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Rebecca Ludvigsen Date

Age at Death Due to Sudden Infant Death Syndrome

for Term and Pre-Term Infants

By

Rebecca Ludvigsen
Master of Public Health

Epidemiology

_____

Penelope P. Howards, Ph.D.
Committee Chair

_____

Carrie Shapiro-Mendoza, MPH, Ph.D.
Committee Member

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By

Rebecca Ludvigsen

Bachelor of Science
Auburn University
2009

Thesis Committee Chair: Penelope P. Howards, Ph.D.

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ABSTRACT

Age at Death Due to Sudden Infant Death Syndrome for Term and Pre-Term Infants

By Rebecca Ludvigsen

Introduction: Premature infants are at increased risk for Sudden Infant Death Syndrome (SIDS), the third leading cause of US infant mortality. The relationship between gestational age at birth and age at death among SIDS cases may have important implications for understanding physiological changes occurring during the critical developmental period after birth. We compared age at death distributions between SIDS infants born preterm and term, and also stratified by race and Hispanic origin and sex.

Methods: Data were obtained from the US Birth Cohort Linked Birth/Infant Death Data Sets for 2003-2005. Analysis was restricted to singleton infants born to US resident mothers between 28 and 41 weeks gestation, who died of SIDS in the postneonatal period (n=5,017). SIDS cases were identified from the death certificate underlying International Classification of Diseases-10th revision (ICD-10) cause-of-death code, R95. Infants were categorized into four gestational age categories: very preterm (28-33 weeks), late preterm (34-36 weeks), early term (37-38 weeks), and term gestations (39-41 weeks). We compared age at death distributions and used Analysis of Variance (ANOVA) to evaluate differences in mean chronological age at death between gestational age categories.

Results: Chronological age at death distributions for each gestational age group peaked at approximately 9 weeks. Mean chronological age at death of SIDS was 15.2 weeks among very preterm infants, 14.6 weeks among late preterm infants, 13.9 weeks among early term infants and 14.3 weeks among term infants. Mean chronological ages at death by gestational age group stratified by race and Hispanic origin or infant sex were similar.

Discussion: We report no clinically meaningful difference between gestational age at birth and chronological age at death for SIDS infants. Race-specific and sex-specific findings are similar. Use of clinically meaningful gestational age cut points provides an insight into the relationship between gestational age at birth and chronological age at death for SIDS. Contrary to prior reports, the critical window of vulnerability does not appear to be modified by gestational age at birth. Caregivers should be aware of the increased SIDS risk among preterm infants, but should practice SIDS risk reduction for all infants regardless of gestational age at birth.

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CHAPTER I: LITERATURE REVIEW

Background

Sudden unexpected infant deaths (SUID) are defined as infant deaths that occur suddenly and unexpectedly, and whose manner and cause of death are not immediately obvious prior to investigation [1]. These infant deaths occur in previously healthy infants, and exclude deaths with an obvious cause, such as a motor vehicle accident.

Several causes of death are included under the umbrella of SUID. These include Sudden Infant Death Syndrome (SIDS); cause unknown/unspecified; Accidental Suffocation and Strangulation in Bed (ASSB); other accidental suffocation and strangulation; and neglect, abandonment and other maltreatment syndromes [2]. SIDS, the most frequently reported type of SUID, is defined as "the sudden death of an infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" [3].

Sudden Infant Death Syndrome (SIDS) is the leading cause of death among infants aged 1–12 months, and is the third leading cause overall of infant mortality in the United States [4]. SIDS accounted for approximately 2,400 or 8% of all infant deaths in 2007[5]. While the US infant mortality rate was 6.8 infant deaths per 1,000 live births, defined as the death of an infant before his or her first birthday, the SIDS-specific infant mortality rate was 0.6 per 1000 live births[5]. The majority of all SIDS deaths occur during 2-4 months of age [6].

Definitions

The first SIDS definition, referred to as the 1969 Seattle definition, was "the sudden death of an infant or young child which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death." Twenty years later, this definition was revised in 1989 by the National Institute of Child Health and Human Development (NICHD) to limit SIDS classification to infants under one year of age: "The sudden death of an infant under one year of age, which remains unexplained after a thorough case

investigation, including performance of a complete autopsy, examinations of the death scene, and review of the clinical history" [3]. Various SIDS definitions have been proposed since the initial definition in 1969. The 2004 San Diego definition, the most recent to date, has gained some attention by limiting the 1989 definition to deaths that occur during sleep : "SIDS is defined as the sudden unexpected death of an infant < 1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history" [7].

Changes in definition over time, as well as the lack of a uniform definition accepted nationwide and worldwide, contribute to our inability to accurately and/or consistently monitor trends in SIDS or SUID. Byard and Marshall examined 50 papers published in 2005 involving SIDS, and found that 58% of reports had either not specified a definition of SIDS or had used non-standard definitions. Of those papers that stated a definition, 30% used the NICHD definition, 10% used the San Diego definition, and 2% used the Seattle definition [8].

Difficulties in classification and changes in SIDS certification

SIDS is one of the most frequently reported causes of SUID, but differentiating SIDS from other causes of SUID remains difficult. Several studies indicate a change in classification and reporting of SIDS following the implementation of the 1992 National Back to Sleep campaign[2, 3, 9, 10]. Since 1999, US surveillance data suggest that medical examiners and coroners may be shifting away from SIDS as a cause-of death diagnosis, and opting for other classifications that indicate deaths due to other unexplained causes or Accidental Strangulation and Suffocation in Bed (ASSB), a category of injury-related infant deaths. ASSB includes suffocation by soft bedding, overlaying, or wedging and entrapment of an infant, as well as strangulation by asphyxiation.

