, 2008-2009
- TABLE 8. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, 2003 Birth Certificate Sub-Analysis, Stratified by Birth Weight, United States, 2008-2009
- TABLE 9. Odds Ratio Estimates and 95% Confidence Intervals of Selected Maternal and Infant Characteristics for the Multivariable Logistic Regression Analysis Stratified by Birth Weight, 2003 Birth Certificate Sub-Analysis, United States, 2008-2009

LIST OF FIGURES

FIGURE 1. Proportion of Neonatal vs. Postneonatal Deaths Overall and by Birth Weight,
United States, 2008-2009

FIGURE 2. Proportion of Infectious Disease Infant Deaths by Birth Weight,
United States, 2008-2009

FIGURE 3. Log Odds Ratio by Birth Weight for Cases compared to Controls
adjusting for Select Maternal and Infant Characteristics, United States, 2008
2009

1. Introduction

1.1. Problem Statement

Infectious diseases (IDs) are a public health threat both globally and in the United States (World Health Organization, 2011; U.S. Department of Health and Human Services, 2012). The burden of ID morbidity and mortality globally is high among all ages, and the majority of IDs are preventable (World Health Organization, 1999). ID deaths in children less than 5 years old are still a major problem globally (World Health Organization, 1999), especially among infants less than 28 days old (neonates) (World Health Organization, 2013b).

Implementation of vaccines and other disease prevention programs have reduced IDs in the United States (National Center for Environmental Health; National Center for Health Statistics; National Center for Infectious Diseases; CDC, 1999) During 1900-1980, the mortality rate due to IDs decreased in the United States (G.L. Armstrong, Conn, & Pinner, 1999). However, ID agents are becoming resistant to medication, new IDs are emerging, and IDs that were a problem of the past are re-emerging in the United States and worldwide (National Center for Environmental Health; National Center for Health Statistics; National Center for Infectious Diseases; CDC, 1999). There were at least 335 IDs that emerged in humans globally from 1940 to 2004. (Jones et al., 2008)

There is a lack of information on the infant mortality rate due to overall ID in the United States. In fact, no information could be found on the infant mortality rate due to overall ID in the United States after the 1980s (Read, Troendle, & Klebanoff, 1997). Also, no information could be found on the maternal and infant risk factors for infant overall ID deaths since the 1980s (Read, Troendle, & Klebanoff, 1997); however, risk

factors for infant death due to specific diseases have been addressed (Singleton et al., 2009; Mehal et al., 2012). Knowledge of the risk factors for ID infant death in the United States is important in order to reduce ID deaths among infants. Knowledge of disparities related to infant ID deaths would help strategize ID prevention measures to reduce the mortality and morbidity among infants.

1.2. Purpose Statement

The objective of this study is to determine the maternal and infant risk factors associated with infant deaths due to ID in the United States. Furthermore, this study aims to determine the role that birth weight and infant race in particular have on infant ID mortality.

1.3. Significance Statement

It is important to know risk factors for infant ID deaths and whether or not risk factors have changed over time; Knowing risk factors for infant ID deaths is key to prevention, and should influence future investigations regarding infant ID death. Mothers may be able to reduce the risk of an ID death outcome for their infant with certain behavioral practices, such as eliminating smoking and alcohol which are known to increase the risk of infant mortality due to lower respiratory tract infections (Singleton et al., 2009). Knowing the disparities that exist in ID infant deaths can help direct the focus of future studies to determine why these disparities exist. Determination of risk factors, such as maternal marital status or live birth order, should lead to more focus in ID prevention measures during a child's first year of life.

1.4. Definition of Terms

An infant is a child that is less than one year of age. The term “neonate” refers to an infant that is less than 28 days old. The term “postneonate” refers to an infant that is at least 28 days old. The term “low birth weight (LBW) infants” refers to infants that weigh less than 2500 grams at delivery. Normal birth weight (NBW) infants are those that weigh at least 2500 grams at delivery.

2. Review of the Literature

2.1. *Global Burden of Infectious Disease*

In 1998, at least 13.3 million deaths (25% of all deaths) globally were caused by IDs (World Health Organization, 1999). This may be an underestimate of the true percentage of ID deaths because infections could be an underlying cause of cancer, respiratory/digestive, and cardiovascular deaths, but not reported as an ID death (World Health Organization, 1999). IDs caused 63% of deaths among children less than 5 years old and 48% of deaths in people <44 years of age worldwide (World Health Organization, 1999). The top 6 diseases that accounted for the majority of ID deaths (90%) globally in 1998 were acute respiratory infections (including influenza and pneumonia) (3.5 million deaths), acquired immunodeficiency syndrome (AIDS) (2.3 million deaths), diarrhoeal diseases (2.2 million deaths), tuberculosis (TB) (1.5 million deaths), malaria (1.1 million deaths), and measles (0.9 million deaths) (World Health Organization, 1999). AIDS and TB caused more deaths worldwide in people over 5 years old than in children less than 5, whereas diarrhoeal diseases, malaria, and measles caused more deaths in children less than 5 (World Health Organization, 1999). Acute respiratory infections affected all ages equally (World Health Organization, 1999). ID was not only a major cause of death globally in 1998, but also caused a significant loss in Disability Adjusted Life Years (DALYs), with at least 365 million DALYs lost, the majority due to acute respiratory infections (83 million), diarrhoeal diseases (73 million), and human immunodeficiency virus (HIV)/AIDS (71 million) (World Health Organization, 1999).

By 2000, IDs were responsible for a third of worldwide deaths; 14% of deaths in developed regions were caused by IDs and 55% of deaths in developing regions were caused by IDs, showing a disparity in the burden of IDs (University of California, Santa

Cruz, 2007). In 2001, HIV/AIDS, lower respiratory infections, diarrhoeal diseases, malaria, tuberculosis, and measles were among the top 10 causes of death in developing countries (University of California, Santa Cruz, 2007). Lower respiratory infections and tuberculosis were among the top 10 causes of death in developed countries, with lower respiratory infections ranking fourth (University of California, Santa Cruz, 2007). A large proportion of these deaths were preventable using strategies already established. (University of California, Santa Cruz, 2007)

In 2008, lower respiratory infections, diarrhoeal diseases, HIV/AIDS, and tuberculosis were among the top ten causes of death in low- and middle-income countries (World Health Organization, 2013a). Lower respiratory infections were the 5th leading cause of death in high-income countries. (World Health Organization, 2013a)

Sixty-eight percent of approximately 9 million deaths of children less than 5 years old worldwide were due to IDs in 2008 (Black et al., 2010). Pneumonia, diarrhea, and malaria were top ranked IDs in causing child mortality and IDs altogether were the most important contributors to child mortality (Black et al., 2010). Eighteen percent of deaths worldwide in children less than 5 years old were due to pneumonia, 15% due to diarrhea, and 8% due to malaria. Almost all countries still suffer from child mortality due to preventable causes and a challenge is to reduce these deaths. These estimates may underestimate the true burden of IDs because countries with the highest number of deaths provide limited data on the causes of child mortality. (Black et al., 2010)

Tuberculosis mortality decreased by more than a third from 1990 to 2009 but the number of new cases worldwide continued to increase due to the population growing at a faster pace than the incidence rate per capita was decreasing (World Health Organization,

2011). The number of HIV cases globally has also increased (World Health Organization, 2011). The number of cases was 23% higher in 2009 than it was in 1999. This is mainly due to people living longer with HIV because of antiretroviral therapy – the annual number of new HIV cases is estimated to have declined by 19% in this same time period (World Health Organization, 2011).

There are many cost-effective strategies for preventing ID deaths. These strategies include childhood vaccinations, bednets, oral rehydration therapy, antibiotics, condom promotion, and sex education (World Health Organization, 1999). While there are some IDs that are close to eradication or elimination, there are new and re-emerging IDs of concern, including infections resistant to antibiotics. (World Health Organization, 1999)

2.2. Global Infant Mortality

Mortality rates for children <5 years of age have decreased globally from 1990 to 2009, but rates of decline in neonatal mortality rates are less than those in older children (World Health Organization, 2011). Neonatal deaths comprised 40% of deaths in children that were less than 5 years of age in 2009 (World Health Organization, 2011). In 1990 the global neonatal mortality rate was 33 per 1000 live births. It decreased to 29 per 1000 live births in 2000 and to 24 per 1000 live births in 2009 (World Health Organization, 2011). The infant mortality rate decreased from 62 per 1000 live births in 1990 to 54 in 2000 and 42 in 2009. (World Health Organization, 2011) Antenatal care has been shown to improve chances of infant survival (Partridge, Balayla, Holcroft, & Abenhaim, 2012). In 2000-2010, 80% of pregnant women worldwide had at least one prenatal visit (World Health Organization, 2011). The World Health Organization (WHO) recommends at least

four prenatal visits; only 53% of pregnant women during 2000-2010 had at least four prenatal visits (World Health Organization, 2011). Birth rate is also a predictor of newborn survival and health; (World Health Organization, 2011) LBW is associated with ID mortality. (Jason, 1989) An estimated 15% of newborns had a LBW in 2000-2009. (World Health Organization, 2011) The neonatal mortality rate in developed regions decreased from 7 deaths per 1,000 live births in 1990 to 4 deaths per 1,000 live births in 2010, a 43% decrease (United Nations Inter-agency Group for Child Mortality Estimation, 2011). The neonatal mortality rate in developing regions decreased from 36 deaths per 1,000 live births in 1990 to 25 deaths per 1,000 live births in 2010, a 31% decrease. (United Nations Inter-agency Group for Child Mortality Estimation, 2011)

In 2008, IDs were an important cause of death globally among neonates, particularly pneumonia and sepsis (Black et al., 2010) In 2010, there were 3.1 million neonatal deaths globally and infections were the cause of approximately 1/3 of these deaths. (World Health Organization, 2013b)

2.3. Infectious Disease in the United States

IDs have been on the decline in industrialized countries for most of the 20th century, but toward the end of the 20th century there has been the emergence and reemergence of IDs. (G. L. Armstrong & Pinner, 1999) ID outpatient and inpatient visit rates and ID mortality rates can estimate the burden of IDs in the United States.

In a study using the National Ambulatory Medical Care Survey, it was estimated that in the years 1980 to 1996, 19% of outpatient visits for all ages were due to IDs (G. L. Armstrong & Pinner, 1999). The average rate of ID outpatient visits for all ages was 526

per 1000 people per year. The highest rate of ID outpatient visits by age group was among children <5 years of age; 45% of outpatient visits were due to IDs compared with about 16% of outpatient visits combining all other age groups. This study also showed disparities in ID outpatient visits. ID outpatient visit rates were higher for females compared to males and higher in non-Hispanic whites compared to non-Hispanic blacks and Hispanics. There was a significant increase in the ID outpatient visit rate between 1980 and 1990 ($P=0.006$) and a significant decrease in ID outpatient visits ($P=0.03$), as well as a significant decrease in the proportion of ID visits ($P=0.02$) from 1990 to 1996. Upper and lower respiratory tract infections, otitis media and otitis externa, and skin infections comprised 76.4% of the ID visits.

