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Infant and Maternal Risk Factors Related to Necrotizing Enterocolitis-Associated Infant Death in the United States, 2007-2009

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Infant and Maternal Risk Factors Related to Necrotizing Enterocolitis-Associated Infant Death in the United States, 2007-2009

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Abstract

Infant and Maternal Risk Factors Related to Necrotizing Enterocolitis-Associated Infant Death in the United States, 2007-2009

By Sara Seeman

PURPOSE: The purpose of this study is to evaluate necrotizing enterocolitis (NEC)-associated deaths among infants in the United States and to identify risk factors for NEC mortality.

METHODS: The United States Period Linked Birth/Infant Death dataset for 2007-2009 was utilized to determine the infant and maternal risk factors associated with NEC-associated infant death. Infant mortality rates (IMR) were calculated and a retrospective case-control analysis was performed. A case was defined as an infant having the *International Classification of Diseases, Tenth revision* code for NEC listed anywhere on the death record. Controls were infants who survived at least to the end of their first year of life and were randomly selected. Multivariable logistic regression models stratified by birth weight (very low birth weight [VLBW], moderately low birth weight, and normal birth weight) were conducted to determine the risk factors for infant NEC death. Additionally, a sub-analysis of the 2003 birth certificate revision was conducted to determine the association of maternal education and NEC-associated infant death.

RESULTS: The overall NEC IMR was 15.5 deaths per 100,000 live births and was higher among VLBW compared to NBW infants as well as black infants compared to white. Among VLBW infants, the multivariable analysis identified male sex, 5-minute Apgar score of < 7, maternal age of ≤ 19 years, and an interaction between maternal race and maternal marital status to be related with NEC-associated death. Among VLBW infants of white race in the 2003 birth certificate revision sub-analysis, infants with mothers completing less than a high school education had higher odds of NEC-associated death compared to an education of more than high school.

DISCUSSION: Necrotizing enterocolitis-associated IMR did not significantly change from 2007-2009; however, the average annual IMR is still larger compared to previous studies. Since NEC infant death is strongly associated with VLBW, this larger IMR is possibly due to the decreased mortality rate in low birth weight infants. Race disparities may exist and should be the focus of future studies. In addition, mothers and physicians should be aware of the factors related to NEC-associated infant death to improve prevention and reduce mortality rates.

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1. Introduction

1.1. Problem Statement

Necrotizing enterocolitis (NEC) is a gastrointestinal disease that continues to be an important contributor to neonatal morbidity and mortality in the United States (Holman, Stoll, Clarke, & Glass, 1997). Infants who are preterm and of low birth weight experience the greatest risk (Holman et al., 1997); consequently, recent improvements in overall survival of low birth weight preterm infants may lead to an increased risk of developing NEC (Holman et al., 1997; Guthrie, Gordon, Thomas, Thorp, Peabody, & Clark, 2003). Overall infant mortality rates have decreased in recent years, which may be associated with the introduction of exogenous surfactant in the early 1990s that has been shown to decrease mortality in low birth weight infants (Holman et al., 1997; Hobar, Wright, & Onstad, 1993). Although advances have decreased mortality rates low birth weight infants, 10-50% of NEC cases lead to death (Henry, & Moss, 2009).

1.2. Purpose Statement

The purpose of this study is to evaluate NEC-associated deaths among infants in the United States and to identify risk factors for NEC mortality. In addition, this study aims to determine the role that birth weight and infant race have on infant NEC mortality.

1.3. Significance Statement

It is important to know the risk factors associated with infant NEC mortality in order to create preventative measures to reduce mortality rates. The latest study performed on NEC infant death was on 1990-1992 data. This study will determine if certain risk factors have

changed over time. As a result, physicians and mothers can become more aware of the associated risk factors and potentially change their behavior to decrease NEC mortality.

2. Review of the Literature

2.1. History

NEC was first described in 1891 by Genersich where a 45-hour premature infant who experienced vomiting, abdominal distention and cyanosis died the following day; the autopsy of the infant showed inflammation and perforation of the ileum (Santulli, Schullinger, & Heird, 1975). Diagnoses of NEC were first reported in the 1950s by Europeans Schmid and Quaiser at Babies Hospital (Lee, & Pollin, 2003) and the first surgery occurred in 1967 (Santull et al., 1975). At that time, Schmid and Quaiser's definition of NEC was death from necrotic lesions of the gastrointestinal tract. An increase of incidence and awareness of NEC began from there (Santulli et al., 1975). In 1979 *The International Classification of Diseases* established a unique code for NEC (P77) that allowed investigators to distinguish the disease from other gastrointestinal causes of death (Lin & Stoll, 2006).

As neonatal and infant mortality rates in the United States have declined since the mid-1980s, NEC mortality rates have increased (Holman et al., 1997). This continued reduction in infant mortality rates is partly due to the introduction of exogenous surfactant in the 1990s. Surfactant therapy has been shown to improve respiratory function in premature neonates (Hobar etal., 1993). The incidence of NEC briefly declined in the 1980s just before these surfactants became common (Holman et al., 1997). Afterwards, mortality rates in preterm low birth weight infants decreased while incidence of NEC increased possibly due to the association between NEC development and low birth weight infants (Guthrie et al, 2003).

2.2. Biology

The most common first signs of NEC are abdominal distention, feeding intolerance, haematochezia, lethargy, apnoea, respiratory failure and circulatory instability. Some of these early signs can lead to an incorrect diagnosis such as sepsis (Lin, Nasr, & Stoll, 2008). Abdominal radiographs indicated pneumatosis intestinalis to be the cardinal sign of NEC, which most likely leads to rapid perforation of the intestines (Lee et al., 2003). Pneumatosis intestinalis is described as the accumulation of gas produced by gas forming bacteria in the submucosa or suberosa (Ricketts, 1994). Parts of the intestines most commonly affected are the terminal ileum, cecum, and ascending colon (Hopkins, Gould, Stevenson, & Oliver, 1970).

The main outcome in the disease process of NEC is immaturity of intestinal motility and digestion. The second trimester of pregnancy marks the development of intestinal motility and the third trimester is when intestinal motility matures in a fetus (Sanderson, 1999; Sase, Lee, Park, Thakur, Ross, & Buchmiller-Crair, 2001). More specifically, this is the time when tight junctions and a glycoprotein mucin layer form in the epithelium. Since NEC occurs primarily in premature infants, unformed tight junctions and other intestinal immaturities are likely outcomes (Piena-Spoel, Albers, & ten Kate, 2001). Decreased motility of the intestines increases the chance of being exposed to toxic substances in the intestinal epithelium. This can also lead to decreased digestion and absorption (Henry et al., 2009); incompletely digested molecules could contribute to intestinal injury (Lebenthal, 1999). The first signs of NEC are only seen after the first infant feeding has occurred and is not seen in stillborn infants and only occurs postnatally (Lin et al., 2006).

Differing levels of prostaglandins, nitric oxide (NO) and epidermal growth factor (EGF) in the intestines determine intestinal epithelial growth. Prostaglandins regulate formation of tight

junctions and NO is a product of NO synthase (NOS) which has three forms: endothelial NOS, which increases mucosal blood flow and maintains microvascular tone; neuronal NOS, which maintains intestinal homeostasis and keeps NO levels low; and inducible NOS, which results in an increase of NO. High levels of NO may cause intestinal epithelium injury, and is commonly found in infants diagnosed with NEC (Chokshi, 2008). Nitric oxide is the primary vasodilator stimulus in newborn intestinal circulation and Endothelin (ET)-1 is the primary vasoconstrictor stimulus; homeostasis of the intestinal epithelium is maintained by a unique balance of these two stimuli. Greater vasodilation at a steady state requires an increased production of NO. Greater ET-1 occurs in endothelial dysfunction reducing blood flow to the intestines later resulting in tissue injury (Nankervis, Giannone, & Reber, 2008). This imbalance may be due to reduced endothelial production of NO (Lin et al., 2006). The severity of intestinal injury is reduced due to the production of EGF. It increases the migration and proliferation of the intestinal epithelial cells (Nair, Warner, & Warner, 2008); therefore, decreased levels of EGF, found in the saliva and serum of infants with NEC, leads to injured epithelial tissue (Shin, Falcone, & Stuart, 2000). Experimental studies have been performed on animals where introduction of EGF increased the strength of the intestinal barrier and decreased the extent at which experimental NEC developed (Clark, Doelle, & Halpren, 2006). The strength in the intestinal barrier is linked to the expression of particular genes. Commensal bacteria regulate the expression of these genes and an imbalance of this bacterium is more likely to arise in NEC infants (Hooper, Wong, & Thelin, 2001).