A 2009 study by Shapiro-Mendoza et al. reported an average annual percent increase of 14% [95% Confidence Interval (CI): 11% to 16%] in ASSB and a 2% increase [95% CI: 1% to

3%] in cause unknown deaths from 1996 to 2004. During this time, SIDS rates declined 4% [95% CI: -5% to -3%], suggesting that the increase in ASSB and unknown cause rates can account for some of the decline in SIDS rates. Further, the total SUID rate during this time remained stagnant overall (average annual percent change -1% [95% CI: -2% to 0%]), indicating a change in classification and reporting [11]. Similarly, Malloy and MacDorman suggest that the lack of decline in postneonatal mortality rates from 1999 to 2001, coupled with the decrease in SIDS postneonatal rates by 55% between 1992 and 2001, indicate that a reclassification of SIDS cases is occurring [9].

Relying on SIDS as an accurate cause of death from the death certificate has several limitations. The cause-of-death code in the ICD (International Classification of Diseases)[12] is generated by the National Center for Health Statistics (NCHS). The certifier (medical examiner or coroner) is reliant upon the death scene investigation, autopsy, and review of clinical history. However, there is a large variation in the methods and wording used in the medicolegal investigation and certification of infant deaths [13]. This is due to the nature of SIDS, a nonspecific diagnosis of exclusion. Several terms from the death certificate are collapsed in to the SIDS ICD-10 code R95. These include “Cot death”, “Crib death”, “Sudden Unexpected Death in Infancy”, “Sudden Infant Death”, “Sudden Unexplained Death of an Infant”, and “Sudden Unexpected Infant Death (SUID)”[14]. Furthermore, there is currently no US standard for infant death scene investigation or autopsy, and US infant death investigation practices vary widely[15]. A 2004 census of medical examiners and coroners reported that 34% of all medical examiner and coroner offices that use SIDS as a cause of death did not have protocols in place for conducting death scene investigations and autopsies for SUID[16].

Demographic factors

Approximately 10% of all SIDS deaths occur during the neonatal period, defined as the first month of life. SIDS deaths peak around two and four months of age. Less than 10% of SIDS deaths occur after 8 months of age. Male infants are more likely to die than females, with a ratio

of 6:4 [17]. In the US, racial and ethnic disparities persist despite the overall decline in SIDS worldwide following the Back to Sleep campaign. In 2006, SIDS rates were approximately twice as high for American Indians and Alaskan Natives and African Americans- than those for non-Hispanic white mothers, 2.1 and 1.9 times respectively [18] .

Risk factors

Several environmental and genetic risk factors have been associated with the incidence of SIDS. Environmental risk factors include maternal smoking during pregnancy or second-hand smoke exposure after birth [19], soft bedding, prone or side sleep positioning, and prematurity. There has been a large focus on sleep practices and risk of SIDS following the initiation of the Back to Sleep campaign, an effort to encourage supine sleep positioning. The Back to Sleep campaign was based on the 1992 AAP Task Force recommendation to place infants on their sides or backs after review of several epidemiological studies in Australia and Europe that showed prone sleeping increased SIDS risks[20]. The Chicago Infant Mortality Study examined risk factors for SIDS in a matched case-control study. The study included all 260 Chicago infant residents whose death between November 1993 and April 1996 was determined to be caused by SIDS. One living control infant was matched to each case infant on maternal race/ethnicity, age at death, and birthweight. The study found that SIDS infants were more likely than living control infants (matched on maternal race/ethnicity, age at death/interview, and birth weight) to have the following factors in the sleep environment: soft sleep surface, (aOR 5.1; 95% CI: 2.9-9.2), pillow use (aOR 3.1; 95% CI: 1.6-5.8), covering of face or head (aOR 2.5; 95% CI: 1.2-5.2), prone sleep position (aOR 2.3; 95% CI: 1.5-2.3), bedsharing with anyone (aOR 2.0; 95% CI: 1.2-3.3), and room sharing (aOR 1.2; 95% CI 0.9-2.3). Protective factors against SIDS included ever breastfeeding (aOR 0.4; 95% CI: 0.2-0.7), current breastfeeding (aOR 0.3; 95% CI: 0.2-0.7), and pacifier use (aOR 0.3; 95% CI: 0.2-0.5). Additionally, the study found that the combined presence of prone sleeping and soft bedding had a greater effect than expected based on the

effects of each factor alone indicating a strong interaction between the two risk factors (aOR 21.0; 95% CI: 7.8-56.2) [21].

Back to Sleep Campaign

In 1992, the American Academy of Pediatrics (AAP) recommended that infants be laid down for sleep in a non-prone position to reduce the risk of SIDS [20]. The National Institute of Child Health and Human Development began conducting national surveys of infant care practices to evaluate the implementation of the AAP recommendation nationwide. In 1994, the "Back to Sleep" campaign was initiated in the United States by the National Institute of Child Health and Human Development, the AAP, the US Public Health Service, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs [22].

The National Infant Sleep Position (NISP) is an annual national telephone survey that collects national data concerning infant care practices related to SIDS and the efficacy of the Back to Sleep campaign. The surveys were first conducted in 1993. From 1993 to 2000, there was a statistically significant increase in supine positioning and decrease in prone positioning. In 1993, 16.9% of all mothers surveyed usually placed their infant supine, compared to 76.8% in 2006 [23]. Since 1993, there has been a considerable decrease in the overall SIDS rate; this decline may be due in part to the increase in prone positioning that resulted from the Back to Sleep campaign. In 1993, the SIDS rate for the US was 1.3 infant deaths per 1000 live births [24]; this rate dropped to 0.55 infant deaths per 1000 live births by 2006 [18]. Supine sleep positioning reached a plateau around 75% in 2006. However, racial disparities in sleep positioning persist. Stratifying by maternal race (Black, White Hispanic and Asian/Other), Blacks, had the lowest use of the supine position in the years following the Back to Sleep campaign[23].