A study using the National Hospitalization Discharge Survey for the years 1980 to 1994 showed an increasing burden of IDs between 1989 and 1994 due to an increasing proportion of ID hospitalizations (Simonsen, Conn, Pinner, & Teutsch, 1998). The ID hospitalization rate declined by 12% from 1980 to 1994 but the proportion of ID hospitalizations increased. Another study used the Nationwide Inpatient Sample for the years 1998-2006 to look at ID hospitalizations within the United States (Christensen et al., 2009). This study focused on trends and the epidemiology of hospitalizations due to first-listed IDs, discharge records with an ID as the primary diagnosis. The study found that the average annual age-adjusted rate of hospitalization for those that had a first-listed ID was 154.4 hospitalizations per 10,000 people (95% confidence interval (CI): 153.3-155.5). There was a small increase in the rate of first-listed ID hospitalizations over the time period ($P < 0.001$) with the lowest rate observed in 1998 and the highest rate seen in 2005. The in-hospital ID fatality rate over the study period was 4% (Standard Error (SE):

0.02%). There was a slight decrease in the overall in-hospital fatality rate from 1998-2006. Trends in ID hospitalizations over time varied by race. The hospitalization rate increased slightly for patients of Hispanic origin, decreased slightly for people of non-Hispanic black and Asian/Pacific Islander race and there was not a significant change for people of non-Hispanic white race. Patients of black race had the highest ID rates. Excluding adults that were at least 80 years old, children under the age of 5 years had the highest hospitalization rate due to IDs. The largest percentage of first-listed ID hospitalizations was due to lower respiratory tract infections, making up 34.3% (SE: 0.10%) of hospitalizations with an ID primary diagnosis. The burden of ID hospitalizations are also reflected in the hospital charges, with more than 865 billion (SE: 9.6 billion) in hospital charges for all of the ID hospitalizations in the years 1998-2006. ID hospitalizations in this period had a median charge of \$11,651 (IQR: \$6,457-\$22,423).

The mortality rate due to IDs increased in the last decades at the end of the 20th century (G.L. Armstrong, Conn, & Pinner, 1999; Pinner et al., 1996). A study that looked at IDs as the underlying cause of death from the Multiple Cause of Death data for 1980-1992 found that ID mortality increased by 58% in this period (41 deaths per 100,000 population in 1980 to 65 deaths per 100,000 population in 1992) (Pinner et al., 1996). However, the ID mortality rate for children less than 5 years old decreased in this period (28 per 100,000 in 1980 to 20 per 100,000 in 1992). The ID mortality rate for people of black race was 36% higher than the overall population ID death rate in 1992, showing racial disparities in ID deaths. One main reason for the increase in the ID death rate from 1980 to 1992 was the emergence of HIV (Pinner et al., 1996). However, the ID death rate during 1980-1992 still increased by 22% when all deaths in which the death certificate

mentioned HIV were excluded (Pinner et al., 1996). In 1980, IDs were the fifth leading underlying cause of death in the United States, whereas in 1992 this increased to third (Pinner et al., 1996). This study was conservative in estimating and reporting ID burden in the United States because it only reported mortality and not hospitalizations, outpatient visits, or other measures of ID burden that did not ultimately end in death (Pinner et al., 1996). ID mortality was calculated based on the underlying cause of death in this study. There are instances where IDs could be listed on the death certificate and are attributable to the death but are not the underlying cause of death. Also, some ICD-9 codes represent IDs sometimes but not all the time and these codes were excluded from the analysis. Some illnesses might be caused by IDs but the etiology is unknown at this point which could lead to under-reporting of ID deaths. Another study looked at the trends in mortality due to IDs from 1900 to 1996 (G.L. Armstrong, Conn, & Pinner, 1999). The ID mortality rate decreased from 1900 (797 deaths per 100,000) to 1980 (36 deaths per 100,000), increased from 1980 to 1995 (63 deaths per 100,000) and then dropped in 1996 (59 deaths per 100,000). While the ID mortality rate decreased in the first half of the 20th century, the non-infectious disease mortality rate stayed relatively constant. The increase in the ID mortality rate from 1981 to 1995 was consistent, increasing 4.8% each year. A decrease in AIDS mortality was a factor in the ID mortality rate decreasing from 1995 to 1996 (G.L. Armstrong, Conn, & Pinner, 1999).

A study looking at the difference in ID mortality between people of black and white race in the United States showed that there was still a disparity between races from 1979 to 1989 (Richardus & Kunst, 2001). This study used the National Longitudinal Mortality Study to obtain data. The ID mortality rate ratio comparing blacks to whites

was 1.53 (95% CI: 1.33-1.76) after adjusting for sex and age. The disparity was lessened but still remained when also adjusting for education and family income (RR=1.34, 95% CI: 1.16-1.54). While income and education played a role in the ID mortality disparity, it did not explain all of the disparity. This racial disparity has been shown to exist for HIV/AIDS, tuberculosis, septicemia, and infections of the kidneys and urinary tract. ID deaths made up 4.9% of deaths due to any cause, but approximately 9% of the difference in black all-cause death rates compared to white all-cause death rates were due to IDs.

Vaccines are a successful way to prevent IDs and there is still a need to increase the vaccine coverage rate in the United States (U.S. Department of Health and Human Services, 2012). Vaccines are a preventive health measure and are ranked high in terms of cost-effectiveness (U.S. Department of Health and Human Services, 2012). Vaccines save 33,000 lives per birth cohort and the direct costs of health care decrease by 9.9 billion dollars for each birth cohort that receives routine immunizations (U.S. Department of Health and Human Services, 2012). Vaccine-preventable diseases still kill 300 children and around 42,000 adults each year in the United States (U.S. Department of Health and Human Services, 2012). Mortality due to IDs can be decreased by increasing the immunization rate and increasing disease surveillance. (U.S. Department of Health and Human Services, 2012)

2.4. Burden of Infectious Disease in Infants in the United States

A study looking at all deaths that took place in 1980 using mortality data from the National Center for Health Statistics (NCHS) found that 12.5% of infant deaths were due to IDs and 4.7% of infant deaths had a first-listed ID death (Jason & Jarvis, 1987). The

highest percentage of deaths due to IDs was in the postneonatal age group, specifically infants dying at 10 to 11 months old. ID deaths accounted for a higher proportion of deaths in black infants (13.7%) than in white infants (11.9%). The “other” race group had the highest proportion of deaths related to IDs (14.9%). Black infants had a higher ID-related mortality rate (2.9 per 1,000 live births) than white infants (1.3 per 1,000 live births). Black infants also had a higher LBW related mortality rate (10.4 per 1,000 live births) than white infants (4.5 per 1,000 live births). NBW infants with no congenital defects had the highest proportion of ID related deaths, compared to the proportion of ID deaths in LBW infants and those with congenital defects. The proportion of infant deaths related to IDs was greatest in the postneonatal period for LBW infants (31%) but greatest in the neonatal period for NBW infants with no congenital defects (29.1%); multiple cause-of-death data were used for this study. Thus the proportions showed deaths related to IDs. This study did not show if the ID was a main cause in the death. The authors still believe that the burden of IDs are underrepresented in this study due to the possibility that the mother had an ID that led to other factors that increase the chance of infant death such as early delivery, congenital defects, or LBW. Also some ICD codes were not included that could represent an ID. The authors suggest that some prevention strategies would be to focus on improving the vaccination process available to infants for diseases that are common in infancy. It is also important to understand the ways IDs in the mother could be transferred to or affect the infant and to develop and improve prevention strategies. Furthermore, infants can contract nosocomial infections in the neonatal intensive care units and more infants are going to day cares where infections can spread. Work needs to be done on preventing infections in these environments.

A study using Linked Birth/Infant Death data from NCHS for the years 1983 to 1987 examined maternal and infant characteristics and how the characteristics are related to ID deaths (Read, Troendle, & Klebanoff, 1997). Nine percent of infant deaths from 1983 to 1987 were caused by IDs. The infant ID mortality rate in 1983 was 93 deaths per 100,000 live births. This significantly decreased ($P < 0.001$) by 1987 to 86 deaths per 100,000 live births. Most of the noncongenital ID deaths were for postneonatal infants. Looking only at noncongenital infections (which comprised approximately 90% of all ID deaths), infants born to a young mother (< 20 years old) had higher death rates than older mothers in the early neonatal, late neonatal, and postneonatal periods. Infants born to mothers of black race had the highest mortality rates in the early and late neonatal periods, and infants born to mothers of Native American race had the highest mortality rates in the postneonatal period closely followed by infants born to mothers of black race. Infants born to a mother with less than a high school education had higher mortality rates than those born to a mother with at least a high school degree. An unmarried mother, less than 10 prenatal visits, male gender, LBW, and higher live birth order also were associated with higher ID death rates. Infants of mothers of black race had a higher risk of dying from noncongenital infections in the postneonatal period than infants of mothers of white or Asian race (odds ratio (OR): 1.45, 95% CI:1.37-1.53). Very LBW infants (< 1500 grams) had much higher odds of dying of a noncongenital ID in the postneonatal period compared to NBW infants (OR: 22.83, 95% CI: 21.12-24.68). Moderately LBW (1500-2499 grams) infants also had higher odds of dying from noncongenital infections in the postneonatal period than NBW infants (OR: 3.23, 95% CI: 3.01-3.46). Other factors that increased risk of dying from noncongenital infections in the postneonatal

period were an inadequacy in prenatal care, higher live birth order, male gender, and being born to an unmarried, young, or less educated mother. ID deaths ranked fourth in leading causes of death in this dataset, and ranked as the third leading cause of postneonatal death in this dataset.

A study using the 2003 Kids' Inpatient Database shows that approximately 42.8% of infant hospitalizations in 2003 were due to a primary diagnosis of IDs (Yorita, Holman, Sejvar, Steiner, & Schonberger, 2008). The overall hospitalization rate for IDs was 7010.8 hospitalizations per 100,000 live births (95% CI: 6618.3-7403.3). The postneonatal hospitalization rate was greater than the neonatal hospitalization rate, and two month-old infants had the greatest proportion of hospitalizations due to IDs. Hispanic infants had the highest hospitalization rate due to IDs (7341.1 hospitalizations per 100,000 live births [95% CI: 6306.5-8675.7]) followed by non-Hispanic blacks (5812.8 [95% CI: 5088.8-6526.8]). The hospitalization rate for non-Hispanic whites was 3921.6 (95% CI: 3623.0-4220.2). Septicemia of the newborn was the leading cause of death among neonates and acute respiratory failure was the leading cause of death among postneonates. Approximately 59% of ID hospitalizations in infants were due to lower respiratory tract infections. The burden of infant ID hospitalizations can also be seen through hospital charges, which have increased over time and are a considerable expense. IDs in infants accounted for almost 3 billion dollars in total hospital charges for 2003.