2.3. Treatment

Much research has gone into treating infants diagnosed with NEC. Treatments include medical and surgical interventions with debate on which is the best treatment. One article even

mentions that after NEC diagnosis, little can be done to change the fate of the disease (Lee, & Polin, 2003).

Immediate medical treatment of cases is necessary once NEC is suspected (Henry et al., 2009). Medical interventions include bowel rest, decompression of the gastrointestinal tract by placing an orogastric tube (Henry et al., 2009), systemic antibiotics, and parenteral nutrition (Lee et al., 2003). Necrotizing enterocolitis only occurs after first infant feeding making it common in the 1970s to delay the start of feeding (Brown, & Sweet, 1978). This practice has shown to delay the onset of NEC; however, mucosal atrophy and increased mucosal permeability are associated risks (Rothman, 1985).

Twenty to 40% of NEC infants undergo surgical treatment (Guthrie et al., 2003). A majority of these infants are preterm and have a very low birth weight (Blakely, Lalley, & McDonald, 2005). Infants who were diagnosed earlier, and sicker infants requiring mechanical ventilator support during the first day of life, are most likely to undergo surgery (Guthrie et al., 2003). Surgery is suggested if deterioration and perforation of the intestines persist, which can be seen in a radiograph (Lee et al., 2003; Henry et al., 2009). One specific type of surgery is called peritoneal drainage where a small incision is made in the right lower quadrant of the abdomen and a small rubber drain is placed so that drainage of fluid and gas can occur (Henry et al., 2009).

Research has shown that 60% of infants treated with surgery have a good quality of life post-surgery (Vennarecci, Kato, Misiakos, Neto, Verzaro, Pinna, Nery, Khan, Thompson, & Tzakis, 2000); 24% of neonates die post-surgery (Guthrie et al., 2003). Many studies have shown great benefits to surgery where a majority of infants who had NEC no longer have NEC-related

gastrointestinal problems and do not develop neurologic and motor problems afterwards (Patel, Tepas, Huffman, & Evans, 1998). After surgical intervention, gastrointestinal function recovers and the patients are able to have a good quality of life long-term (Abbasi, Pereira, Johnson, Stahl, Durara & Watkins, 1984). The most severe post-surgery complication is short bowel syndrome (Petty, & Ziegler, 2005), which is due to large bowel resectioning (Patel et al., 1998). Some infants who undergo an initial surgery to treat NEC require additional surgeries due to recurring episodes of NEC or further complications such as liver failure, recurrent catheter sepsis and loss of intravenous access (Vennarecci et al., 2000).

2.4. Prevention

Although medical and surgical intervention have been shown to help NEC infants to a point, prevention of NEC may be where the greatest impact on outcome can be realized. Prevention strategies today include feeding strategies and microbiological flora in the gastrointestinal tract (Henry et al., 2009).

The biggest debate regarding prevention of NEC in infants is whether breast-feeding is protective or not. Breast milk contains bioactive factors, which can influence immunity, protect the mucosa of the intestines and increase the population of gastrointestinal bacterial colonization needed for mature intestines (Caplan, & Jilling, 2002). Most studies published show a reduction in the incidence of NEC for those infants that undergo breastfeeding. One meta-analysis, reported that human milk reduces the risk of NEC by almost 80% compared to formula feeding (Boyd, Quigley, & Brocklehurst, 2007). However, in other studies, results were not statistically significant or the study was limited to a small sample. Due to this, these individual studies do not have enough power to show a clinically significant reduction of NEC in those infants who

were fed with human milk (Henderson, Anthony, & McGuire, 2007). Most researchers agree that large randomized controlled trials examining the rate of NEC in premature infants fed human milk are necessary (Henry et al., 2009). The type of milk NEC infants are fed is not the only concern; the time at which the infant is introduced to feeding is also of concern in the onset of NEC. Early feeding may increase the risk of NEC although early initiation of enteral feedings in preterm infants is a way to promote growth (Kennedy, Tyson, & Chamnanvanikij, 2008).

Introduction of probiotics is another way of preventing NEC due to its role in promoting healthy colonization of bacteria in the premature intestines (Martin, & Walker, 2008). Additional large randomized studies to confirm the benefit of probiotics have also been recommended (Henry et al., 2009).

2.5. Epidemiology

Mortality among NEC infants range from 10-50% and the majority of deaths occur in very low birth weight infants and those who undergo surgery (Holman, Stoll, Curns, Yorita, Steiner, & Schonberger, 2006). Five to 25% of NEC cases have been reported in full-term infants; however infants weighing less than 1000g at birth and under 28 weeks gestation are at greatest risk (Lee et al., 2003). Research done by the National institute of Child Health and Human Development (NICHD) during the years 1998 to 2001 reported NEC affecting 11.5% of infants weighing 401-750g, 9% of infants weighing 751-1000g, 6% of infants weighing 1001-1250g and 4% of infants weighing 1251-1500g (Guillet, Stoll, & Cotton, 2006). In a study done in the same year, 66% of infants hospitalized with NEC weighed less than 1500g and 27% weighed between 1500 and 2499g at birth (Holman et al., 2006). The risk of NEC is most evident before 36 weeks gestation (Lee et al., 2003); more than 90% of infants with NEC were

born prior to 36 weeks gestation (Henry et al., 2009). Due to the link between premature infants and the timing of the onset of NEC, this disease is more rare in countries were prematurity is uncommon (Ostlie Spilde, & St. Peter, 2003). Greater than 40% of NEC is diagnosed on the first day of life with a median age of 2 days (Stoll, 1994). The hospitalization rate associated with this disease in 2000 was 1.1 per 1000 live births and median length of stay was 49 days (Holman et al., 2006).

Most studies have not found a drastic difference in risk, if any, between male and female infants (Lee et al., 2003); however, some studies have shown males of low birth weight to have higher mortality rates and incidence rates (Holman et al., 1997, Guillet et al., 2006). In a multivariable logistic regression model, increased risk was associated with black infants, those born to an unmarried mother, those born to a mother ≤17 years of age and those having fewer or no prenatal care visits. Although 5-minute Apgar score was not significant in multivariable analysis after accounting for other infant and maternal risk factors, there was a greater risk of NEC-associated death among infants with a 5-minute Apgar score of <7 in the univariate analysis (Holman et al., 1997). Guillet et al. did not find 5-minute Apgar score to be a significant factor in explaining NEC-associated infant death (Guillet et al., 2006). Even after controlling for birth weight and other characteristics, a racial disparity is evident in the death rates of NEC with infants of black race having the greatest rate. Infants of lower birth weight having a greater risk of dying in the postneonatal period (≥28 days; Holman et al., 1997).