Pathophysiology

To find the cause of SIDS, including potential infectious, genetic, neurological, endocrine, pulmonary, and cardiac causes, several hypotheses have been suggested. According to the triple risk hypothesis [25], SIDS occurs when three factors are present at the same time for a

given infant. These three factors include a critical development period, exogenous factors, and a vulnerable infant. The critical development period spans the first 6 months of an infant's life. During this period, significant physiological changes in homeostasis occur that increase an infant's vulnerability to SIDS, including heart rate, breathing, waking, sleeping, blood pressure, and temperature. A second factor for SIDS involves the vulnerable infant. A vulnerable infant has an underlying birth defect or abnormality. This defect can alter physiological processes, resulting in SIDS. The third factor, and the most preventable in the model, is exogenous factors. These include adverse environmental and external factors that a normal infant can overcome, but a vulnerable infant cannot. Exogenous factors include known risk factors for SIDS, such as soft and loose bedding, bedsharing, second hand smoke, overheating, and prone sleep position.

Several observational case-control studies have reported an association between prone positioning and SIDS[20, 21, 26]. Since this association was observed, physiological studies have focused on factors that might trigger infant death in this position. The hypotheses to explain the risk of prone sleep position include asphyxia due to airway compression or rebreathing of exhaled gases in the face-down position, restricted heat loss leading to hyperthermia when face is pressed into bedding, impaired cardiorespiratory regulation related to heat stress, and a compromised arousal in response to asphyxia that is generated in the prone position [27].

A study by Rognum et al. showed that SIDS infants exhibited significant periods of hypoxia prior to death as measured by hypoxanthine levels [28]. In the 1970s and 1980s, the sleep apnea theory was developed suggesting infants with atypical breathing patterns or sleep apneas were at a high risk for SIDS[29, 30]. More recently, molecular and genetic studies have been conducted in an attempt to explore the potential role of genetics with SIDS. Bajonowski suggests that disturbances of cardiac function could be one pathophysiological mechanism leading to a sudden death in a subgroup of SIDS victims [31].

Gestational Age: Definitions, Availability and Limitations

Gestational age refers to the time elapsed between the first day of the last menstrual period (LMP) and the date of birth. The first day of the LMP typically occurs two weeks prior to ovulation. Methods to estimate gestational age include LMP-based estimates, clinical estimates (including ultrasound based-estimates) and obstetric estimate. These calculations are used to classify pre-term and full-term births.

LMP is the primary gestational age source on the birth certificate. This method is widely used and is based on maternal self-report. Variation in menstrual cycle duration, non-menstrual vaginal bleeding, imperfect maternal recall, and clerical errors affect the accuracy of the LMP [32]. The LMP assumes a 28-day menstrual cycle with ovulation and conception occurring at day 14. Munster et al. demonstrated that 18.6% of women have at least one short cycle less than 21 days and 29.5% of women have at least one long cycle more than 35 days over the course of a year [33, 34]. A study of planned pregnancies found that 9% of women reported bleeding during the first 8 weeks of pregnancy; vaginal bleeding during early pregnancy can contribute to gestational age underestimation [34]. Maternal recall can also be biased due to digit preference [35] as well as social desirability in regards to premarital conception[36]. LMP estimates have both systematic and random error, which in turn affects classification of pre-term birth.

NCHS uses the clinical estimate (CE) for national reports when LMP month and year are missing, or when the CE is compatible with birth weight but the LMP is not. The method used to obtain the CE is not reported on the birth certificate, and can include prenatal and neonatal clinical assessments. Prenatal assessments can include fundal height and ultrasound measures, whereas postnatal assessments may involve birth weight and neurophysical assessments [32]. Therefore, the CE may be inaccurate among infants whose maturation or growth occurs quite differently than the reference used [37].

Most recently, the obstetric estimate (OE) was introduced to the 2003 birth certificate. The OE excludes the use of neonatal examinations and uses instead findings from ultrasound and

other perinatal factors such as fundal height, onset of pregnancy symptoms, heartbeat detection, quickening, and biochemical tests for fetal maturation.

Age calculations and classification of preterm birth

The AAP recommends the use of four standardized terms when defining ages and comparing fetuses and newborns during the perinatal period: gestational age, chronological age, postmenstrual age and corrected age [38]. Gestational age is reported in completed weeks and measures the time elapsed between the first day of the last menstrual period and the day of delivery. Chronological age is defined as the time elapsed from birth, and can be reported in days, weeks and months. Postmenstrual age refers to the sum of gestational age and the chronological age, reported in weeks. Corrected age, in weeks or months, is the chronological age reduced by the number of weeks born before 40 weeks of gestation.

There is currently a need for the understanding and proper application of age terminology in infant studies. The literature uses a vast array of age determinants that compromise comparisons across infant studies and may introduce misclassification bias into study design. Varying age classification methods may place the same infant in higher or lower risk categories, which makes it difficult to draw meaningful public health conclusions depending on the calculated age. This is of particular interest when comparing SIDS risks between preterm and full term infants. Comparing pre-term vs. term status alone may not be sufficient in determining differential risk among these two distinct populations.

Though preterm infants are defined by the AAP, the American College of Obstetricians and Gynecologists (ACOG) and World Health Organization (WHO) as births that occur on or before the end of the last day of the 37th week, preterm infants are a heterogeneous population. In 2005, the National Institute of Child Health and Human Development (NICHD) proposed the use of the term “late-preterm” to describe those infants born between 36 and 38 weeks of gestation[39]. Late-preterm infants are often the size and weight of term infants (gestations 37-41 weeks), but are physiologically and metabolically immature. In order to sub classify the heterogeneity of

preterm infants, “very preterm” is often used to described infants born between 28 and 33 weeks, and “late preterm” is used to describe infants born between 34 and 36 weeks. Such distinctions among preterm infants are needed to adequately characterize differential risks experienced in these populations. Infants born very preterm have higher risks of morbidity and mortality compared to infants born late preterm and at term.