LBW has been shown to be associated with infant mortality, especially in the perinatal and neonatal period. (Jason & Jarvis, 1987) LBW has also been shown to be a risk factor for ID deaths. (Read, Troendle, & Klebanoff, 1997) A study that used mortality data from the NCHS for the years 1968 to 1982 showed that although the

number and percentage of LBW live-birth infants decreased during this period, the proportion of IDs associated with LBW infant deaths and the infant mortality rates related to IDs in LBW infants increased (Jason, 1989). A disparity between white and black infants is shown in this study. In the four-year period from 1979 to 1982, black infants had a higher ID LBW mortality rate than white infants for each year. Sepsis played an important role in LBW infant deaths that were associated with IDs; 44% of early neonatal ID deaths, 47% of late neonatal ID deaths, and 35% of postneonatal ID deaths from 1968 to 1982 were due to sepsis. During 2000-2009, eight percent of newborns were considered LBW. (World Health Organization, 2011)

Studies have shown racial disparities in infant mortality, including disparities in ID deaths. A study using the 1995 to 1997 linked birth/infant death data sets in California that restricted the data to infants born to black, Latina, and white mothers showed the disparity in all-cause mortality and in ID deaths (Hessol & Fuentes-Afflick, 2005). The study showed that the infant mortality rate was highest among infants of black mothers. The neonatal and the postneonatal mortality rate due to infectious and parasitic diseases was highest in infants born to black mothers, although the infectious and parasitic disease infant neonatal mortality rate among infants born to black mothers was similar to that of infants born to white mothers. The neonatal mortality rate due to infectious and parasitic diseases was 2.98 deaths per 100,000 live births for infants born to mothers of black race, 2.54 deaths per 100,000 live births for infants born to mothers of white race, and 1.05 deaths per 100,000 live births for infants born to Latina mothers. The postneonatal mortality rate due to infectious and parasitic diseases was 16.90 deaths per 100,000 live births for infants born to mothers of black race, 12.33 deaths per 100,000 live births for

infants born to Latina mothers and 7.43 deaths per 100,000 live births for infants born to mothers of white race. This study stratified by ethnicity in the multivariable logistic regression analyses to determine if risk factors for infant mortality changed between ethnicities and found that neonatal and postneonatal mortality were different based on mother's ethnicity.

Another study using the 1999-2007 North Carolina linked birth/infant death dataset showed that infants had a higher risk for postneonatal death if they were born to a mother of black race but that the risk for neonatal mortality was similar among all race and ethnic groups after adjusting for infant and maternal characteristics (Kitsantas & Gaffney, 2010). Death rates due to infection and LBW in both the neonatal and postneonatal periods were higher for infants with a mother of black race. The neonatal mortality rate due to infections was 50.75 per 100,000 live births for infants born to mothers of black race, 17.98 per 100,000 live births for infants born to mothers of white race and 18.26 per 100,000 live births for infants born to mothers of Hispanic race/ethnicity. The postneonatal mortality rate due to ID was 23.5 per 100,000 live births for infants born to mothers of black race, 7.38 per 100,000 live births for infants born to mothers of white race, and 14.75 per 100,000 live births for infants born to mothers of Hispanic race/ethnicity. The neonatal mortality rate due to prematurity or LBW was 295.2 per 100,000 live births for infants born to mothers of black race, 61.19 per 100,000 live births for infants born to mothers of white race and 89.23 per 100,000 live births for infants born to mothers of Hispanic race/ethnicity. The postneonatal mortality rate due to prematurity or LBW was 4.8 per 100,000 live births for infants born to mothers of black race, 1.1 per 100,000 live births for infants born to mothers of white race, and 2.1 per

100,000 live births for infants born to mothers of Hispanic race/ethnicity. This study shows that a disparity between race groups exists and that LBW is associated with higher risk for both neonatal mortality and postneonatal mortality.

Recent studies using the linked infant birth/infant death data set have focused on infant mortality rates and selected maternal and infant risk factors for specific ID infant deaths (Singleton et al., 2009; Mehal et al., 2012). No information could be found since the 1980s on infant mortality rates and maternal and infant risk factors for overall ID infant mortality.

3. Methodology

3.1. 2008 and 2009 Period Linked Birth/Infant Death Data Set

For this study, the Period Linked Birth/Infant Death public use data files for 2008 and 2009 from the National Center for Health Statistics (NCHS) were analyzed (National Center for Health Statistics, 2011, 2012). The Period Linked Birth/Infant Death public use data comes in three files. One file (“linked” file) links the death certificate of infants who died in the specified year (2008 or 2009) to their birth certificate; the birth could have occurred the same year the infant died or the year before (as long as death occurred at less than one year of age). A second file (NCHS natality file) contains all live births that took place in the specified year (2008 or 2009). The third file (“unlinked” file) contains all of the infant death certificates from 2008 or 2009 for which no matching birth certificate could be found. Only 1.3% of records in 2008 and 1.4% of records in 2009 were unlinked. Records in the “linked” file are weighted to account for the unlinked death certificates (National Center for Health Statistics, 2011, 2012).

Some states still use the 1989 revision of the U.S. Standard Certificate of Live Birth, while other states have implemented the 2003 revision (National Center for Health Statistics, 2011, 2012). Twenty-two states (53% of U.S. births in 2007) had implemented use of the 2003 revision of the U.S. Standard Certificate of Live Birth on or before January 1st, 2007 (Mathews & MacDorman, 2012). The number of states using the 2003 revision of the U.S. Standard Certificate of Live Birth had increased to 27 (65% of U.S. births in 2008) by January 1st, 2008 (Mathews & MacDorman, 2012) and 28 (66% of U.S. births in 2009) by January 1st, 2009 (National Center for Health Statistics, 2012). Some variables are not comparable between these revisions including maternal smoking

status, maternal education, and the trimester prenatal care began (Mathews & MacDorman, 2012, 2013).

Maternal age, marital status, and race as recorded on the birth certificate were missing for less than 1% of records in both 2008 and 2009. (Mathews & MacDorman, 2012, 2013) These values were imputed by NCHS if they were missing (National Center for Health Statistics, 2011, 2012). For records in the “linked” file with missing birth weight, gestational age was used to impute birth weight (less than 1 percent of records) (Mathews & MacDorman, 2012, 2013).

3.2. Study Design

Infant ID deaths occurring in 2008 or 2009 were examined using the Period Linked Birth/Infant Death public use data. A retrospective case-control study was conducted to determine infant and maternal risk factors for infant mortality due to IDs. Cases were defined as singleton infants born in the United States to U.S. residents with an infectious disease International Classification of Diseases, 10th Revision (ICD-10) code listed as the underlying cause of death (“World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD-10). 10th ed. Geneva: World Health Organization; 1992.,”). Infectious disease ICD-10 codes were adapted from a table of ICD-9 infectious disease codes in an article by Pinner (Pinner et al., 1996). Controls were selected from singleton infants born in the United States to U.S. residents using simple random sampling to obtain a 1:1 ratio of cases to controls and are defined as those infants who survived to the end of their birth year.

3.3. Variables

The outcome variable of interest was whether or not an ID was the underlying cause of an infant's death. Predictor variables were maternal and infant characteristics; those of interest were the sex of the infant (male and female), birth weight (low birth weight [LBW, <2500 grams] and normal birth weight [NBW, ≥2500 grams] in all models except the spline model which treated it as continuous), 5-Minute Apgar score (<7 and ≥7), maternal age (≤19, 20-24, 25-29, and ≥30 years), maternal marital status (married and unmarried), race (white, black, American Indian/Alaska Native (AI/AN), and Asian/Pacific Islander (A/PI)), Hispanic origin (Hispanic and non-Hispanic), and live birth order (first, second, third, and fourth or more). Maternal race and ethnicity as indicated on the birth certificate are more reliable than infant race and ethnicity reported on the death certificate and were therefore used to represent infant race and ethnicity in this study (National Center for Health Statistics, 2011, 2012). Variables of interest that were not comparable between the 1989 and 2003 birth certificates were maternal smoking status (smoked and didn't smoke during pregnancy), maternal education (less than a high school degree, high school degree, and more than a high school degree) and trimester the prenatal care began (no prenatal care, first trimester, second trimester, and third trimester). A sub-analysis of only the birth records using the 2003 birth certificate was conducted in order to measure the effect of these variables. For the sub-analysis, a variable for the Adequacy of Prenatal Care Utilization Index (APNCU index) was created using a formula developed by the creator of the index, Milton Kotelchuck (Kotelchuck, 1994). The APNCU is generally categorized as inadequate, intermediate, adequate, and adequate-plus, but adequate and adequate-plus were collapsed into one adequate category

and inadequate and intermediate were collapsed into a less than adequate category for this study (Holman, Shay, Curns, Lingappa, & Anderson, 2003). The APNCU index, referred to as prenatal care in this study, accounts for number of prenatal care visits and the trimester that prenatal care began, thus any analysis examining the APNCU index excluded the number of prenatal visits and trimester prenatal care began variables because they are highly correlated with the APNCU index. Since this variable is created using trimester prenatal care began, it is only available in the 2003 birth certificate sub-analysis.

3.4. Analyses

An overall analysis was conducted using the eight variables that were comparable between the 1989 and 2003 birth certificates: sex, birth weight, 5-minute Apgar score, maternal age, maternal marital status, race, Hispanic origin, and live birth order. A descriptive analysis was performed on all of these variables. The number and proportion of cases and controls were calculated within the levels of each variable. Chi-square tests were performed to test if there was a difference in the proportion of cases within the different levels of each variable. Age at death was examined by graphing the proportion of neonatal and postneonatal deaths overall and within LBW and NBW infants. Univariate analysis was conducted for each of the predictor variables using logistic regression. Predictor variables with univariate significance, defined as $P < 0.10$, along with predictors for the interaction of these variables with birth weight and with race were added to a multivariable logistic regression model. Birth weight and race interaction terms were added since previous studies of infant mortality and risk factors for infant

death due to specific IDs have shown differences among birth weight and race categories, (Singleton et al., 2009; Mehal et al., 2012) and birth weight and race could substantially influence infant ID mortality. Hierarchical backward elimination was then used to determine significant variables and interactions within the multivariable model. Predictors and interaction terms were retained in the model if they were significant at the 0.05 significance level. A Hosmer and Lemeshow Goodness-of-Fit test was conducted to see if the model was a good fit at the 0.05 significance level.