3. Methods

3.1. Epidemiological Methods

Period linked birth/infant death data for the United States from 2007 through 2009 were obtained from the National Center for Health Statistics, Centers for Disease Control and Prevention. For each year of data, infant death certificates for infant deaths that occurred within one year after birth are linked to their corresponding birth certificate (National Center for Health Statistics, 2010, 2011, 2012). This dataset includes information from both the birth and death certificate including maternal and infant characteristics. A weight was provided in the data to correct for biases due to incomplete linkage between the death and birth certificates. The percentage of all death certificates that were not linked to their corresponding birth certificate were 1.6%, 1.3%, and 1.4% from 2007-2009, respectively (National Center for Health Statistics, 2010, 2011, 2012). The *International Classification of Diseases, Tenth Revision* (ICD-10) code for NEC of fetus or newborn is P77 (World Health Organization, 1992). A case was defined as an infant having this code listed as one of up to 20 causes of death on the death record. The proportion of NEC-associated infant deaths with NEC listed as the underlying cause of death was calculated.

The 1989 and 2003 revisions of the U.S. Standard Certificate of Live Birth were both used during the study period. The 2003 revision was used by 22 states in 2007 (52% of births), 27 states in 2008 (62%), and 28 states in 2009 (66%). Some variables were not comparable between revisions and were excluded from select analyses. Variables that were comparable and of interest included sex (male, female), gestational age (<37 weeks, ≥37 weeks), birth weight (<1500g, very low birth weight [VLBW]; 1500-2499g, moderately low birth weight [MLBW];

≥2500g, normal birth weight [NBW]), 5-minute Apgar score (<7, ≥7), maternal age (≤19 years, 20-24 years, 25-29 years, ≥30 years), maternal race (white, black, Asian/Pacific Islander [A/PI], American Indian/Alaska Native [AI/AN]), maternal marital status (married, unmarried), maternal Hispanic origin (Hispanic, non-Hispanic), live birth order (first, second, third, fourth or more) and plurality (singleton, non-singleton). Maternal race and ethnicity on the birth certificate was used to represent infant race and ethnicity because it is more reliable than infant race and ethnicity on the death certificate (National Center for Health Statistics, 2010, 2011, 2012). Due to the high correlation between gestational age and birth weight (0.78) and the unreliability of gestational age, gestational age was not considered in the multivariable modeling (Kramer, McLean, Boyd, & Usher, 1988).

A sub-analysis of the 2003 U.S. Standard Certificate of Live Birth was performed using the variables described above as well as others that were not comparable to the 1989 revision. These variables included maternal education (less than high school, high school, more than high school), maternal smoking status (smoker, non-smoker), prenatal care index (adequate, inadequate) and cyanotic heart disease (reported, not reported). The adequacy of prenatal care utilization (APNCU) index was calculated and defined to characterize prenatal care utilization dependent on two concepts (Kotelchuck, 1994). The first measures how early prenatal care began; it is thought the earlier prenatal care beings, the more adequate the care. The second concept measures the adequacy of the visits made by taking a ratio of the number of actual prenatal visits to the expected number of visits. The expected number of visits is based on the American Congress of Obstetricians and Gynecologits (ACOG) prenatal care visitation standards for uncomplicated pregnancies and is adjusted for the gestational age at the beginning of prenatal care and gestational age at time of delivery. All these variables are available on the 2003 U.S.

Standard Certificate of Live Birth. When these two concepts are combined, inadequate prenatal care is defined as either late initiation of prenatal care (after the 4th month of pregnancy) or fewer than 50% of recommended visits and adequate prenatal care is defined as the alternative (Kotelchuck, 1994).

3.2. Age at Death

Mean age at death in days was compared between the birth weight groups using one-way Analysis of Variance (ANOVA). If the F statistic resulted in a p-value of <0.05 then Tukey's method was used to determine the birth weight groups for which the mean age at death differed. This method is only used when pairwise comparisons of the group means are of interest (Kutner, Nachtscheim, Neter, & Li, 2005).

3.3. Infant Mortality Rates

Infant mortality rates (IMR) were computed as the weighted number of NEC-associated infant deaths per 100,000 live births. Denominators for the study were calculated from a file containing birth certificate information from all live births, which is provided with each year of the linked data (National Center for Health Statistics, 2010, 2011, 2012). IMR for the neonatal and post neonatal periods were computed using person time as the denominator. The number of infants who died within a given age range, either neonatal or post neonatal, was divided by the total number of person-years contributed to that specific age range and was then expressed as deaths per 100,000 person-years. Poisson regression was used to calculate rate ratios (RR) and 95% confidence intervals to compare rates between levels of each variable. The trend in annual IMR was tested with Poisson regression.

3.4. Case-Control Methods

A retrospective case-control study was conducted to measure the infant and maternal risk factors associated with NEC-associated infant death. Cases were defined as infant deaths with NEC found anywhere on the death record. Controls were randomly selected using a random number selection process in SAS version 9.3 with a 1:4 ratio of NEC-associated deaths to controls. Controls were defined as infants who survived at least to the end of their first year of life. Univariate analysis was conducted for each variable individually using logistic regression with NEC-associated death as the outcome of interest. To determine univariate significance, chi-square tests were conducted to test if there was significance level of $p<0.10$ in the proportion of cases within the levels of each variable. If the number of infant deaths in a particular group was less than or equal to 5 then exact logistic regression was performed.

Infant and maternal characteristics that were significantly associated with NEC-associated infant mortality in the univariate analysis were further assessed by fitting a multivariable logistic regression model. Unconditional maximum likelihood estimation was performed because of the large number of infants and small number of predictor variables. The statistic used to find the final multivariable logistic regression model is the -2 log likelihood (-2logL) statistic (Kleinbaum, 2002). The test statistic is computed through the following process: $\hat{L}_1$ is the estimated likelihood of the full model and $\hat{L}_2$ is the estimated likelihood of the reduced model, which is a subset of the full model with one predictor removed. If $\hat{L}_2$ is much larger than $\hat{L}_1$, the ratio becomes a very small fraction, approaching zero. Taking the log of this fraction makes it a negative number with the log of the fraction approaching negative infinite. Multiplying the log likelihood ratio by -2 allows this number to approach positive infinite. A very similar result occurs with the chi square statistic. In the same way, if $\hat{L}_2$ is essentially equal

to $\hat{L}_1$, this means the ratio is approximately one. Taking the log and multiplying by -2 makes this number approach zero which again is expected from the chi square statistic. A difference between two log likelihood statistics has approximately a chi square distribution in large samples with degrees of freedom equal to the difference in degrees of freedom between the two models being compared (Kleinbaum, 2002).

Hierarchical backward selection to obtain the best fit multivariable model was performed in the following way: each significant univariate predictor variable and all possible two-way interactions with maternal race were initially entered into the full model. Maternal race interactions were computed to test any racial disparities. The significance of each predictor variable was tested by removing it from the full model to create a reduced model. The difference in the -2logL between the full and reduced models was calculated under the chi square distribution with degrees of freedom of the predictor variable that was removed. The variable with the least significant effect was then removed to create a new full model and the process was repeated until all remaining predictor variables were significant at <0.05 level. Interaction terms were tested first and removed until all remaining interaction terms were significant. Then main effects not involved in significant interaction terms were tested one at a time and were removed from the model until all predictor variables were significant. If a large standard error resulted for a particular interaction with maternal race, this interaction term was initially removed from the model before backward selection was conducted due to the instability of the interaction. Due to convergence issues caused by the small numbers in the "other" race category, these models were performed with using white and black maternal race only A final model was found for VLBW, MLBW and NBW infants. These methods were repeated for the 2003 birth certificate revision sub-analysis. Although, with 42% of records missing maternal smoking status and 44% missing

prenatal care index, these two predictors were not considered in the multivariable logistic regression model. In addition, cyanotic heart disease was deemed unstable due to small numbers and was also not considered for the multivariable model.