Association of pre-term birth with SIDS

Evidence that SIDS incidence is increased among preterm infants in comparison to full term infants is well established. There is an inverse relationship between gestational age and mortality due to SIDS. Infants born prematurely or who have low birthweight have up to four times the risk of SIDS compared to term infants, and risk increases with decreasing gestational age or birthweight [17]. However, little is known about how the age at death for infants who die of SIDS are affected by gestational age at birth.

It is well established that preterm infants are at increased risk for low birth weight. In the past, low birthweight was used as an indicator for preterm birth due to difficulties estimating accurate gestational age at birth. Infants with low birth weight have an increased risk of mortality and morbidity throughout infancy and childhood compared to those infants born at normal weight. A study by Grether and Schulman found that infants with very low birth weight died from SIDS at a later age than infants born at normal birth weight, though the study did not assess any potential interaction between gestational age and birth weight. Multivariate logistic regression included birth weight, but not gestational age in the model [40] .

A New Zealand study by Thompson et al. sought to determine if risk factors for SIDS and their magnitude differed among preterm (less than 38 weeks gestation) and term infants (38 weeks gestation or greater) with a case control study and a case-cohort study. Multivariate analysis in a case control study reported that SIDS infants were 2.1 times more likely to be preterm (95% CI: 1.2-3.7), and multivariate analysis in a case-cohort study reported that SIDS infants were 4 times more likely to be preterm (95% CI: 1.1-15.3) [26]. Multivariate analysis found

that four modifiable risk factors analyzed were significant risk factors for SIDS among both term and preterm infants: smoking, sleep position, breast feeding, and bedsharing. The study also found a combined risk of preterm birth and prone positioning (aOR 17.4, 95% CI: 8.2-37.2).

Age at death and SIDS

Several studies have examined the relationship between gestational age and age at death in SIDS infants. Using linked birth/death records for the cohort of infants born between 1979 and 1981 in five states, Adams et al. found median age at death decreased as length of gestation increased in white postneonates, but found no association between length of gestation and age at death in Black postneonates.[41]

Malloy and Hoffman analyzed 1987 NCHS birth cohort linked birth and death certificates to evaluate whether preterm infants (less than 37 weeks gestation) are at an increased risk for SIDS and to determine if the postmenstrual age of death (referred to as postconceptional age in the study) varies by gestational age at birth. Postconceptional age at death was calculated by adding the chronological age at death to the gestational age. Multivariate logistic regression predicting SIDS risk found that adjusted ORs increased as gestational age decreased when the referent group was 37 or more weeks gestation. The analysis found relatively consistent postconceptional age of death between gestational age categories, but a 4 to 6 week difference in chronological age at death between preterm and term infants for the peak vulnerability for SIDS: 24-28 weeks (mean=17.9 weeks), 29-32 weeks (mean=16.1 weeks), 33-36 weeks (mean=12.8 weeks), and $\geq$37 weeks (mean=12.8 weeks) [42].

A study by Halloran and Alexander used data for infants born between 1996 and 1998 from the National Center for Health Statistics Birth Cohort Linked Birth/Infant Death Data Sets[43]. Mean age of death was compared to length of gestation (as determined by gestational age). The study determined that mean age of SIDS death decreases as gestational age at birth increases; mean age at death was 20.3 weeks for infants born 22-27 gestational weeks, 15.7 weeks for infants born 28-32 gestational weeks, 14.1 weeks for infants born 32-35 gestational weeks, 13.8

weeks for infants born 36-37 weeks, 13.9 weeks for infants born 38-39 gestational weeks, 14.0 weeks for infants born 40-41 gestational weeks, and 13.4 weeks for infants born more than 42 gestational weeks.

A study by Lipsky, et al. sought to characterize the typical age at SIDS deaths in former premature infants who died from SIDS with survival analysis using a database of all SIDS cases occurring between 1987 and 1991[44]. Chronological and postmenstrual age at death between preterm and term infants was compared. A major limitation of this study is the exclusion of infants born at 32 to 36 weeks. The authors eliminated this group of infants to eliminate the possibility of inaccurate gestational age assessment in the borderline premature infant group, and therefore this group is not represented in the analysis or conclusions of the study's findings. Survival analysis demonstrated a different pattern between the preterm (less than 32 weeks) and term (37 weeks or greater) infants. The death rate at each postnatal age point analyzed was significantly lower in the preterm infants compared to the term infants. Term infants followed a typical SIDS distribution of age at death, with peak incidence occurring at 8-12 weeks. In contrast, the preterm infants showed a much wider distribution of age at death. By 32 weeks chronological age, 95% of all SIDS deaths had occurred in term births, but it was not until 44 weeks chronological age that 95% of all SIDS deaths had occurred in the premature group.

A need to understand the relationship between gestational age at birth and age at death

Although the overall rate of SIDS in the United States has declined by more than 50% since 1990 possibly due to the Back-to-Sleep Campaign, there has been little decrease in the rate of SIDS since 1996 [2]. Preventing SIDS, including providing risk reduction messages prevention messages, remains an important public health priority.