The final model contained multiple significant birth weight interactions, so a descriptive analysis was conducted to compare the proportion of maternal and infant characteristics stratified by birth weight. A chi-square test was performed on all of the predictors to test for differences in the distribution of the predictors among LBW infants compared to NBW infants. Further analysis was stratified by birth weight. Using the same methodology as previously described, LBW cases were selected to obtain a 1:1 ratio with LBW controls and NBW cases were selected to obtain a 1:1 ratio with NBW controls. The descriptive analysis, univariate regression, and multivariable regression model building as described above were conducted within each birth weight group; however, birth weight interactions were no longer examined in the multivariable logistic regression analysis. Adjusted ORs and 95% CIs were calculated for the significant maternal and infant risk factors within each of the final multivariable regression models stratified by birth weight.

Birth weight was also analyzed as a continuous variable to examine the effect of continuous birth weight on all of the other variables and to see the trend of birth weight with the log odds ratio. A descriptive analysis was conducted to determine the mean and

standard deviation of birth weight overall, for cases, and controls. A t-test was performed to determine if there was a significant difference between the mean infant birth weight between cases and controls. A fit plot of the proportion of cases against birth weight was created to look at the trend and to determine the number of knots to put in the generalized additive logistic regression model (spline model). All of the predictor variables plus the smoothing factor for birth weight were added to the multivariable spline model and multiple models were fit, each with a different number of knots, to find the best fit model. The best fit model would mirror the fit plot and have a stable effective degrees of freedom less than $k-1$ where k is the number of knots. After choosing the number of knots, hierarchical backward elimination was then used to determine significant variables to be kept in the final multivariable spline model. Predictor terms were retained in the model if they were significant at the 0.05 significance level. The final model was fit and a plot of birth weight against the log odds ratio of ID deaths was created. Adjusted ORs and 95% CIs were calculated for all of the maternal and infant risk factors in the final model.

In order to examine maternal education, maternal smoking status and prenatal care, variables that are non-comparable between birth certificate revisions, a sub-analysis of births that used the 2003 birth certificate was conducted. A descriptive analysis, univariate logistic regression analysis, and multivariable logistic regression analysis was conducted as described above; birth weight was again categorized as LBW and NBW. Maternal smoking status was removed from all analyses because more than 20% of observations were missing due to the non-reporting of Florida in 2008 and 2009 and the non-reporting or non-comparability of the data from Georgia and Michigan in 2009.

(Mathews & MacDorman, 2012, 2013) The final multivariable logistic regression model in the overall sub-analysis also contained multiple significant birth weight interactions, so this was also stratified by LBW and NBW as described above. Race interactions were excluded from the LBW multivariable model because of non-convergence of the model due to insufficient numbers. For comparability, race interactions were also excluded from the NBW model. Adjusted ORs and 95% CIs were calculated for the stratified analyses using logistic regression.

4. Results

4.1. Overall Analysis

There were a total of 3,798 infant deaths due to ID during 2008 and 2009 in the United States. The distribution of each of the eight predictor variables was significantly different ($p < 0.05$) in cases compared to controls (Table 1). Seventy percent of cases were LBW compared to only 6% of controls. Forty-five percent of cases had a 5-minute Apgar score < 7 compared to 1% of controls. The proportion of cases that were infants of black race (33.0%) was higher than the proportion of controls that were infants of black race (15.6%). The proportion of cases that were infants of white race (61.4%) was lower than the proportion of controls that were infants of white race (77.9%). Overall, approximately 60% of the ID deaths were in neonates. (Figure 1) LBW infants had a higher percentage of neonatal ID deaths (~70%) compared to NBW infants (~35%).

All predictor variables were significant in univariate logistic regression and included as potential predictors in the multivariable logistic regression model along with the interaction terms defined above. Each predictor remained significant in the final multivariable model along with the interactions of live birth order, Hispanic origin, and maternal marital status with birth weight. The Hosmer and Lemeshow Goodness-of-Fit test showed that the final multivariable logistic regression model was a good fit ($p = 0.5016$). Due to the presence of multiple significant birth weight interaction terms, chi-square tests were conducted to compare maternal and infant characteristics by birth weight group. The distribution of each maternal and infant characteristic, with the exception of sex, significantly differed ($p < 0.05$) between LBW and NBW infants. (Table

2) These differences, along with the significant interaction terms, led to stratification of the multivariable logistic regression model by birth weight.

4.2. Stratification by Birth Weight

4.2a. Low Birth Weight

There were a total of 2,633 ID deaths among LBW infants in 2008 and 2009. The proportion of cases with a 5-minute Apgar score <7 (60.9%) was significantly higher ($p<0.0001$) than the proportion of controls with a 5-minute Apgar score <7 (5.8%). (Table 3) The distribution of race was significantly different ($p<0.0001$) in cases compared to controls. There was a higher proportion of cases with infants of black race (37.5%) compared to the proportion of controls with infants of black race (28.1%). There was a lower proportion of cases with infants of white race (57.8%), AI/AN race (0.9%) and A/PI race (3.8%) compared to the proportion of controls with infants of white race (63.3%), AI/AN race (1.6%) and A/PI race (7.0%).

All predictor variables, with the exception of Hispanic origin, were significant in univariate logistic regression and added to the LBW multivariable logistic regression model. Maternal marital status and all interaction terms were removed during hierarchical backward elimination. The Hosmer and Lemeshow Goodness-of-Fit test showed that the final multivariable logistic regression model was a good fit ($p=0.0650$).

4.2b. Normal Birth Weight

A total of 1,158 ID deaths among NBW infants occurred in 2008 and 2009. The proportion of cases that had a 5-minute Apgar score <7 (8.6%) was significantly higher

($p < 0.0001$) than the proportion of controls that had a 5-minute Apgar score < 7 (1.0%). (Table 3) The distribution of maternal age in cases was significantly different ($p < 0.0001$) than the distribution of maternal age in controls. There was a higher proportion of cases with a maternal age < 25 years than controls. The proportion of cases with an unmarried maternal marital status (59.9%) was significantly higher ($p < 0.0001$) than the proportion of controls with an unmarried maternal marital status (42.1%). The distribution of race in cases was significantly higher ($p < 0.0001$) than the distribution of race in controls. The proportion of cases with an infant of black or AI/AN race was higher than the proportion of controls with an infant of black or AI/AN race. The proportion of cases with an infant of white or A/PI race was lower than the proportion of controls with an infant of white or A/PI race.

All predictor variables were significant in the univariate analysis and were added to the multivariable logistic regression model along with interaction terms. Race and all associated interaction terms were removed from the model during hierarchical backward elimination, leaving sex, 5-minute Apgar score, maternal age, maternal marital status, live birth order, and Hispanic origin in the final multivariable logistic regression model. The Hosmer and Lemeshow Goodness-of-Fit test showed that the final multivariable logistic regression model was a good fit ($p = 0.1289$).

4.2c. Multivariable Logistic Regression Models

Male sex and low 5-minute Apgar score were associated with ID death among LBW and NBW infants. (Table 4) The odds of death among male infants compared to female infants was similar for LBW (OR: 1.24, 95% CI: 1.08-1.42) and NBW (OR: 1.23,

95% CI: 1.03-1.46) infants. A LBW infant with a 5-minute Apgar score <7 was approximately 26 (95% CI: 21.62-31.38) times more likely to die of an ID death than a LBW infant with a 5-minute Apgar score ≥ 7 . A NBW infant with a 5-minute Apgar score <7 was 11.3 (95% CI: 6.31-22.11) times more likely to die from an ID death than a NBW infant with a 5-minute Apgar score ≥ 7 . Younger maternal age (<19 and 20-24 years) was associated with ID death among both LBW and NBW infants. A maternal age of 25-29 years was also associated with ID death among NBW infants. Among LBW infants, a live birth order of fourth or more was significantly associated with infant ID death compared to a live birth order of second (OR: 1.38, 95% CI: 1.08-1.75). For NBW infants, a live birth order of fourth or more also led to increased odds of death (OR: 1.75, 95% CI: 1.30-2.35); however, a live birth order of first decreased odds of death (OR: 0.71, 95% CI: 0.57-0.89). Non-Hispanic ethnicity and having an unmarried mother were both associated with increased odds of ID death in NBW infants, while for LBW infants, black race was associated with increased odds of death.

4.3. Continuous Birth Weight

The mean infant birth weight was 2,450 grams (standard deviation (St. dev): 1215, range: 227-6340 grams). Nine infants were missing birth weight; there were 3,791 cases and 3,796 controls. The mean birth weight for cases (1601.4 grams, St. Dev: 1215.1) was significantly different than that for controls (3298.5 grams, St. Dev: 546.3) at a 0.05 significance level (t value: 78.44, $p < 0.0001$).

The fit plot of the proportion of cases against birth weight showed an approximately linear decreasing trend from the minimum of 227 grams to around 4000

grams and a linear increase thereafter (Figure 2). A generalized additive logistic regression spline model was fit to examine the effect of birth weight on ID deaths adjusting for all of the other predictors. The plot of birth weight against the log odds ratio of ID deaths matched the fit plot of the proportion of cases against birth weight at seven knots and the effective degrees of freedom was stable at 4.77 (table 5), so the model with seven knots was chosen as the final generalized additive multivariable logistic regression spline model. The trend of birth weight against the log odds of infant ID death mirrored the fit plot – decreased in a linear fashion from 227 grams to just around 4000 grams and then it increased as birth weight increased (Figure 3)

In the continuous birth weight model, Hispanic ethnicity, a first live birth order, and a maternal age ≥ 30 were protective risk factors for an infant ID death, adjusting for all other predictors. (Table 5) An unmarried maternal marital status, fourth or more live birth order, male, AI/AN race, ≤ 19 and 20-24 year maternal age and < 7 5-minute Apgar score are significantly higher risks.

4.4. 2003 Birth Certificate Sub-Analysis

There were a total of 2,434 ID deaths in 2008 and 2009 among infants with a 2003 revision of the U.S. Standard Certificate of Live Birth. The distribution of each of the predictor variables, with the exception of prenatal care, was significantly different ($p < 0.05$) in cases compared to controls. (Table 6)

All of the predictor variables were significant in univariate logistic regression and were added to the multivariable model along with terms for their interactions with birth weight and race. Race was dropped from the model in the hierarchical backward

elimination along with all of the interactions except for the interactions of 5-minute Apgar score, Hispanic origin, maternal marital status, and prenatal care with birth weight. The Hosmer and Lemeshow Goodness-of-Fit test showed that the final multivariable logistic regression model was a good fit ($p=0.1003$). The multiple significant birth weight interactions led to chi-square testing of the proportion of maternal and infant characteristics by birth weight. The distributions of all of the maternal and infant characteristics within LBW infants compared to NBW infants were significantly different ($p<0.05$). (Table 7) As in the model using both birth certificate revisions, these differences, along with the significant interaction terms, led to stratification of the model by birth weight.