Odds ratios (OR) were used as the measure of association since logistic regression was utilized. Risk ratio cannot be directly estimated from a logistic model because these estimates require conditional probabilities of the form P(D|E); however, only estimates of the form P(E|D) are possible, where D stands for disease and E stands for exposure. This is true in this study because the status of disease was previously chosen (Kleinbaum, Klein, & Pryor, 2002).

4. Results

4.1. Overall Analysis

During 2007-2009, the weighted number of NEC-associated infant deaths reported in the Linked Period/Infant Death dataset was 1970 (Table 1). Eighty-one percent (n=1592) of cases had NEC listed as the underlying cause of death. There were fewer NEC-associated infant deaths in 2009 (n=595) than in 2007 (n=694) but no decreasing trend in mortality rate (p=0.08). Almost 84% of VLBW infants with a NEC-associated death died before the end of the neonatal period (Figure 1). Mean age at death among VLBW infants (Mean: 23.5, SE: 27.4) was older compared to MLBW infants (Mean: 14.4, SE: 23.2; $p<0.0001$) but was statistically similar to NBW infants (Mean: 17.4, SE: 31.4; p=0.6372). The most common contributing cause of death that was not related to prematurity was bacterial sepsis of newborn, unspecified (ICD-10 code: P36.9) which was ranked 4th, 3rd, and 2nd among VLBW, MLBW, and NBW infants, respectively. More than 51% of VLBW infants with a NEC-associated death had extreme prematurity of newborn (ICD-10 code: P07.2) listed on their death record, making it the most frequently-listed code (Table 2).

4.1.1. Infant Mortality Rates

The NEC-associated IMR in 2007 was 16.1 deaths per 100,000 live births and was 14.4 in 2009; these rates were similar (Table 1). The rate was higher among male infants (RR:1.3, 95% CI: 1.2-1.4) and those who were VLBW compared to NBW (RR: 1042.6, 95% CI: 848.7-1280.8). Infants with black race had a higher IMR than all other race categories. There was no difference in IMR among white and A/PI maternal race (Table 1). The IMR was higher among infants dying within the neonatal period compared to the post neonatal period (RR: 73.5, 95%

CI: 64.9-83.3). This rate was higher among infants with a 5-minute Apgar score of <7 compared to ≥7 (RR: 24.2, 95% CI: 22.0-26.7) and in infants with a gestational age of <37 weeks compared to ≥ 37 weeks (RR: 106.2, 95% CI: 88.5-127.6). Infants born to a mother ≤19 years of age had a higher IMR than all other age categories. There was no difference in IMR among infants born to a mother ≥30 years of age compared to 25-29 years (Table 1). This rate was higher among infants born to non-Hispanic mothers (non-Hispanic vs. Hispanic RR: 1.3, 95% CI: 1.2-1.4) and married mothers (unmarried vs. married RR: 0.5, 95% CI: 0.4-0.5). Infants with a live birth order of fourth or more had a higher IMR than all other live birth order categories. There was no difference in IMR among a live birth order of third compared to second (Table 1).

4.2. Stratification by Birth Weight

4.2.1. Very Low Birth Weight

During 2007-2009, there were a weighted total of 1625 NEC-associated deaths among VLBW infants. Among these deaths, 1339 (82%) had NEC listed as the underlying cause of death. In the univariate analysis, all tested characteristics were significant predictors of NEC-associated infant death except for maternal Hispanic origin (Table 3). Therefore, all other predictors (sex, maternal race [white and black], 5-minute Apgar score, maternal age, maternal marital status, plurality and live birth order) were initially entered into a multivariable logistic regression model. The significant main effect characteristics were sex, 5-minute Apgar score, and maternal age (Table 4). Necrotizing enterocolitis-associated death among VLBW infants is more likely to occur for males (OR: 1.3, 95% CI: 1.2-1.5), those with a 5-minute Apgar score of <7 (OR: 1.6, 95% CI: 1.4-1.8), and those born to mothers ≤19 years of age compared to 25-29 years of age (OR: 1.3, 95% CI: 1.1-1.6). There was no difference between NEC-associated

infant deaths among mothers ≥30 years of age compared to mothers 25-29 years of age (Table 4). There was a significant interaction between maternal race and maternal marital status. Among infants of white race, the odds of NEC-associated infant death were higher for those born to unmarried mothers (OR: 1.4, 95% CI: 1.2-1.6). Among infants of black race, there was no difference in maternal marital status (Table 4).

4.2.2. Moderately Low Birth Weight

During 2007-2009, there were a weighted total of 246 NEC-associated deaths among MLBW infants. Among these deaths, 190 (77%) had NEC listed as the underlying cause of death. In the univariate analysis, all tested characteristics were significant predictors of NEC-associated infant death except for maternal Hispanic origin and plurality (Table 3). All other predictors (sex, maternal race [white and black], 5-minute Apgar score, maternal age, maternal marital status, and live birth order) were initially entered into a multivariable logistic regression model. The significant main effects were sex, live birth order, and maternal marital status (Table 4). Among MLBW infants, the odds of NEC-associated death were higher for male infants (OR: 1.9, 95% CI: 1.4-2.6; Table 4), and those born to an unmarried mother (OR: 1.5, 95% CI: 1.1-2.1). Compared to second born, a live birth order of fourth or more was associated with NEC-associated death (OR: 1.8, 95% CI: 1.2-2.9). Live birth order of first and third resulted in statistically similar odds of NEC-associated death compared to second born (Table 4). A significant interaction occurred between maternal race and 5-minute Apgar score. Among infants of white race, the odds of NEC-associated infant death were higher for those with a 5-minute Apgar score of <7 (OR: 6.8, 95% CIL 3.5-13.1). Among infants of black race however, 5-minute Apgar score was not significantly associated with NEC-associated death (Table 4).

4.2.3. Normal Birth Weight

During 2007-2009, there were a weighted total of 96 NEC-associated deaths among NBW infants. Among these deaths, 60 (63%) had NEC listed as the underlying cause of death. In the univariate analysis, the only statistically significant predictors were maternal race, 5-minute Apgar score, maternal marital status, and live birth order (Table 3). These predictors were initially entered into a multivariable logistic regression model that included infants of white or black race only. The significant main effects were 5-minute Apgar score, and live birth order (Table 4). Among NBW infants, the odds of NEC-associated death were greater for those infants with a 5-minute Apgar score of <7 (OR: 69.4, 95% CI: 12.7->1000). Compared to second born, a live birth order of first was associated with decreased odds of NEC-associated death (OR: 0.5, 95% CI: 0.3-0.9). The odds of a NEC-associated infant death were statistically similar for a live birth order of third and fourth or more. There were no statistically significant interactions with maternal race (Table 4).

4.3. 2003 Birth Certificate Sub-Analysis

A total of 1164 birth records (60%) linked to a NEC-associated infant death record, utilized the 2003 birth certificate revision. Maternal education was the only additional predictor for the 2003 birth certificate sub-analysis. Only one multivariable logistic regression model was made for the 2003 sub-analysis due to maternal education being the only significant predictor in the univariate analysis among VLBW infants (Table 5).