Review of preterm infant and SIDS studies raises a need to evaluate age at death distributions of preterm and term SIDS infants with clinically meaningful gestational age cut points. Though previous studies have assessed age at death distributions between preterm and term infants, the studies predate the large increase in preterm births in the US during the past two

decades. The profile of preterm births has also changed during this time, which may affect the risk of SIDS. The preterm birth rate in the US increased from 9.1 to 12.3% from 1981 to 2003 [39], and the proportion of all preterm births that were late preterm births (34-36 weeks gestation) has also increased[45]. Determining if age at death distributions differ between preterm and term SIDS infants has important implications for physiological studies aimed to better understand the underlying etiology of SIDS. Further, it is imperative to deliver an accurate and consistent SIDS prevention message for parents and caregivers of the critical window of vulnerability for their infants because the duration of this vulnerability period may be increased for pre-term infants due to delayed physiological maturation. Accurate and meaningful age at death distributions are necessary to communicate any differential SIDS risk in pre-term and full term infants. Furthermore, comparing age at death distributions between non-Hispanic whites and non-Hispanic blacks, as well as between male and female infants, is important to determine if racial or sex differences exist in the critical window of vulnerability to SIDS. To explore the relation between gestational age and age at death among SIDS infants, we will use data obtained from the US Birth Cohort Linked Birth/Infant Death Data Sets for 2003-2005. This is a large, nationally representative dataset that includes all live US births from 2003-2005 and all deaths occurring to infants born within these three years. This cohort of infants includes live births that reflect recent trends in increased preterm birth, as well as SIDS deaths that occurred more than 10 years after the initiation of the Back to Sleep campaign.

CHAPTER II

ABSTRACT

Age at Death Due to Sudden Infant Death Syndrome for Term and Pre-Term Infants

Rebecca Ludvigsen, MPH[1, 2], Carrie Shapiro-Mendoza, PhD, MPH[3], Penelope P. Howards, PhD[2]

1. Oak Ridge Institute for Science and Education Fellow, Centers for Disease Control and Prevention, Division of Reproductive Health, Atlanta, Georgia;
2. Rollins School of Public Health, Emory University, Atlanta, Georgia
3. Centers for Disease Control and Prevention, Division of Reproductive Health, Atlanta, Georgia;

Introduction: Premature infants are at increased risk for Sudden Infant Death Syndrome (SIDS), the third leading cause of US infant mortality. The relationship between gestational age at birth and age at death among SIDS cases may have important implications for understanding physiological changes occurring during the critical developmental period after birth. We compared age at death distributions between SIDS infants born preterm and term, and also stratified by race and Hispanic origin and sex.

Methods: Data were obtained from the US Birth Cohort Linked Birth/Infant Death Data Sets for 2003-2005. Analysis was restricted to singleton infants born to US resident mothers between 28 and 41 weeks gestation, who died of SIDS in the postneonatal period (n=5,017). SIDS cases were identified from the death certificate underlying International Classification of Diseases-10th revision (ICD-10) cause-of-death code, R95. Infants were categorized into four gestational age categories: very preterm (28-33 weeks), late preterm (34-36 weeks), early term (37-38 weeks), and term gestations (39-41 weeks). We compared age at death distributions and used Analysis of Variance (ANOVA) to evaluate differences in mean chronological age at death between gestational age categories.

Results: Chronological age at death distributions for each gestational age group peaked at approximately 9 weeks. Mean chronological age at death of SIDS was 15.2 weeks among very preterm infants, 14.6 weeks among late preterm infants, 13.9 weeks among early term infants and 14.3 weeks among term infants. Mean chronological ages at death by gestational age group stratified by race and Hispanic origin or infant sex were similar.

Discussion: We report no clinically meaningful difference between gestational age at birth and chronological age at death for SIDS infants. Race-specific and sex-specific findings are similar. Use of clinically meaningful gestational age cut points provides an insight into the relationship between gestational age at birth and chronological age at death for SIDS. Contrary to prior reports, the critical window of vulnerability does not appear to be modified by gestational age at birth. Caregivers should be aware of the increased SIDS risk among preterm infants, but should practice SIDS risk reduction for all infants regardless of gestational age at birth.

INTRODUCTION

Sudden Infant Death Syndrome (SIDS), defined as infant deaths that occur suddenly and unexpectedly, and whose manner and cause of death are not immediately obvious prior to investigation[1], is the third leading cause of infant mortality in the United States. The overall SIDS mortality rate in 2007 was 57 deaths per 100,000 live births, accounting for approximately 2,400 or 8% of all infant deaths in 2007 [4]. SIDS mortality rates are 1.5 times greater for male infants than female infants.

In the US, racial and ethnic disparities in overall infant mortality also remain in SIDS specific mortality rates. In 2007, SIDS mortality rates were 1.9 times greater for infants of non-Hispanic black mothers (107.9 per 1000,000 live births) than for infants of non-Hispanic white mothers (58 per 100,000 live births). Disparities in preterm birth rates are similar: preterm birth among non-Hispanic blacks was 1.6 times greater than the preterm birth rate among non-Hispanic whites in 2007. [46]

Preterm birth is a well-established risk factor for SIDS[17, 26,42], but less is known about how age at death is affected by gestational age at birth. Most SIDS deaths occur between 2-4 months of age, a period of critical development [6].

Several investigators have explored the role of gestational age at birth and age at death and found that age at death for preterm SIDS infants was later than for term infants[41-44]. However, these studies were conducted more than a decade ago and it is unknown if the observed relationship between gestational age and age at death continues in the years following the Back to Sleep campaign. Understanding the role of gestational age at birth and age at death may have important implications for understanding the role of physiological changes related to homeostatic control that occur during the critical developmental period from 1 to 6 months; this period is considered one of the three components of the triple risk model. According to the model, SIDS results from the intersection of three factors: an underlying vulnerability in the infant, a critical developmental period in homeostatic controls, and exogenous stressor(s)[25].

Understanding the age at death among both preterm and term SIDS cases is an important public health concern. It is essential to identify the critical window of risk to determine if advice needs to be tailored based on preterm or term status, or by the race or sex of the infant. The purpose of this study is three-fold. First, we will compare age at death distributions between preterm and term SIDS infants. Second, because increased incidence of pre-term birth as well as SIDS incidence among African Americans compared to whites is well documented, we will compare age at death distributions among non-Hispanic whites and non-Hispanic blacks to determine if racial differences in age at death exist in SIDS infants. Third, because increased incidence of SIDS among males compared to females is well documented, we will compare age at death distributions among males and females.