4.4a. Low Birth Weight

There were a total of 1,689 LBW infant ID deaths in 2008 and 2009 out of all the infants that had the 2003 revision of the U.S. Standard Certificate of Live Birth. There were no significant differences in the distributions of Hispanic origin, live birth order, and prenatal care in LBW cases compared to LBW controls. (Table 8) The proportion of cases that had a 5-minute Apgar score <7 (62.7%) was significantly higher ($p<0.0001$) than the proportion of controls that had a 5-minute Apgar score <7 (7.71%) The distribution of race was significantly different ($p<0.0001$) in cases compared to controls. The proportion of cases with an infant of black race was higher than the proportion of controls with an infant of black race. The proportion of cases with an infant of white (61.1%) or A/PI (3.1%) race was lower than the proportion of controls with an infant of

white (67.5%) or A/PI (6.8%) race. The proportion of cases with an infant of AI/AN race (0.7%) was similar to the proportion of controls with an infant of AI/AN race (0.8%).

All of the predictors except for Hispanic origin, live birth order, and prenatal care were significant ($p < 0.10$) in the LBW univariate logistic regression analysis. The significant predictors were added to the LBW multivariable logistic regression model. The only significant predictors after hierarchical backward selection were sex, race, maternal age, and 5-minute Apgar score. The Hosmer and Lemeshow Goodness-of-Fit test showed that the final multivariable logistic regression model was a good fit ($p = 0.6926$).

4.4b. Normal Birth Weight

There were a total of 742 NBW infant ID deaths in 2008 and 2009 out of all the infants that had the 2003 revision of the U.S. Standard Certificate of Live Birth. There were no significant differences in the distributions of Hispanic origin and sex in NBW cases compared to NBW controls. (Table 8) The proportion of cases that had a 5-minute Apgar score < 7 (9.6%) was significantly higher ($p < 0.0001$) than the proportion of controls that had a 5-minute Apgar score < 7 . The distribution of maternal age was significantly different ($p < 0.0001$) in cases compared to controls. There was a higher proportion of cases with a maternal age ≤ 19 years (17.7%) than controls (8.8%). The proportion of cases with a maternal age 20-24 years (34.1%) was higher than the proportion of controls with a maternal age 20-24 years (21.3%). The proportion of cases with a maternal age 25-29 years (23.5%) or ≥ 30 years (24.8%) was lower than the proportion of controls with a maternal age 25-29 years (28.4%) or (41.5%). The

proportion of cases with an unmarried maternal marital status (57.6%) was significantly higher ($p < 0.0001$) than the proportion of controls with an unmarried maternal marital status (38.0%). The distribution of maternal education is significantly different ($p < 0.0001$) in cases compared to controls. Cases had a higher proportion than controls of mothers with less than a high school degree (32.0% vs. 20.3%) whereas controls had a higher proportion than cases of mothers with more than a high school degree (54.5% vs. 38.5%). The proportion of cases with less than adequate prenatal care (41.9%) was significantly higher ($p < 0.0001$) than the proportion of controls with less than adequate prenatal care (25.7%).

All of the predictors except for Hispanic origin and sex were significant ($p < 0.10$) in the NBW univariate logistic regression analysis. The significant predictors were added to the NBW multivariable logistic regression model. The only significant predictors after hierarchical backward selection were 5-minute Apgar score, maternal age, maternal marital status, live birth order, and prenatal care. The Hosmer and Lemeshow Goodness-of-Fit test showed that the final multivariable logistic regression model was a good fit ($p = 0.9009$).

4.4c. Multivariable Logistic Regression Models

The odds of male LBW infants dying of an ID death were 1.31 (95% CI: 1.11-1.55) times the odds of female LBW infants. (Table 9) Black infants were 1.41 (95% CI: 1.17-1.70) times more likely to die of an ID death compared to white infants. The odds ratios for AI/AN and A/PI LBW infants compared to white LBW infants were not significant. The odds of NBW infants born to an unmarried mother dying an ID death

were 1.58 (95% CI: 1.23-2.03) times the odds of NBW infants born to a married mother. NBW infants who were the fourth or more live birth were 1.70 (95% CI: 1.16-2.51) times more likely than those with a second live birth order to die of an ID death. NBW infants with less than adequate prenatal care were 1.71 (95% CI: 1.34-2.19) times more likely to die of an ID death than NBW infants with adequate prenatal care. Both LBW and NBW infants born to a mother ≤ 19 or 20-24 years of age were at a significantly higher risk of dying of an ID death than infants born to a mother 25-29 years of age. NBW infants born to a mother ≥ 30 years old compared to 25-29 years old were also at a higher risk of an ID death, but this same risk in LBW infants was not significant. Both LBW and NBW infants with a 5-minute Apgar score < 7 were at a significant risk of an ID death compared to those with a 5-minute Apgar score ≥ 7 (OR: 20.00, 95% CI: 16.31-24.71 for LBW infants, OR: 9.37 95% CI: 4.85-20.04 for NBW infants).

5. Discussion

A majority of the ID deaths (~70%) were in LBW infants; LBW infants were at a higher risk for ID death if they had a live birth order of fourth or more, male sex, black race, maternal age <25 and a 5-minute Apgar score <7. NBW infants had the same risk factors for ID death as LBW infants except that black race was no longer a risk factor but NBW infants born to unmarried mothers, a maternal age of 25-29, a second live birth order and non-Hispanic infants were also at a higher risk for ID death. LBW infants with a live birth order of fourth or more were no longer at a higher risk for ID death when maternal education and prenatal care were added in the sub-analysis. The other risk factors did not change when maternal education and prenatal care were added in the sub-analysis. Male sex, a first live birth order, and non-Hispanic were no longer a risk factor for NBW infant ID deaths when maternal education and prenatal care were added to the model in the sub-analysis and maternal age ≥ 30 switched from being protective to a higher risk than a maternal age of 25-29. Less than adequate prenatal care put NBW infants at a higher risk of ID deaths. The risk factors for infant ID death in the continuous birth weight model were also very similar to the NBW model that did not include maternal education and prenatal care; non-Hispanic, unmarried marital status, a live birth order of second or fourth or more, male sex, maternal age <30 and 5-minute Apgar score <7 put an infant at higher risk of ID death. However, AI/AN race was also an elevated risk for ID death when birth weight was continuous.

Risk factors for ID death have not changed much since the most recent study of maternal and infant risk factors for infant ID deaths which analyzed data from 1983-1987 (Read, Troendle, & Klebanoff, 1997) A younger maternal age was a risk factor in both

studies along with black race, unmarried maternal marital status, male gender and a high live birth order. In the 1983-1987 study, a lower number of prenatal visits (<10) and beginning prenatal care after the first trimester put an infant at higher risk for ID death. The present study did not look at number of prenatal visits or trimester prenatal care began directly, but found that less than adequate prenatal care put NBW infants at a higher risk of ID death. The present study found that non-Hispanic infants as well as those with a 5-minute Apgar score <7 were at a higher risk for ID death; Hispanic ethnicity and 5-minute Apgar score were not accounted for in the previous study. The previous study found that a lower maternal education put an infant at a higher risk for ID death. The present study found no association between maternal education and infant ID death. The similarities and differences in risk factors between these two studies are good to note but the studies are not directly comparable. The previous study looked at noncongenital postneonatal ID deaths among white, black, and Asian infants whereas the present study looked at all infant ID deaths within all races but stratified by birth weight and looked at continuous birth weight.

Racial disparities continue to exist in infant mortality due to IDs. In the present study, black race was a risk factor for ID death in LBW infants and AI/AN race was a risk factor for ID death when looking at continuous birth weight. Previous studies found that the infant mortality rate due to infection was highest in infants born to black mothers (Hessol & Fuentes-Afflick, 2005; Kitsantas & Gaffney, 2010) and that the postneonatal mortality rate due to ID was significantly higher in rural AI/AN infants compared to rural white infants (Baldwin et al., 2009). While the present study and past studies show racial disparities, they are not directly comparable because the previous studies on black race

looked at infant mortality rates due to ID and were state specific and the present study looked at risk factors for infant mortality due to ID and is for all infants born in the United States to U.S. residents. The past study on AI/AN race analyzes rural infants stratified by age at death and the present study analyzes all infant deaths of U.S. residents born in the United States.

There are some limitations to this study. The non-comparability of the 1989 and 2003 revisions of the U.S Standard Certificate of Live Birth inhibited a complete analysis of important risk factors for infant ID death such as smoking status, maternal education, and trimester prenatal care began. A sub-analysis of the states that implemented the 2003 revision of the birth certificate was conducted in order to include these variables; However, this sub-analysis is not directly applicable to the U.S. general population of infants and it still did not include maternal smoking status due to the non-reporting or non-comparability of data from Florida (2008 and 2009), Georgia (2009), and Michigan (2009).

Another limitation in this study is the reliance on ICD-10 coding for IDs. ICD-10 coding is subject to miscoding or misdiagnosis that could lead to both the inclusion and exclusion of ID deaths. Infectious diseases also may be underreported because of the unknown role they may play in certain chronic diseases such as diabetes mellitus type 1, heart conditions and some cancers (National Center for Environmental Health; National Center for Health Statistics; National Center for Infectious Diseases; CDC, 1999). In regards to AI/AN race, there was only a small number of AI/AN infant ID deaths in 2008 and 2009 which may be affected by racial misclassification of AI/ANs (Stehr-Green, Bettles, & Robertson, 2002).

Mothers and healthcare providers of infants with a higher live birth order, male sex, AI/AN race, 5-minute Apgar score <7 should be aware of the higher risk of ID infant death. Unmarried mothers and young mothers should also be aware of the increased risk of ID death for their infant. Mothers and healthcare providers of LBW infants with black race and mothers and healthcare providers of non-Hispanic NBW infants or NBW infants with less than adequate prenatal care or a mother that is outside the 25-29 year age range should be aware of increased risk of ID death. Awareness of these risk factors should lead to more care in prevention of ID for a child with these risk factors in their first year of life. Future studies should focus further on determining why disparities in infant ID death exist between races, Hispanic ethnicity, and maternal marital status. They should also focus on ways to reduce the number of infants with a low 5-minute Apgar score. Future studies should also focus on the epidemiology behind male sex and high live birth order being risk factors for infant ID death and on the underlying reason why infants of young mothers are at increased risk of ID deaths. Future studies are warranted to investigate the population of mothers not receiving adequate prenatal care and the reasons behind not receiving adequate prenatal care.