During 2007-2009, there were a weighted total of 951 NEC-associated deaths among VLBW infants with the 2003 birth certificate revision. Among these deaths, 775 (81%) of them had NEC listed as the underlying cause of death. In the univariate analysis, maternal education

was significant along with sex, maternal race, maternal Hispanic origin, 5-minute Apgar score, maternal age, maternal marital status, live birth order, and plurality (Table 5). The significant main effects in the multivariable logistic regression model were sex, 5-minute Apgar score, live birth order and maternal age (Table 6). Among VLBW infants with the 2003 birth certificate revision, the odds of NEC-associated death were greater for males (OR: 1.3, 95% CI: 1.1-1.5) and those with a 5-minute Apgar score of <7 (OR: 1.6, 95% CI: 1.3-1.9). Compared to second born, firstborn infants had higher odds of NEC-associated death (OR: 1.3, 1.1-1.6). Infants with a live birth order of third and fourth or more had statistically similar odds compared to second (Table 6). Compared to 25-29 years, maternal age of 20-24 years had higher odds of NEC-associated death (OR: 1.4, 95% CI: 1.2-1.8); the odds for maternal age ≥30 years of age were statistically similar to 25-29 years of age. A significant interaction occurred between maternal race and maternal education (Table 6). Among infants of white race, infants with mothers completing less than a high school education had higher odds of NEC-associated death compared to an education of more than high school (OR: 1.8, 95% CI: 1.4-2.4). Among infants of black race, infants with mothers completing less than a high school education and completing high school had statistically similar odds of NEC-associated infant death compared to an education of more than high school (Table 6).

5. Discussion

Necrotizing enterocolitis-associated IMR did not significantly change from 2007-2009; however, the IMR is still larger compared to previous studies, possibly due to the decreased mortality rate in preterm low birth weight infants. From 2007-2009 the NEC-associated IMR was 15.5 compared to a rate of 12.3 among singleton infants from 1990-1992 (Holman et al., 1997). Consistent with previous reports, low birth weight was found to be a risk factor for NEC-associated death (Holman et al., 1997, Lee et al., 2003). Necrotizing enterocolitis-associated death is strongly associated with VLBW, with this group comprising 83% of NEC-associated deaths. This association with VLBW infants has also been found in NEC-associated hospitalizations. Holman et al. reported 66% of NEC hospitalizations in neonates were among VLBW infants (Holman et al., 2006).

Similar to previous reports, racial disparity is evident in the death rates of NEC even after controlling for birth weight (Holman et al., 1997). In the multivariable analysis, maternal race interactions with maternal marital status and maternal education among VLBW infants and with 5-minute Apgar score among MLBW infants were significant in the present study. Although infants of black race had the greatest odds of a NEC-associated death in the univariate analysis, which was also found in Holman et al. (1997), the greatest odds were among infants of white race in the multivariable analysis. Among infants of white race, those with a 5-minute Apgar score of <7 had the greatest odds overall.

Sex and maternal age were previously found to be related with NEC-associated infant death. Males (birth weight-adjusted relative risk: 1.6, 95% CI: 1.4-1.8) and maternal age ≤17 years of age compared to 25-29 years of age (birth weight-adjusted relative risk: 1.7, 95% CI:

1.2-2.3) among LBW infants had higher relative risks even after controlling for other infant and maternal risk factors. Very low birth weight infants comprised 75% of the LBW NEC-associated infant deaths in this previous study. The birth weight-adjusted relative risk estimates for sex were more similar among VLBW infant death OR and the relative risk estimates for maternal age were more similar among MLBW infant death OR in the present study. Necrotizing enterocolitis-associated deaths among infants were also related to maternal marital status (unmarried vs. married birth weight-adjusted relative risk: 1.3, 95% CI: 1.1-1.5) and race but their interaction was not examined (Holman et al., 1997). The ORs among VLBW and MLBW infant deaths were higher in the present study. From this analysis, NEC deaths among VLBW infants were more associated with maternal characteristics than biological infant characteristics. Mothers and physicians should be aware of the factors related to NEC-associated infant death to reduce mortality rates.

In the 2003 birth certificate revision sub-analysis, sex, 5-minute Apgar score, live birth order, and maternal age were the significant main effects along with an interaction between maternal race and maternal education. Contrary to previous research done by Holman et al. (1997), maternal education was found to be associated with NEC-associated infant death; the less education the mother completed, the greater the odds of a NEC-associated infant death.

Very low birth weight infants with a NEC-associated death died at an older mean age compared to MLBW infants. This is similar to what was found in a previous study, with infants of lower birth weight having a greater risk of dying in the postneonatal period (Holman et al., 1997). Feeding introduced quickly and frequently among VLBW infants to increase their body weight does not explain why infants in this group die at an older age, especially since feeding has been found to increase the development of NEC (Lin et al., 2006).

Among MLBW infants the greatest odds were found in male infants and those with a live birth order of fourth or more. A similar increased risk of fourth or more born was found (birth weight-adjusted relative risk: 1.3, 95% CI: 1.1-1.6; Holman et al., 1997). Contrary to previous research, 5-minute Apgar score was associated in the present study even after accounting for other infant and maternal risk factors among MLBW infants. Among infants with mothers of white race, those with a 5-minute Apgar score of <7 had higher odds of developing NEC.

Possibly due to the small weighted number of NEC-associated infant deaths among NBW infants (n=96), the only significant associated infant characteristics were 5-minute Apgar score and live birth order. This small percentage was also reported by Lee et al. presenting that 5-25% of NEC cases were NBW (Lee et al., 2003). A 5-minute Apgar score of <7 was very strongly associated with NEC-associated infant death (OR: 69.4, 95% CI: 12.7->1000). A small number of deaths among NBW infants with a 5-minute Apgar score of <7 (n=13), may make this analysis unstable however. Decreased odds of NEC-associated infant death were found among NBW infants who were the firstborn.

This increase in NEC-associated IMR from earlier years of research to the present study could be due to the introduction of exogenous surfactant; this issue has been previously investigated (Henry et al., 2009). The introduction of exogenous surfactant has enabled preterm and infants of low birth weight to survive increasing the risk of developing diseases such as NEC, which are more common among VLBW infants. Bacterial sepsis is the highest ranked contributing cause of death after prematurity related ICD-10 codes, which may be explained by the fact that sepsis is the most common misdiagnosis among NEC-associated diseases (Lin et al., 2008). Also the fact that VLBW infants died at an older mean age compared to MLBW infants may emphasize the effects of intervention, such as exogenous surfactant for VLBW infants.

Moderately low birth weight infants may be sent home from the hospital at a vulnerable state leading to death at a younger age. Therefore, bringing the fetus to full term where the infant is more likely to be of NBW is the goal.

A limitation in this study is using ICD-10 codes to define cases due to the dependability of correct diagnosis and coding. Another limitation is utilizing two different U.S. Standard Certificates of Live Birth. The non-comparability of the 1989 and 2003 revisions did not allow all variables of interest to be analyzed in an overall analysis. Performing a sub-analysis of the 2003 revision cannot directly be generalized to the entire U.S. since not all the states were included. Lastly, when multivariable logistic regression was performed through SAS, any infant death that was missing data for any of the variables included in the model was deleted. As a result, this limited the number of infants included in the analysis due to high percentages of missing data for some variables.

Necrotizing enterocolitis is a biologically complicated disease with unknowns regarding its biological development. The recent increase in the rate of deaths associated with NEC may be due to the introduction of exogenous surfactant and other methods that enable preterm low birth weight infants at a vulnerable state to survive. Treatment, such as surgery, has been found to be beneficial. Understanding the risk factors of this disease can only further determine which groups of infants are at risk and explain the racial disparities that may exist. With these risk factors being known, prevention measures can take place to decrease the number of NEC-associated deaths among infants.