METHODS

Study Population

The study population was comprised of US singleton infants who died of SIDS and were born to US resident mothers from 2003 through 2005. SIDS cases were defined by the 10th revision of the International Classification of Diseases (ICD-10) underlying cause-of-death code R95[12]. Data were obtained from the US Birth Cohort Linked Birth/Infant Death Data Sets for 2003-2005; at the time of analysis, 2005 was the most recent year of cohort data available[47-49]. Infants born before 28 weeks of gestation were excluded due to issues about differential risk of viability and other causes of mortality. Infants born posterm (after 41 weeks) were excluded. Consistent with other SIDS studies, we excluded all infants who died during the postneonatal period (less than 28 days of life) [41, 44].

Estimating Gestational Age

We used the gestational age estimated by NCHS, primarily based on LMP (last menstrual period) [50-52]. When LMP is missing or inconsistent with the infant's birthweight, NCHS uses the obstetric estimate or the clinical estimate. Because the criteria applied by NCHS for determining if LMP is inconsistent with the infant birthweight is conservative, we applied birthweight and

gestational age inclusion criteria developed by Alexander, et al. to exclude all observations with implausible birthweight-gestational age calculations (n=24) [53]. Additionally, imputed values for gestational age by NCHS were excluded (n=110); gestational age is imputed when LMP month and year are available but day is missing. Infants were categorized into four gestational age categories: very preterm (28-33 weeks), late preterm (34-36 weeks), early term (37-38 weeks), and term gestations (39-41 weeks). More precise categorization of preterm (<37 weeks) and term (≥37 weeks) gestations allows for a more detailed understanding of differences in the distributions of age at death across gestational age categories in SIDS infants. The final study population included 5,017 infants.

Chronological age at death

We defined chronological age at death as the number of completed weeks since birth at the time of the death. We converted chronological age at death reported by NCHS in days into completed weeks by dividing age at death reported in days by 7 and rounding down to the nearest whole number.

Analysis

We used descriptive analysis to characterize SIDS infants across the four categories of gestational age by infant and maternal factors. Distributions of age at death were compared between gestational age categories. To evaluate differences in age at death distributions across gestational age-at-birth categories, we used Analysis of Variance (ANOVA). Because age at death was not normally distributed and skewed to the right, probability distributions were estimated using kernel density estimation. We compared age at death distributions between infants born preterm and term for all SIDS cases and stratified by race and Hispanic origin and infant sex. Analyses were carried out with SAS version 9.2 (SAS Institute, Cary, NC). The study was approved by the International Review Board at Emory University.

RESULTS

Maternal and infant characteristics of postneonatal SIDS are presented in Table 1. Of the postneonatal SIDS deaths 6.7% were born very preterm, 15.0% were born late preterm, 32.3% were born early term, and 46.1% were born term. Gestational age-specific mortality rates showed SIDS incidence was lower among the more common gestational ages at birth. The mortality rate for infants born very preterm was the highest, (142.5 deaths per 100,000 live births), followed by infants born late preterm (82.6 deaths per 100,000 live births), early term (50.7 deaths per 100,000 live births), and term (32.0 deaths per 100,000 live births).

The majority of postneonatal SIDS deaths was white (56.1%), entered prenatal care in the second trimester (68.2%), and was born between 2,500 to 3,499 grams (60.4%). However, the racial distribution of SIDS deaths does not reflect the racial distribution of live births during this time and highlights the disparity among African-Americans compared to whites. From 2003-2005, the SIDS infant mortality rate among non-Hispanic black infants was 99.1 deaths per 100,000 compared to 51.2 deaths per 100,000 among non-Hispanic whites.

Chronological age at death distributions for each gestational age group peaked at around 9 weeks (Figure 1). This peak is observed for all infants, for non-Hispanic white and non-Hispanic black infants (Figure 2), and for male and female infants (Figure 3). Mean chronological age at death of SIDS was 15.2 weeks among very preterm infants, 14.6 weeks among late preterm infants, 13.9 weeks among early term infants and 14.3 weeks among term (Table 2). Mean chronological ages at death by gestational age group stratified by race and Hispanic origin or sex, were not meaningfully different from observed means for all infants. Approximately 85% of SIDS occurred before 6 months of age (n=4,368) overall and for all gestational age groups.

DISCUSSION

In contrast to previous studies (all conducted with data collected before 1998) that have demonstrated shifts towards later chronological age at death in younger gestational age groups, we observed no clinically meaningful difference between gestational age at birth and

chronological age at death for SIDS. We also find no differences for race-specific and sex-specific analyses.

Malloy and Hoffman reported chronological age of death increased among SIDS infants as gestational age decreased and that postmenstrual age of peak vulnerability differs by 4 to 6 weeks in term and preterm US infants born in 1987 [42]. However, 10% of all SIDS deaths among infants born in 1987 were excluded due to gestational age calculations inconsistent with birthweight. This exclusion may have substantially altered their conclusions. Our analysis only excluded 0.005% of SIDS infants due to inconsistent gestational age and birthweight. Halloran and Alexander reported a shift towards later chronological age at death for younger gestational age groups by comparing age at death distributions across three categories of gestational age in infants born between 1996 and 1998. However, their analysis could not clearly distinguish differences in age at death distributions between preterm and term infants, as infants born between 33-44 weeks were combined into one comparison group [43]. When using the gestational age at birth cut points analyzed by Halloran and Alexander (22-27, 28-32 and 33-44 weeks), we also demonstrate in our study population similar shifts in age at death (data not shown). It appears that this demonstrated shift is a result of combining preterm, term, and post-term infants into one comparison group, but the implications for clinical practice of combining these groups is unclear.