REFERENCES

- Armstrong, G. L., Conn, L. A., & Pinner, R. W. (1999). Trends in infectious disease mortality in the United States during the 20th century. *Jama*, *281*, 61-66. doi: 10.1001/jama.281.1.61.
- Armstrong, G. L., & Pinner, R. W. (1999). Outpatient visits for infectious diseases in the United States, 1980 through 1996. *Arch Intern Med*, *159*(21), 2531-2536. doi: 10.1001/archinte.159.21.2531.
- Baldwin, L. M., Grossman, D. C., Murowchick, E., Larson, E. H., Hollow, W. B., Sugarman, J. R., . . . Hart, L. G. (2009). Trends in perinatal and infant health disparities between rural American Indians and Alaska natives and rural Whites. *Am J Public Health*, *99*(4), 638-646. doi: 10.2105/AJPH.2007.119735
- Black, R. E., Cousens, S., Johnson, H. L., Lawn, J. E., Rudan, I., Bassani, D. G., . . . Unicef. (2010). Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*, *375*(9730), 1969-1987. doi: 10.1016/S0140-6736(10)60549-1
- Christensen, K. L., Holman, R. C., Steiner, C. A., Sejvar, J. J., Stoll, B. J., & Schonberger, L. B. (2009). Infectious disease hospitalizations in the United States. *Clin Infect Dis*, *49*(7), 1025-1035. doi: 10.1086/605562
- Hessol, N. A., & Fuentes-Afflick, E. (2005). Ethnic differences in neonatal and postneonatal mortality. *Pediatrics*, *115*(1), e44-51. doi: 10.1542/peds.2004-0478
- Holman, R. C., Shay, D. K., Curns, A. T., Lingappa, J. R., & Anderson, L. J. (2003). Risk factors for bronchiolitis-associated deaths among infants in the United States. *Pediatr Infect Dis J*, *22*(6), 483-490.
- Jason, J. M. (1989). Infectious disease-related deaths of low birth weight infants, United States, 1968 to 1982. *Pediatrics*, *84*(2), 296-303.
- Jason, J. M., & Jarvis, W. R. (1987). Infectious diseases: preventable causes of infant mortality. *Pediatrics*, *80*(3), 335-341.
- Jones, K. E., Patel, N. G., Levy, M. A., Storeygard, A., Balk, D., Gittleman, J. L., & Daszak, P. (2008). Global trends in emerging infectious diseases. *Nature*, *451*(7181), 990-993. doi: 10.1038/nature06536
- Kitsantas, P., & Gaffney, K. F. (2010). Racial/ethnic disparities in infant mortality. *J Perinat Med*, *38*(1), 87-94. doi: 10.1515/JPM.2010.014
- Kotelchuck, M. (1994). An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. *Am J Public Health*, *84*(9), 1414-1420.
- Mathews, T. J., & MacDorman, M. F. (2012). Infant Mortality Statistics from the 2008 Period Linked Birth/Infant Death Data Set. *Natl Vital Stat Rep*, *60*(5), 1-27.
- Mathews, T. J., & MacDorman, M. F. (2013). Infant Mortality Statistics from the 2009 Period Linked Birth/Infant Death Data Set. *Natl Vital Stat Rep*, *61*(8), 1-46.
- Mehal, J. M., Esposito, D. H., Holman, R. C., Tate, J. E., Callinan, L. S., & Parashar, U. D. (2012). Risk factors for diarrhea-associated infant mortality in the United States, 2005-2007. *Pediatr Infect Dis J*, *31*(7), 717-721. doi: 10.1097/INF.0b013e318253a78b
- National Center for Environmental Health; National Center for Health Statistics; National Center for Infectious Diseases; CDC. (1999). Achievements in Public Health,

- 1900-1999: Control of Infectious Diseases. *Morbidity and Mortality Weekly Report*, 48(29), 621-629.
- National Center for Health Statistics (2011). *User Guide to the 2008 Period Linked Birth/Infant Death Public Use File*. Hyattsville, MD: National Center for Health Statistics.
- National Center for Health Statistics (2012). *User Guide to the 2009 Period Linked Birth/Infant Death Public Use File*. Hyattsville, MD: National Center for Health Statistics.
- Partridge, S., Balayla, J., Holcroft, C. A., & Abenhaim, H. A. (2012). Inadequate prenatal care utilization and risks of infant mortality and poor birth outcome: a retrospective analysis of 28,729,765 U.S. deliveries over 8 years. *Am J Perinatol*, 29(10), 787-793. doi: 10.1055/s-0032-1316439
- Pinner, R. W., Teutsch, S. M., Simonsen, L., Klug, L. A., Graber, J. M., Clarke, M. J., & Berkelman, R. L. (1996). Trends in infectious diseases mortality in the United States. *Jama*, 275(3), 189-193. doi: doi:10.1001/jama.1996.03530270029027
- Read, J. S., Troendle, J. F., & Klebanoff, M. A. (1997). Infectious disease mortality among infants in the United States, 1983 through 1987. *Am J Public Health*, 87(2), 192-198.
- Richardus, J. H., & Kunst, A. E. (2001). Black-White differences in infectious disease mortality in the United States. *Am J Public Health*, 91(8), 1251-1253.
- Simonsen, L., Conn, L. A., Pinner, R. W., & Teutsch, S. (1998). Trends in infectious disease hospitalizations in the United States, 1980-1994. *Arch Intern Med*, 158, 1923-1928. doi: doi:10.1001/jama.1996.03530270029027
- Singleton, R. J., Wirsing, E. A., Haberling, D. L., Christensen, K. Y., Paddock, C. D., Hilinski, J. A., . . . Holman, R. C. (2009). Risk factors for lower respiratory tract infection death among infants in the United States, 1999-2004. *Pediatrics*, 124(4), e768-776. doi: 10.1542/peds.2009-0109
- Stehr-Green, P., Bettles, J., & Robertson, L. D. (2002). Effect of racial/ethnic misclassification of American Indians and Alaskan Natives on Washington State death certificates, 1989-1997. *Am J Public Health*, 92(3), 443-444.
- U.S. Department of Health and Human Services. (9/6/2012). Immunization and Infectious Diseases. Retrieved April 8, 2013, from <http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicId=23>
- United Nations Inter-agency Group for Child Mortality Estimation. (2011). Levels & Trends in Child Mortality. Retrieved April 8, 2013, from http://www.who.int/maternal_child_adolescent/documents/childmortality_booklet_2011.pdf
- University of California, Santa Cruz. (2/12/2007). The UC Atlas of Global Inequality. *Cause of Death*. Retrieved April 8, 2013, from <http://ucatlas.ucsc.edu/cause.php>
- World Health Organization. (1999). Removing Obstacles to Healthy Development. *World Health Organization Report on Infectious Diseases*. Retrieved April 8, 2013, from <http://www.who.int/infectious-disease-report/index-rpt99.html>
- World Health Organization. (2011). *World health statistics 2011*. Geneva: World Health Organization

- World Health Organization. (2013a). Global Health Observatory (GHO). *Causes of death in 2008*. Retrieved April 8, 2013, from http://www.who.int/gho/mortality_burden_disease/causes_death_2008/en/index.html
- World Health Organization. (2013b). Maternal, newborn, child and adolescent health. Retrieved April 8, 2013, from http://www.who.int/maternal_child_adolescent/epidemiology/newborn/en/index.html
- World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD-10). 10th ed. Geneva: World Health Organization; 1992.
- Yorita, K. L., Holman, R. C., Sejvar, J. J., Steiner, C. A., & Schonberger, L. B. (2008). Infectious disease hospitalizations among infants in the United States. *Pediatrics*, *121*(2), 244-252. doi:10.1542/peds.2007-1392

APPENDIX

Table 1. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, United States, 2008-2009⁺

Characteristics	Cases N (%)	Controls N (%)	Chi-Square Statistic*	P-Value
Total	3798	3798		
Sex			7.11	0.0076
Male	2078 (54.7)	1962 (51.7)		
Female	1720 (45.3)	1836 (48.3)		
Birth Weight (grams)			3291.77	<0.0001
<2500	2633 (69.5)	215 (5.7)		
≥2500	1158 (30.6)	3581 (94.3)		
5-Minute Apgar Score			2014.01	<0.0001
< 7	1659 (44.8)	47 (1.3)		
≥ 7	2041 (55.2)	3724 (98.8)		
Maternal Age (years)			100.19	<0.0001
≤19	621 (16.4)	416 (11.0)		
20-24	1147 (30.2)	940 (24.8)		
25-29	915 (24.1)	1061 (27.9)		
≥30	1115 (29.4)	1381 (36.4)		
Race			331.09	<0.0001
White	2331 (61.4)	2958 (77.9)		
Black	1255 (33.0)	592 (15.6)		
AI/AN	59 (1.6)	32 (0.8)		
A/PI	153 (4.0)	216 (5.7)		
Maternal Marital Status			255.11	<0.0001
Married	1534 (40.4)	2230 (58.7)		
Unmarried	2264 (59.6)	1568 (41.3)		
Hispanic Origin			16.87	<0.0001
Hispanic	798 (21.3)	952 (25.3)		
Non-Hispanic	2955 (78.7)	2816 (74.7)		
Live Birth Order			42.44	<0.0001
First	1671 (44.6)	1523 (40.4)		
Second	974 (26.0)	1178 (31.2)		
Third	579 (15.4)	651 (17.3)		
Fourth or more	527 (14.1)	420 (11.1)		

* Pearson Chi-Square

⁺ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander

Table 2: Proportion of Selected Maternal and Infant Characteristics by Birth Weight, United States, 2008-2009⁺

Characteristics	LBW Infants (<2500g) N (%)	NBW Infants (≥2500g) N (%)	Chi-Square Statistics*	P-Value
Total	2848	4739		
Sex			0.10	0.7540
Male	1522 (53.4)	2515 (53.1)		
Female	1326 (46.6)	2224 (46.9)		
5-Minute Apgar Score			2903.17	<0.0001
< 7	1574 (56.9)	128 (2.7)		
≥7	1193 (43.1)	4572 (97.3)		
Maternal Age (years)			28.36	<0.0001
≤19	458 (16.1)	579 (12.2)		
20-24	769 (27.0)	1315 (27.8)		
25-29	678 (23.8)	1295 (27.3)		
≥30	943 (33.1)	1550 (32.7)		
Race			394.59	<0.0001
White	1662 (58.4)	3621 (76.4)		
Black	1051 (36.9)	793 (16.7)		
AI/AN	24 (0.8)	67 (1.4)		
A/PI	111 (3.9)	258 (5.4)		
Maternal Marital Status			137.24	<0.0001
Married	1164 (40.9)	2595 (54.8)		
Unmarried	1684 (59.1)	2144 (45.2)		
Hispanic Origin			5.50	0.0190
Hispanic	612 (21.8)	1138 (24.2)		
Non-Hispanic	2195 (78.2)	3571 (75.8)		
Live Birth Order			58.90	<0.0001
First	1321 (47.0)	1871 (39.8)		
Second	692 (24.6)	1459 (31.0)		
Third	413 (14.7)	816 (17.3)		
Fourth or more	386 (13.7)	561 (11.9)		