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Appendix

Table 1. Nectrotizing Enterocolitis-Associated Deaths and Infant Mortality Rates (IMR) for Select Infant and Maternal Characteristics, United States, 2007-2009.*

Characteristics	Deaths	Live Births	IMR	RR (95% CI)†
Total	1970	12,694,624	15.5	
Sex				
Female	848	6,199,288	13.7	Reference
Male	1123	6,495,336	17.3	1.3 (1.2-1.4)
Birth weight (g)°				
<1500 (VLBW)	1625	189,009	860	1042.6 (848.7-1280.8)
1500-2499 (MLBW)	246	853,268	28.8	34.9 (27.6-44.2)
≥2500 (NBW)	96	11,649,855	0.82	Reference
Maternal race				
White	757	6,790,702	11.2	Reference
Black	710	1,859,806	38.2	3.4 (3.1-3.8)
A/PI	75	758,761	9.9	0.9 (0.7-1.1)
AI/AN	31	147,645	20.7	1.9 (1.3-2.7)
Maternal Hispanic origin				
Hispanic	397	3,103,566	12.8	Reference
Non-Hispanic	1562	9,497,420	16.4	1.3 (1.2-1.4)
Year of death				
2007	694	4,316,233	16.1	Reference
2008	682	4,247,726	16.1	1.0 (0.9-1.1)
2009	595	4,130,665	14.4	0.9 (0.8-1.0)
Age at death				
Neonatal	1684	933483	180.4	73.5 (64.9-83.3)
Post neonatal	287	11696983	2.5	Reference
5-minute Apgar score				
<7	567	215,309	263.3	24.2 (22.0-26.7)
≥7	1346	12,393,012	10.9	Reference
Gestational age (weeks)				
<37	1841	1,571,948	117.1	106.2 (88.5-127.6)
≥37	122	11,088,708	1.1	Reference
Maternal age (years)				
≤19	302	1,306,450	23.1	1.8 (1.5-2.0)
20-24	548	3,140,527	17.5	1.3 (1.2-1.5)
25-29	468	3,570,976	13.1	Reference
≥30	652	4,676,671	14	1.1 (1.0-1.2)
Maternal marital status				
Unmarried	817	7,559,327	10.8	0.5 (0.4-0.5)
Married	1154	5,135,297	22.5	Reference

Live birth order				
First	909	5,089,854	17.9	1.5 (1.3-1.7)
Second	474	3,984,806	11.9	Reference
Third	280	2,106,714	13.3	1.1 (1.0-1.3)
Fourth or more	294	1,439,114	20.5	1.7 (1.5-2.0)

*Infant mortality rate (IMR) expressed as the weighted number of necrotizing enterocolitis –associated deaths per 100,000 live births.

ºVLBW: very low birth weight, MLBW: moderately low birth weight, NBW: normal birth weight

† RR indicates rate ratio; CI, confidence interval

Table 2. Most Frequently Listed Contributing Causes of Death for Necrotizing Enterocolitis-Associated Infant Deaths Overall and among VLBW, MLBW and NBW Infants, United States, 2007-2009.*

		VLBW Infants	**MLBW Infants**	**NBW Infants**	**Overall Infants**
ICD-10 Code	*Description*	*Rank (%)*	*Rank (%)*	*Rank (%)*	*Rank (%)*
P07.2	Extreme immaturity of newborn	1 (51.3)			1 (43.0)
P07.3	Other preterm newborn	2 (38.0)	1 (60.2)	2 (12.6)	2 (39.5)
P36.9	Bacterial sepsis of newborn, unspecified	3 (22.4)	2 (28.7)	1 (28.4)	3 (23.5)
P28.5	Respiratory failure of newborn	4 (6.8)	6 (7.8)		5 (6.8)
P78.0	Perinatal intestinal perforation	5 (6.7)	3 (10.7)		4 (7.1)
P29.1	Neonatal cardiac dysrhythmia	6 (6.3)	5 (8.2)	6 (8.4)	6 (6.6)
P29.0	Neonatal cardiac failure	7 (6.1)	7 (6.6)	7 (7.4)	7 (6.2)
P60.0	Disseminated intravascular coagulation of newborn		4 (9.4)		
Q24.9	Congenital malformation of heart, unspecified			3 (11.6)	
R68.8	Other general symptoms and signs			4 (9.5)	
I95.9	Hypotension, unspecified			5 (8.4)	

*VLBW: very low birth weight (<1500g), MLBW: moderately low birth weight (1500-2499g), NBW: normal birth weight (≥2500g)

Table 3. Comparison of Select Infant and Maternal Characteristics between Necrotizing Enterocolitis-Associated Deaths and Infant Survivors, Stratified by Birth Weight, United States, 2007-2009.

Characteristic	VLBW Infants‡			MLBW Infants‡			NBW Infants‡		
	Deaths, n(%)	Survivors, n(%)	OR (95% CI)*	Deaths, n(%)	Survivors, n(%)	OR (95% CI)*	Deaths, n(%)	Survivors, n(%)	OR (95% CI)*
Total	1614	6456		244	976		95	380	
Sex									
Female	700 (43.4)	3292 (51.0)	Reference	95 (38.9)	522 (53.5)	Reference	45 (47.4)	186 (49.0)	Reference
Male	914 (56.6)	3164 (49.0)	1.4 (1.2-1.5)	149 (61.1)	454 (46.5)	1.8 (1.4-2.4)	50 (52.6)	194 (51.0)	1.1 (0.8 - 1.7)
Maternal race									
White	898 (55.6)	4033 (62.5)	Reference	151 (61.9)	685 (70.2)	Reference	71 (74.7)	309 (81.3)	Reference
Black	636 (39.4)	2039 (31.6)	1.4 (1.2-1.6)	75 (30.7)	214 (21.9)	1.6 (1.2-2.2)	18 (19.0)	45 (11.9)	1.7 (1.0-3.2)
Other†	80 (5.0)	384 (5.9)	0.9 (0.7-1.2)	18 (7.4)	77 (7.9)	1.1 (0.6-1.8)	6 (6.3)	26 (6.8)	1.0 (0.4-2.5)
Maternal Hispanic origin									
Hispanic	315 (19.6)	1256 (19.6)	1.0 (0.9-1.1)	54 (22.2)	195 (20.1)	1.1 (0.8-1.6)	69 (74.2)	92 (24.4)	1.1 (0.6 - 1.8)
Non-Hispanic	1292 (80.4)	5140 (80.4)	Reference	189 (77.8)	776 (79.9)	Reference	24 (25.8)	285 (75.6)	Reference
5-minute Apgar score									
<7	518 (33.1)	1424 (22.6)	1.7 (1.5-1.9)	32 (13.3)	34 (3.5)	4.2 (2.5-7.0)	13 (14.1)	3 (0.8)	20.4 (5.4-114.4)
≥7	1047 (66.9)	4888 (77.4)	Reference	209 (86.7)	933 (96.5)	Reference	79 (85.9)	376 (99.2)	Reference
Maternal age (years)									
≤19	253 (15.7)	760 (11.8)	1.5 (1.2-1.8)	34 (13.9)	98 (10.1)	1.7 (1.0-2.8)º	13 (13.7)	40 (10.5)	1.3 (0.6 - 2.8)
20-24	453 (28.1)	1501 (23.2)	1.3 (1.1-1.5)	63 (25.8)	246 (25.2)	1.3 (0.8-1.9)	28 (29.5)	87 (22.9)	1.3 (0.7 - 2.4)
25-29	381 (23.6)	1677 (26.0)	Reference	52 (21.3)	256 (26.2)	Reference	28 (29.5)	113 (29.7)	Reference
≥30	527 (32.6)	2518 (39.0)	0.9 (0.8-1.1)	95 (39.0)	376 (38.5)	1.2 (0.9-1.8)	26 (27.3)	140 (36.9)	0.8 (0.4 - 1.4)
Maternal marital status									
Unmarried	950 (58.9)	3200 (49.6)	1.5 (1.3-1.6)	146 (59.8)	467 (47.9)	1.6 (1.2-2.2)	48 (50.5)	147 (38.7)	1.6 (1.0 - 2.5)º
Married	664 (41.1)	3256 (50.4)	Reference	98 (40.2)	509 (52.1)	Reference	47 (49.5)	233 (61.3)	Reference
Plurality									
Singleton	1278 (79.2)	4698 (72.8)	1.4 (1.2-1.6)	191 (78.3)	729 (74.7)	1.2 (0.9-1.7)	92 (96.8)	378 (99.5)	0.2 (0.1-1.4)
Non-singleton	336 (20.8)	1758 (27.2)	Reference	53 (21.7)	247 (25.3)	Reference	3 (3.2)	2 (0.5)	Reference
Live birth order									
First	779 (48.5)	2804 (43.9)	1.3 (1.1-1.5)	93 (38.2)	390 (40.5)	1.2 (0.8-1.7)	29 (31.2)	155 (41.0)	0.6 (0.4 - 1.1)
Second	378 (23.5)	1741 (27.3)	Reference	59 (24.3)	287 (29.8)	Reference	34 (36.6)	118 (31.2)	Reference
Third	223 (13.9)	985 (15.4)	1.0 (0.9-1.3)	40 (16.5)	166 (17.2)	1.2 (0.8-1.8)	15 (16.1)	73 (19.3)	0.7 (0.4 - 1.4)
Fourth or more	226 (14.1)	852 (13.4)	1.2 (1.0-1.5)º	51 (21.0)	120 (12.5)	2.1 (1.3-3.2)	15 (16.1)	32 (8.5)	1.6 (0.8 - 3.4)