Lipsky, et al.[44] compared chronological and postconceptional age at death between preterm and term SIDS infant deaths between 1987 and 1991. Term infants followed a typical SIDS distribution of age at death, with peak incidence occurring at 8-12 weeks. In contrast, the preterm infants showed a much wider distribution of age at death. However, the authors excluded infants born 32 to 36 weeks to eliminate the possibility of inaccurate gestational age assessment in the borderline premature infant group, and therefore this group, a portion of which would now

be considered late preterm, is not represented in the analysis or conclusions of the study's findings.

Adams et al. found an inverse relation between gestational age and median age at SIDS death among white postneonates using US linked birth/death records for the cohort of infants born between 1979 and 1981, but found no association between length of gestation and median age at death in black infants. Among white infants, median postnatal age at death was 20 weeks for infants born at 28-29 weeks gestation, 16 weeks for infants born 30-31 weeks, 13 weeks for infants born 32-35 weeks, and 11 weeks for infants with gestations 36 weeks or longer. Among black infants, median postnatal age at death was 18 weeks for infants born 28-29 weeks gestation, 12 weeks for infants born 30-31 weeks gestation; 12 weeks for infants born 32-35 weeks; and 10-12 weeks for infants with gestations of 36 weeks or longer [41]. Our analysis found no relationship among non-Hispanic white infants.

However, SIDS infants analyzed in the Adams study were born more than a decade before the Back to Sleep campaign (1979 to 1981); though somewhat later, Malloy and Hoffman (1987) and Lipsky (1987-1991) analyzed SIDS infants born before the campaign. In 1993, before the Back to Sleep campaign, only 16% of infants were placed on their backs[23]; sleep positioning data is not available before 1992, though it can be assumed prevalence of supine positioning was similar or even lower in the years prior to 1992. This number had increased to more than 70% during the birth cohorts analyzed in our study (2003- 2005)[23].

The prone sleep position, a well-known risk factor for SIDS, is associated with impaired arousal from sleep, reduced vasomotor tone, and diminished reflexes[54]. It has been suggested that developmental deficits in neural pathways that support reflexive motor learning may increase the risk associated with prone sleeping[27]. Premature infants have been documented to have fewer and shorter arousal episodes and immature cardiorespiratory functioning[55], which might put them at higher risk for failed responses to asphyxia or hypoxia.

Because the brainstem regulates and maintains autonomic processes such as respiration, sleep and arousal, the relationship between the brain stem and SIDS been a major focus of SIDS etiology research. In a case-control study with SIDS infants and acute control infants who died of causes of death explained at autopsy, Kinney et al. found a neurochemical imbalance of serotonin in the brainstem in SIDS infants[56]. This deficiency can result in a failure of autonomic responses to life-threatening external threats, such as asphyxia from prone sleep position, suggesting that SIDS or a subset of SIDS may be due to a developmental abnormality of the brainstem.

Because the profile of sleep positioning was drastically different during birth cohort years analyzed in our study compared those cohorts analyzed in previous studies before the Back to Sleep campaign, it is possible that effects of gestational age and development on age at death among SIDS infants are attenuated in populations with high prevalences of supine positioning. The infant population who died of SIDS following the Back to Sleep campaign may be different from those prior to the campaign, a period in which the overwhelming majority of infants were placed to sleep in the prone position.

However, this change in the infant population may not explain conflicting conclusions between our study and the study by Halloran and Alexander that analyzed infant deaths occurring soon after the Back to Sleep Campaign from 1996-1998. This study population is the most similar to ours of the age at death studies we assessed. Both study populations included infant deaths that occurred after the Back to Sleep campaign. It is most likely that our study reaches different conclusions due to the categorization of gestational age categories. Halloran and Alexander report a 4-6 week difference in age at death in infants born 22-27 weeks and infants born after 28 weeks. We excluded infants born 22 to 27 weeks of age due to concerns of viability at these early gestations. Without this group, Halloran and Alexander's findings would only differ by one to two weeks between those age groups born after 27 weeks.

In addition to changes in infant sleep positioning since the mid-1990s, US data since 1999 suggest medical examiners and coroners may be shifting away from SIDS as a cause of

death diagnosis, and opting for other classifications that indicate deaths due to other unexplained causes or Accidental Strangulation and Suffocation in Bed (ASSB)[2]. These changes in infant death certification may have altered the profile of infant deaths certified as SIDS in our study population compared to those deaths certified as SIDS in earlier decades analyzed in previous studies.

Strengths

Our analysis is nationally representative and includes the three most recent years of US Birth Cohort Linked Birth/Infant Death Data Sets available for public use [47-49]. Our study provides the most recent assessment of the relationship between gestational age and age at death among SIDS infants, and is one of only two age at death studies conducted since the implementation of the Back to Sleep campaign. We meaningfully categorize preterm and term gestations with clinically relevant cut points, allowing for a more precise assessment of the relationship between gestational age and age at death among SIDS infants.

Limitations

Accurate gestational age estimates are critical to our analysis. Our study includes limitations regarding accurate estimates. Variation in menstrual cycle duration, non-menstrual vaginal bleeding, imperfect maternal recall, and clerical errors affect the accuracy of the LMP, the primary gestational age source on the birth certificate. This method is widely used and is based on maternal self-report [32]. The LMP assumes a 28-day menstrual cycle with ovulation and conception occurring at day 14. Munster et al. demonstrated that 18.6% of women have at least one short cycle less than 21 days and 29.5% of women have at least one long cycle more than 35 days over the course of a year [33, 34]. A study of planned pregnancies found that 9% of women reported bleeding during the first 8 weeks of pregnancy; vaginal bleeding during early pregnancy can contribute to gestational age underestimation [34]. Maternal recall can also be biased due to digit preference [35] as well as social desirability in regards to premarital conception[36]. Because

LMP estimates can have both systematic and random error, inaccurate estimates would affect our classification of SIDS infants into gestational age at birth categories.