* Pearson Chi-Square

⁺ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander, LBW: Low Birth Weight, NBW: Normal Birth Weight

Table 3. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, Stratified by Birth Weight, United States, 2008-2009⁺

Characteristics	LBW		P-Value	NBW		P-Value
	Cases N (%)	Controls N (%)		Cases N (%)	Controls N (%)	
Total	2633	2633		1158	1158	
Sex			<0.0001			0.0016
Male	1425 (54.1)	1273 (48.4)		650 (56.1)	574 (49.6)	
Female	1208 (45.9)	1360 (51.7)		508 (43.9)	584 (50.4)	
5-Minute Apgar Score			<0.0001			<0.0001
< 7	1557 (60.9)	150 (5.8)		98 (8.6)	12 (1.0)	
≥7	998 (39.1)	2459 (94.3)		1043 (91.4)	1138 (99.0)	
Maternal Age (years)			0.0031			<0.0001
≤19	424 (16.1)	359 (13.6)		197 (17.0)	128 (11.1)	
20-24	726 (27.6)	665 (25.3)		419 (36.2)	312 (26.9)	
25-29	628 (23.9)	705 (26.8)		285 (24.6)	321 (27.7)	
≥30	855 (32.5)	904 (34.3)		257 (22.2)	397 (34.3)	
Race			<0.0001			<0.0001
White	1523 (57.8)	1667 (63.3)		804 (69.4)	883 (76.3)	
Black	986 (37.5)	741 (28.1)		266 (23.0)	184 (15.9)	
AI/AN A/PI	23 (0.9) 101 (3.8)	41 (1.6) 184 (7.0)		36 (3.1) 52 (4.5)	18 (1.6) 73 (6.3)	
Maternal Marital Status			<0.0001			<0.0001
Married	1067 (40.5)	1253 (47.6)		464 (40.1)	671 (57.9)	
Unmarried	1566 (59.5)	1380 (52.4)		694 (59.9)	487 (42.1)	
Hispanic Origin			0.8677			0.0039
Hispanic	564 (21.7)	561 (21.5)		234 (20.3)	291 (25.4)	
Non- Hispanic	2033 (78.3)	2045 (78.5)		917 (79.7)	855 (74.6)	

Live Birth Order			0.0038		0.0644
First	1220 (47.0)	1203 (46.2)	449 (39.1)	486 (42.3)	
Second	641 (24.7)	692 (26.6)	332 (28.9)	343 (29.9)	
Third	384 (14.8)	431 (16.6)	194 (16.9)	187 (16.3)	
Fourth or more	353 (13.6)	279 (10.7)	174 (15.1)	133 (11.6)	

⁺ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander, LBW: Low Birth Weight (grams), NBW: Normal Birth Weight (grams)

Table 4. Odds Ratio Estimates and 95% Confidence Intervals of Selected Maternal and Infant Characteristics for the Multivariable Logistic Regression Analysis Stratified by Birth Weight, United States, 2008-2009⁺

Effect	LBW OR (95% CI) [*]	NBW OR (95% CI) [*]
Hispanic Origin		
Hispanic	-	0.67 (0.54-0.82)
Non-Hispanic	-	Reference
Maternal Marital Status		
Unmarried	-	1.69 (1.39-2.05)
Married	-	Reference
Live Birth Order		
First	0.92 (0.78-1.10)	0.71 (0.57-0.89)
Second	Reference	Reference
Third	0.95 (0.76-1.18)	1.15 (0.88-1.50)
Fourth or more	1.38 (1.08-1.75)	1.75 (1.30-2.35)
Sex		
Male	1.24 (1.08-1.42)	1.23 (1.03-1.46)
Female	Reference	Reference
Race		
White	Reference	-
Black	1.35 (1.16-1.57)	-
AI/AN	0.60 (0.31-1.12)	-
A/PI	0.77 (0.56-1.06)	-
Maternal Age (years)		
≤19	1.69 (1.34-2.13)	1.83 (1.33-2.52)
20-24	1.39 (1.15-1.69)	1.47 (1.16-1.86)
25-29	Reference	Reference
≥30	1.02 (0.85-1.23)	0.65 (0.51-0.83)
5-Minute Apgar Score		
<7	25.96 (21.62-31.38)	11.30 (6.31-22.11)
≥7	Reference	Reference

^{*} OR: Odds Ratio, CI: Confidence Interval

⁺ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander, LBW: Low Birth Weight (grams), NBW: Normal Birth Weight (grams)

Table 5. Multivariable Logistic Regression Spline Analysis Results, Select Maternal and Infant Characteristics, United States, 2008-2009⁺

Parameter	Estimate (SE)	P-Value	OR (95% CI)*
Intercept	0.01 (0.11)	0.9009	
Hispanic Origin			
Hispanic	-0.35 (0.07)	<0.0001	0.70 (0.61-0.81)
Non-Hispanic	Reference		Reference
Maternal Marital Status			
Unmarried	0.46 (0.07)	<0.0001	1.58 (1.38-1.82)
Married	Reference		Reference
Live Birth Order			
First	-0.33 (0.07)	<0.0001	0.72 (0.63-0.82)
Second	Reference		Reference
Third	0.15 (0.09)	0.0928	1.16 (0.97-1.39)
Fourth or more	0.57 (0.10)	<0.0001	1.77 (1.45-2.15)
Sex			
Male	0.23 (0.06)	<0.0001	1.26 (1.11-1.42)
Female	Reference		Reference
Race			
White	Reference		Reference
Black	0.01 (0.08)	0.8639	1.01 (0.86-1.18)
AI/AN	1.23 (0.23)	<0.0001	3.42 (2.18-5.37)
A/PI	0.08 (0.14)	0.5527	1.08 (0.82-1.43)
Maternal Age (years)			
≤19	0.61 (0.10)	<0.0001	1.84 (1.50-2.22)
20-24	0.46 (0.08)	<0.0001	1.58 (1.35-1.85)
25-29	Reference		Reference
≥30	-0.38 (0.08)	<0.0001	0.68 (0.58-0.80)
5-Minute Apgar Score			
<7	2.24 (0.16)	<0.0001	9.39 (6.86-12.85)
≥7	Reference		Reference
Approximate Significance of Smooth Term			
Smooth Term	Effective DF	Reference DF	P-Value
Birth Weight (grams)	4.77	4.77	<0.001

* OR: Odds Ratio, CI: Confidence Interval

⁺ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander

Table 6. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, 2003 Birth Certificate Sub-Analysis, United States, 2008-2009⁺

Characteristics	Cases N (%)	Controls N (%)	Chi-Square Statistic*	P-Value
Total	2434	2434		
Sex			17.30	<0.0001
Male	1337 (54.9)	1192 (49.0)		
Female	1097 (45.1)	1242 (51.0)		
Birth Weight (grams)			2098.91	<0.0001
<2500	1689 (69.5)	142 (5.8)		
≥2500	742 (30.5)	2292 (94.2)		
5-Minute Apgar Score			1336.72	<0.0001
< 7	1094 (46.4)	34 (1.4)		
≥7	1265 (53.6)	2380 (98.6)		
Maternal Age (years)			79.36	<0.0001
≤19	401 (16.5)	243 (10.0)		
20-24	736 (30.2)	608 (25.0)		
25-29	570 (23.4)	696 (28.6)		
≥30	727 (29.9)	887 (36.4)		
Race			213.28	<0.0001
White	1593 (65.5)	1908 (78.4)		
Black	742 (30.5)	337 (13.9)		
AI/AN	21 (0.9)	21 (0.9)		
A/PI	78 (3.2)	168 (6.9)		
Maternal Marital Status			149.14	<0.0001
Married	1019 (41.9)	1445 (59.4)		
Unmarried	1415 (58.1)	989 (40.6)		
Hispanic Origin			7.73	0.0054
Hispanic	609 (25.4)	700 (29.0)		
Non-Hispanic	1785 (74.6)	1713 (71.0)		
Live Birth Order			32.48	<0.0001
First	1083 (45.2)	956 (39.4)		
Second	616 (25.7)	786 (32.4)		
Third	370 (15.5)	399 (16.5)		
Fourth or more	326 (13.6)	283 (11.7)		
Maternal Education			83.71	<0.0001
Less than HS Degree	698 (29.7)	496 (20.7)		
HS Degree	752 (32.0)	691 (28.8)		
More than HS Degree	898 (38.3)	1215 (50.6)		
Prenatal Care Utilization Index**			3.32	0.0685
Less than Adequate	685 (32.8)	687 (30.2)		
Adequate	1406 (67.2)	1588 (69.8)		

* Pearson Chi-Square

** Adequate and adequate-plus were collapsed into one adequate category and inadequate and intermediate

were collapsed into a less than adequate category for this study (Kotelchuck, 1994)

⁺ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander

Table 7. Proportion of Selected Maternal and Infant Characteristics by Birth Weight, 2003 Birth Certificate Sub-Analysis, United States, 2008-2009⁺

Characteristics	LBW Infants (<2500g) N (%)	NBW Infants (≥2500g) N (%)	Chi-Square Statistics *	P-Value
Total	1831	3034		
Sex			8.62	0.0033
Male	1001 (54.7)	1527 (50.3)		
Female	830 (45.3)	1507 (49.7)		
5-Minute Apgar Score			1850.51	<0.0001
< 7	1028 (58.1)	99 (3.3)		
≥7	743 (42.0)	2902 (96.7)		
Maternal Age (years)			22.61	<0.0001
≤19	290 (15.8)	354 (11.7)		
20-24	521 (28.5)	823 (27.1)		
25-29	435 (23.8)	829 (27.3)		
≥30	585 (32.0)	1028 (33.9)		
Race			259.43	<0.0001
White	1130 (61.7)	2369 (78.1)		
Black	629 (34.4)	449 (14.8)		
AI/AN	12 (0.7)	30 (1.0)		
A/PI	60 (3.3)	186 (6.1)		
Maternal Marital Status			91.92	<0.0001
Married	765 (41.8)	1698 (56.0)		
Unmarried	1066 (58.2)	1336 (44.0)		
Hispanic Origin			4.64	0.0312
Hispanic	457 (25.5)	852 (28.3)		
Non-Hispanic	1339 (74.6)	2158 (71.7)		
Live Birth Order			43.79	<0.0001
First	857 (47.6)	1181 (39.2)		
Second	435 (24.1)	967 (32.1)		
Third	278 (15.4)	491 (16.3)		
Fourth or more	232 (12.9)	377 (12.5)		
Maternal Education			41.95	<0.0001
Less than HS Degree	496 (28.2)	698 (23.3)		
HS Degree	587 (33.4)	856 (28.6)		
More than HS Degree	675 (38.4)	1437 (48.0)		
Prenatal Care Utilization Index**			10.31	0.0013
Less than Adequate	434 (28.4)	937 (33.1)		