* OR indicates odds ratio; CI, confidence interval

† Other race includes Asian/Pacific Islander and American Indian/Alaska Native

º Indicates a significant associated p-value (<0.05)

‡ VLBW: Very Low Birth Weight (<1500g), MLBW: Moderately Low Birth Weight (1500-2499g), NBW: Normal Birth Weight (≥2500g)

Table 4. Summary of Multivariable Logistic Regression Analysis of Select Risk Factors for Necrotizing Enterocolitis-Associated Infant Deaths as Compared with Infant Survivors, among VLBW, MLBW, and NBW, United States, 2007-2009.†

	VLBW Infants	**MLBW Infants**	**NBW Infants**
Characteristic	*OR (95% CI)**	*OR (95% CI)**	*OR (95% CI)**
Sex			
Female	Reference	Reference	-
Male	1.3 (1.2-1.5)	1.9 (1.4-2.6)	-
5-Minute Apgar Score			
<7	1.6 (1.4-1.8)	-	69.4 (12.7 - >1000)
≥7	Reference	-	Reference
Matneral age			
≤ 19	1.3 (1.1-1.6)	-	-
20-24	1.3 (1.1-1.5)	-	-
25-29	Reference	-	-
≥ 30	1.0 (0.8-1.1)	-	-
Live Birth Order			
First	-	1.0 (0.7-1.5)	0.5 (0.3 - 0.9)
Second	-	Reference	Reference
Third	-	1.0 (0.6-1.6)	0.7 (0.3 - 1.4)
Fourth or more	-	1.8 (1.2-2.9)	1.4 (0.6 - 3.1)
Maternal marital status			
Married	-	Reference	-
Unmarried	-	1.5 (1.1-2.1)	-
Maternal Race			
White			
Maternal marital status			
Married	Reference	-	-
Unmarried	1.4 (1.2-1.6)	-	-
Black			
Maternal marital status			
Married	Reference	-	-
Unmarried	0.8 (0.7-1.0)	-	-
Maternal Race			
White			
5-minute Apgar score			
<7	-	6.8 (3.5-13.1)	-
≥7	-	Reference	-
Black			
5-minute Apgar score			
<7	-	1.6 (0.6-4.3)	-
≥7	-	Reference	-

† "Other" race was excluded due to insufficient number of deaths. VLBW: very low birth weight (<1500g), MLBW: moderately low birth weight (1500-2499g), NBW: normal birth weight (≥2500g)
* OR indicates odds ratio; CI indicates confidence interval

Table 5. Comparison of Select Infant and Maternal Characteristics between Necrotizing Enterocolitis Deaths and Infant Survivors among the 2003 Birth Certificate Revision Sub-Analysis, Stratified by Birth Weight United States, 2007-2009.

	VLBW Infants‡			LBW Infants‡			NBW Infants‡		
Characteristic	*Deaths, n(%)*	*Survivors, n(%)*	*OR (95% CI)**	*Deaths, n(%)*	*Survivors, n(%)*	*OR (95% CI)**	*Deaths, n(%)*	*Survivors, n(%)*	*OR (95% CI)**
Total	945	3780		143	572		73	292	
Sex									
Female	405 (42.9)	1870 (49.5)	Reference	55 (38.5)	305 (53.3)	Reference	34 (46.6)	137 (46.9)	Reference
Male	540 (57.1)	1910 (50.5)	1.3 (1.1-1.5)	88 (61.5)	267 (46.7)	1.8 (1.3-2.7)	39 (53.4)	155 (53.1)	1.0 (0.6-1.7)
Maternal race									
White	572 (60.5)	2521 (66.7)	Reference	96 (67.1)	387 (67.7)	Reference	53 (72.6)	236 (80.8)	Reference
Black	327 (34.6)	1034 (27.3)	1.4 (1.2-1.6)	36 (25.2)	139 (24.3)	1.0 (0.7-1.6)	15 (20.5)	38 (13.0)	1.8 (0.9-3.4)
Other	46 (4.9)	225 (6.0)	0.9 (0.6-1.3)	11 (7.7)	46 (8.0)	1.0 (0.5-1.9)	5 (6.9)	18 (6.2)	1.2 (0.4-3.5)
Maternal Hispanic origin									
Hispanic	240 (25.6)	859 (23.0)	1.2 (1.0-1.4)	41 (28.7)	151 (26.5)	1.1 (0.7-1.7)	18 (25.3)	90 (30.9)	0.8 (0.4-1.4)
Non-Hispanic	698 (74.4)	2874 (77.0)	Reference	102 (71.3)	418 (73.5)	Reference	53 (74.7)	201 (69.1)	Reference
5-minute Apgar score									
<7	317 (35.0)	897 (24.3)	1.7 (1.4-2.0)	17 (12.1)	22 (3.9)	3.4 (1.7-6.5)	9 (12.9)	4 (1.4)	10.5 (2.8-48.1)
≥7	590 (65.0)	2797 (75.7)	Reference	123 (87.9)	537 (96.1)	Reference	61 (87.1)	287 (98.6)	Reference
Maternal age (years)									
≤19	151 (16.0)	453 (12.0)	1.6 (1.2-2.0)	21 (14.7)	71 (12.4)	1.2 (0.7-2.3)	11 (15.1)	29 (9.9)	1.3 (0.6-2.9)
20-24	275 (29.1)	861 (22.8)	1.5 (1.2-1.8)	32 (22.4)	149 (26.1)	0.9 (0.5-1.5)	20 (27.4)	78 (26.7)	0.9 (0.4-1.7)
25-29	209 (22.1)	983 (26.0)	Reference	34 (23.8)	143 (25.0)	Reference	24 (32.9)	80 (27.4)	Reference
≥30	310 (32.8)	1483 (39.2)	1.0 (0.8-1.2)	56 (39.1)	209 (36.5)	1.1 (0.7-1.8)	18 (24.6)	105 (36.0)	0.6 (0.3-1.1)
Maternal marital status									
Unmarried	544 (57.6)	1811 (47.9)	1.5 (1.3-1.7)	87 (60.8)	258 (45.1)	1.9 (1.3-2.7)	40 (54.8)	127 (43.5)	1.6 (0.9-2.6)
Married	401 (42.4)	1969 (52.1)	Reference	56 (39.2)	314 (54.9)	Reference	33 (45.2)	165 (56.5)	Reference
Live birth order									
First	471 (50.3)	1641 (44.1)	1.3 (1.1-1.6)	58 (40.9)	243 (42.8)	1.2 (0.7-1.9)	24 (33.8)	117 (40.3)	0.7 (0.4-1.3)
Second	217 (23.1)	1017 (27.3)	Reference	32 (22.5)	155 (27.3)	Reference	27 (38.0)	96 (33.1)	Reference
Third	119 (12.7)	564 (15.1)	1.0 (0.7-1.3)	21 (14.8)	88 (15.5)	1.2 (0.6-2.1)	11 (15.5)	46 (15.9)	0.9 (0.4-1.8)
Fourth or more	130 (13.9)	503 (13.5)	1.2 (1.0-1.5)	31 (21.8)	82 (14.4)	1.8 (1.0-3.2)°	9 (12.7)	31 (10.7)	1.0 (0.4-2.4)
Plurality									
Singleton	758 (80.2)	2757 (72.9)	1.5 (1.3-1.8)	121 (84.6)	458 (80.1)	1.4 (0.8-2.3)	71 (97.3)	290 (99.3)	0.2 (0.0-3.4)†
Non-singleton	187 (19.8)	1023 (27.1)	Reference	22 (15.4)	114 (19.9)	Reference	2 (2.7)	2 (0.7)	Reference
Maternal education									
Less than high school degree	254 (27.3)	841 (22.7)	1.5 (1.2-1.8)	41 (29.1)	150 (26.9)	1.3 (0.8-2.0)	16 (21.9)	66 (22.8)	1.2 (0.6-2.4)
High school degree	308 (33.1)	1045 (28.3)	1.5 (1.3-1.7)	44 (31.2)	149 (26.7)	1.4 (0.9-2.1)	29 (39.7)	85 (29.4)	1.7 (0.9-3.0)
More than high school degree	368 (39.6)	1814 (49.0)	Reference	56 (39.7)	259 (46.4)	Reference	28 (38.4)	138 (47.8)	Reference
Cyanotic heart disease†									
Reported	5 (0.6)	5 (0.1)	4.0 (0.9-17.5)	3 (2.11)	0 (0.0)	15.4 (2.3-∞)	1 (1.4)	0 (0.0)	4.0 (0.212-∞)