Adequate	1097 (71.7)	1896 (66.9)
* Pearson Chi-Square		
** Adequate and adequate-plus were collapsed into one adequate category and inadequate and intermediate were collapsed into a less than adequate category for this study (Kotelchuck, 1994)		
+ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander, LBW: Low Birth Weight, NBW: Normal Birth Weight		

Table 8. Proportion of Selected Maternal and Infant Characteristics by Cases and Controls, 2003 Birth Certificate Sub-Analysis, Stratified by Birth Weight, United States, 2008-2009⁺

Characteristics	LBW		P-Value	NBW		P-Value
	Cases N (%)	Controls N (%)		Cases N (%)	Controls N (%)	
Total	1689	1689		742	742	
Sex			<0.0001			0.1186
Male	927 (54.9)	804 (47.6)		409 (55.1)	379 (51.1)	
Female	762 (45.1)	885 (52.4)		333 (44.9)	363 (48.9)	
5-Minute Apgar Score			<0.0001			<0.0001
< 7	1023 (62.7)	129 (7.71)		70 (9.6)	10 (1.4)	
≥7	609 (37.3)	1544 (92.3)		656 (90.4)	729 (98.7)	
Maternal Age (years)			0.0072			<0.0001
≤19	270 (16.0)	225 (13.3)		131 (17.7)	65 (8.8)	
20-24	483 (28.6)	431 (25.5)		253 (34.1)	158 (21.3)	
25-29	394 (23.3)	424 (25.1)		174 (23.5)	211 (28.4)	
≥30	542 (32.1)	609 (36.1)		184 (24.8)	308 (41.5)	
Race			<0.0001			0.0066
White	1032 (61.1)	1140 (67.5)		559 (75.3)	597 (80.5)	
Black	594 (35.2)	421 (24.9)		147 (19.8)	101 (13.6)	
AI/AN	11 (0.7)	14 (0.8)		10 (1.4)	7 (0.9)	
A/PI	52 (3.1)	114 (6.8)		26 (3.5)	37 (5.0)	
Maternal Marital Status			0.0001			<0.0001
Married	703 (41.6)	815 (48.3)		315	460	

				(42.5)	(62.0)	
Unmarried	986 (58.4)	874 (51.8)		427	282	
				(57.6)	(38.0)	
Hispanic Origin			0.7077			0.7546
Hispanic	420 (25.4)	432 (25.9)		189	194	
				(25.7)	(26.4)	
Non-Hispanic	1237	1235		547	541	
	(74.7)	(74.1)		(74.3)	(73.6)	
Live Birth Order			0.3930			0.0376
First	783 (47.2)	818 (48.9)		299	273	
				(40.7)	(37.2)	
Second	398 (24.0)	416 (24.9)		218	261	
				(29.7)	(35.6)	
Third	255 (15.4)	236 (14.1)		115	122	
				(15.7)	(16.6)	
Fourth or more	224 (13.5)	202 (12.1)		102	78 (10.6)	
				(13.9)		
Maternal Education			0.0003			<0.0001
Less than HS Degree	465 (28.7)	438 (26.2)		233	148	
				(32.0)	(20.3)	
HS Degree	537 (33.2)	481 (28.8)		215	184	
				(29.5)	(25.2)	
More than HS Degree	617 (38.1)	750 (44.9)		280	397	
				(38.5)	(54.5)	
Prenatal Care Utilization Index*			0.4568			<0.0001
Less than Adequate	397 (28.3)	452 (29.5)		287	177	
				(41.9)	(25.7)	
Adequate	1007	1079		398	513	
	(71.7)	(70.5)		(58.1)	(74.4)	

* Adequate and adequate-plus were collapsed into one adequate category and inadequate and intermediate were collapsed into a less than adequate category for this study (Kotelchuck, 1994)

+ Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander, LBW: Low Birth Weight (grams), NBW: Normal Birth Weight (grams)

Table 9. Odds Ratio Estimates and 95% Confidence Intervals of Selected Maternal and Infant Characteristics for the Multivariable Logistic Regression Analysis Stratified by Birth Weight, 2003 Birth Certificate Sub-Analysis, United States, 2008-2009[†]

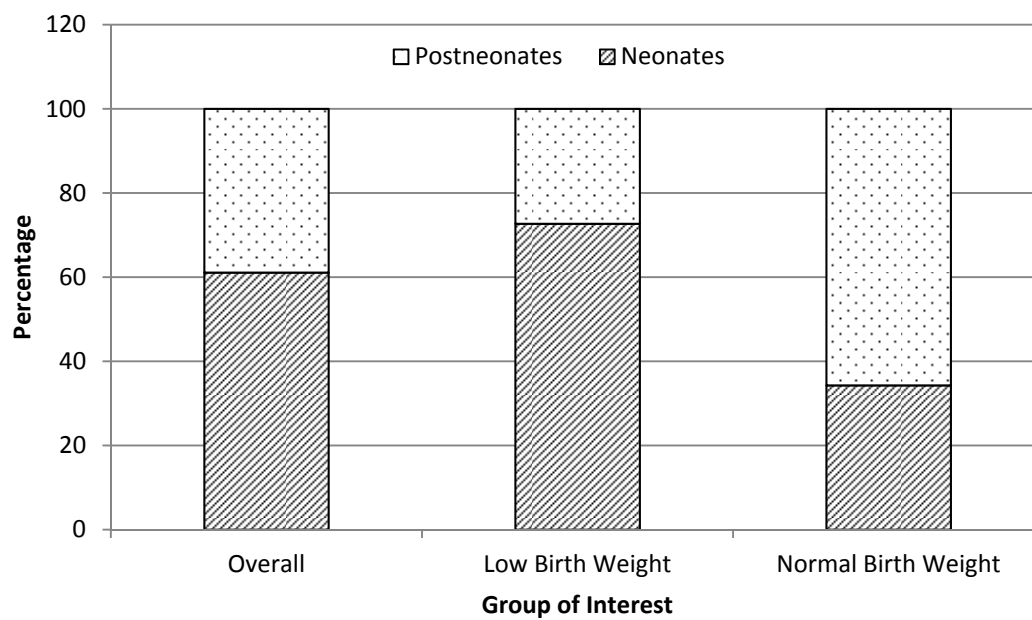
Effect	LBW OR (95% CI) [*]	NBW OR (95% CI) [*]
Sex		
Male	1.31 (1.11-1.55)	-
Female	Reference	-
Race		
White	Reference	-
Black	1.41 (1.17-1.70)	-
AI/AN	0.64 (0.22-1.76)	-
A/PI	0.67 (0.44-1.01)	-
Maternal Age (years)		
≤19	1.49 (1.13-1.97)	2.26 (1.49-3.45)
20-24	1.28 (1.01-1.63)	1.93 (1.41-2.66)
25-29	Reference	Reference
≥30	1.04 (0.83-1.31)	3.08 (2.00-4.78)
5-Minute Apgar Score		
<7	20.00 (16.31-24.71)	9.37 (4.85-20.04)
≥7	Reference	Reference
Maternal Marital Status		
Unmarried	-	1.58 (1.23-2.03)
Married	-	Reference
Live Birth Order		
First	-	0.90 (0.68-1.19)
Second	-	Reference
Third	-	1.27 (0.90-1.80)
Fourth or more	-	1.70 (1.16-2.51)
Prenatal Care Utilization Index ^{**}		
Less than Adequate	-	1.71 (1.34-2.19)
Adequate	-	Reference

^{*} OR: Odds Ratio, CI: Confidence Interval

^{**} Adequate and adequate-plus were collapsed into one adequate category and inadequate and intermediate were collapsed into a less than adequate category for this study (Kotelchuck, 1994)

[†] Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian and Alaska Native, A/PI: Asian/Pacific Islander, LBW: Low Birth Weight (grams), NBW: Normal Birth Weight (grams)

Figure 1: Proportion of Neonatal vs. Postneonatal Deaths Overall and by Birth Weight*, United States, 2008-2009



* Birth Weight is in grams.

Figure 2. Proportion of Infectious Disease Infant Deaths by Birth Weight, United States, 2008-2009

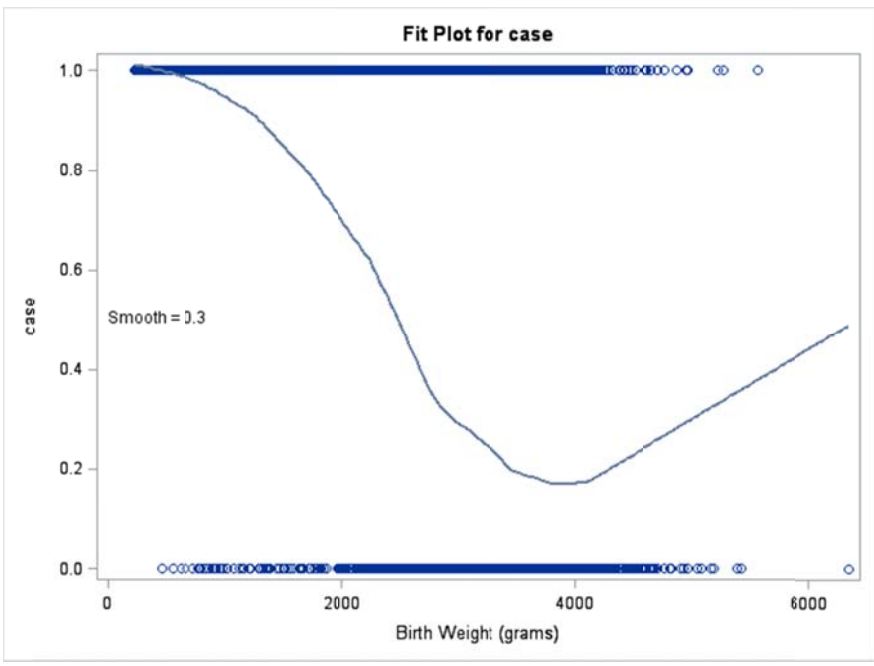


Figure 3. Log Odds Ratio by Birth Weight for Cases compared to Controls adjusting for Select Maternal and Infant Characteristics, United States, 2008-2009