* OR indicates odds ratio; CI, confidence interval

† Exact logistic regression was conducted due to small numbers (n≤5)

Not reported	906 (99.5)	3649 (99.9)	Reference	139 (97.9)	562 (100.0)	Reference	71 (98.6)	290 (100.0)	Reference

[0]Indicates a significant associated p-value (<0.05)

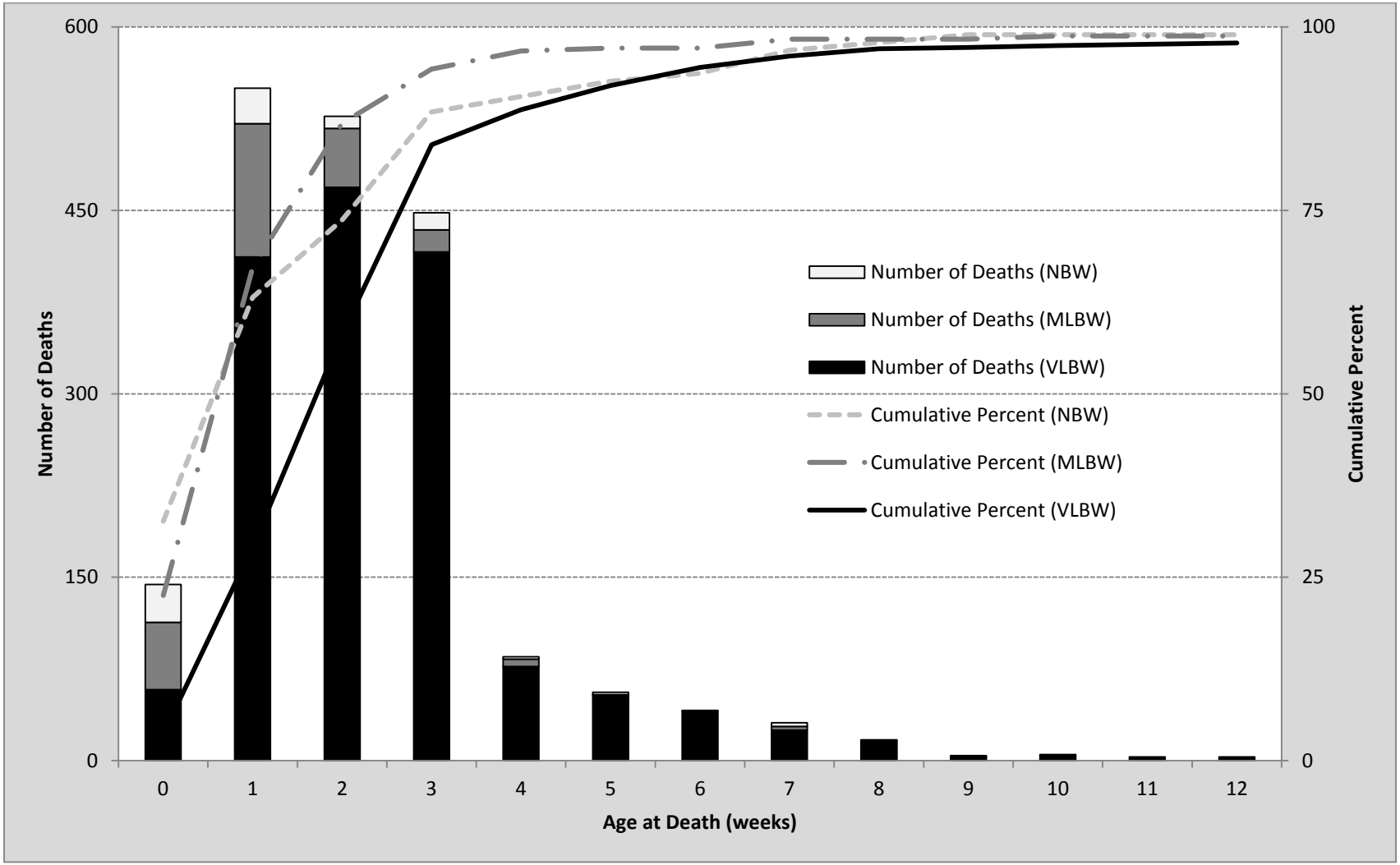
‡VLBW: Very Low Birth Weight (<1500g), MLBW: Moderately Low Birth Weight (1500-2499g), NBW: Normal Birth Weight (≥2500g)

Table 6. Summary of Multivariable Logistic Regression Analysis of Select Risk Factors for Necrotizing Enterocolitis-associated Infant Deaths as Compared with Infant Survivors, among VLBW Infants (<1500g), United States, 2007-2009.

Characteristic	**OR (95% CI)***
Sex	
Female	Reference
Male	1.3 (1.1-1.5)
5-Minute Apgar Score	
<7	1.6 (1.3-1.9)
≥7	Reference
Live Birth Order	
First	1.3 (1.1-1.6)
Second	Reference
Third	1.0 (0.7-1.3)
Fourth or more	1.2 (0.9-1.5)
Maternal age	
≤ 19	1.3 (1.0-1.7)
20-24	1.4 (1.2-1.8)
25-29	Reference
≥ 30	1.1 (0.9-1.3)
Maternal Race	
White	
Maternal education	
Less than high school	1.8 (1.4-2.4)
High school	1.5 (1.2-1.9)
Beyond high school	Reference
Black	
Maternal education	
Less than high school	0.8 (0.5-1.1)
High school	1.1 (0.8-1.5)
Beyond high school	Reference

*OR indicates odds ratio; CI indicates confidence interval

Figure 1. Number of Necrotizing Enterocolitis-Associated Infant Deaths and Cumulative Percent at Age of Death by Birth Weight, United States, 2007-2009.



VLBW: very low birth weight (<1500g), MLBW: moderately low birth weight (1500-2499g), NBW: normal birth weight (≥2500g)