NCHS uses the clinical estimate (CE) for national reports when LMP month and year are missing, or when the CE is compatible with birth weight but the LMP is not. The method used to obtain the CE is not reported on the birth certificate, and can include prenatal and neonatal clinical assessments. Prenatal assessments can include fundal height and ultrasound measures, whereas postnatal assessments may involve birth weight and neurophysical assessments [32]. Therefore, the CE may be inaccurate among infants whose maturation or growth occurs quite differently than the reference used [37]. Although misclassification of gestational age is likely, it would have to be differential by age at SIDS death to bias our study results.

Summary

Our use of clinically meaningful cut points for gestational age provides an insight into the relationship between gestational age at birth and chronological age at death for SIDS. Despite previous reports of older chronological age age death among preterm SIDS infants compared to SIDS infants born at term, we observe no important differences in age at death among infants born 28-41 weeks. The critical risk window also did not differ by race or infant sex. Caregivers and health care providers should be aware of the increased risk of SIDS in preterm infants. However, there does not appear to be a need to expand the critical risk window for preterm births. SIDS risk reduction strategies remain important for all infants, regardless of gestational age at birth.

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TABLES

Table 1. Maternal and Infant Characteristics of Postneonatal SIDS Deaths, US, 2003-2005

Characteristics:	ALL n=5,017	Gestational Age (%) 28-33 weeks (n=331)	34-36 weeks (n=752)	37-38 weeks (n=1620)	39-41 weeks (n=2,314)
All		6.7%	15.0%	32.3%	46.1%
Maternal age (years)					
<20	19.9	27.8	21.3	17.8	19.8
20-24	42.1	38.1	41.8	41.7	43.2
25-29	21.2	13.0	20.9	23.3	21.0
30-34	10.8	11.8	10.2	10.9	10.7
≥35	6.0	9.4	5.9	6.4	5.2
Parity*					
1	28.8	30.6	29.5	24.7	31.2
2	33.9	32.1	29.5	35.3	34.6
≥3	37.3	37.3	41.0	40.0	34.2
Maternal race/ethnicity					
Non-Hispanic white	56.1	47.3	53.6	57.0	57.5
Non-Hispanic black	26.9	37.2	29.0	26.8	24.9
Asian/Pacific Islander	2.2	2.4	1.5	2.1	2.5
American Indian/ Alaskan Native	2.6	1.2	2.3	2.4	3.0
Hispanic	12.2	11.9	13.7	11.6	12.3
Prenatal Care Entry*					
First trimester	69.6	70.3	66.8	69.9	70.3
Second trimester	23.9	25.82	26.7	23.2	23.2
Third trimester	5.8	3.3	5.6	6.3	6.0
None	0.7	0.7	1.0	0.7	0.6
Infant Sex					
Male	60.7	61.3	60.4	62.6	59.4
Female	39.3	38.7	39.6	37.4	40.6
Infant birthweight (grams)†					
500-1,499	2.3	28.7	1.6	0.3	0.2
1,500-2,499	15.0	54.7	34.4	12.7	4.6
2,500-3,499	60.4	15.4	57.2	68.0	62.5
3,500-4,499	21.7	1.2	6.8	18.3	31.9
≥4,500	0.6	0.0	0.0	0.7	0.9

*Missing data: Parity (n=19), Prenatal Care Entry (n=189); † Excluded observations: n=24;
Note: Distributions may not sum to 100% due to rounding.

Table 2. Mean Chronological Age at Death among SIDS infants by Gestational Age and Race and Infant Sex, United States, 2003-2005.

Gestational age at birth (weeks)	Mean (SD) Chronological age (weeks)				
	Overall	Non-Hispanic white	Non-Hispanic black	Male	Female
28-33	15.2 (8.6)	14.9 (8.5)	15.4 (9.0)	15.4 (8.5)	14.9 (8.8)
34-36	14.6 (8.7)	14.8 (8.0)	13.9 (8.0)	14.2 (8.4)	15.3 (9.0)
37-38	13.9 (8.4)	13.7 (8.2)	13.8 (8.5)	14.0 (8.3)	13.8 (8.5)
39-41	14.3 (8.3)	14.5 (8.8)	14.0 (8.8)	14.1 (8.4)	14.6 (9.1)

FIGURES

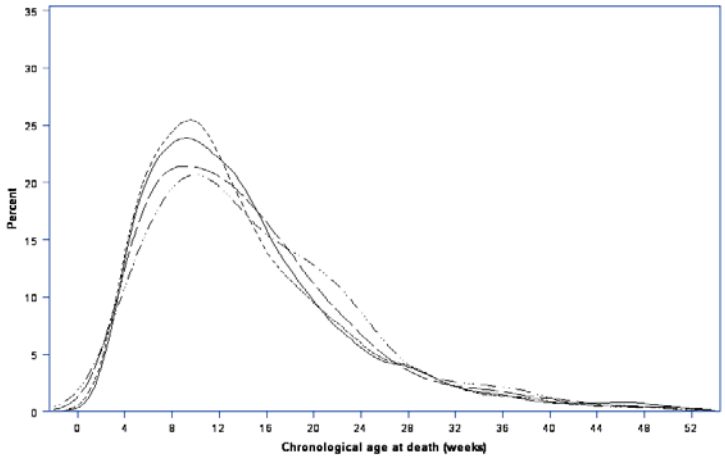

Figure 1. Chronological age at death distributions among gestational age at birth groups in SIDS infants. Solid line: 38-41 weeks; Dotted line: 37-38 weeks; Long dashed line: 33-36 weeks; Dashed and Dotted line: 28-33 weeks.

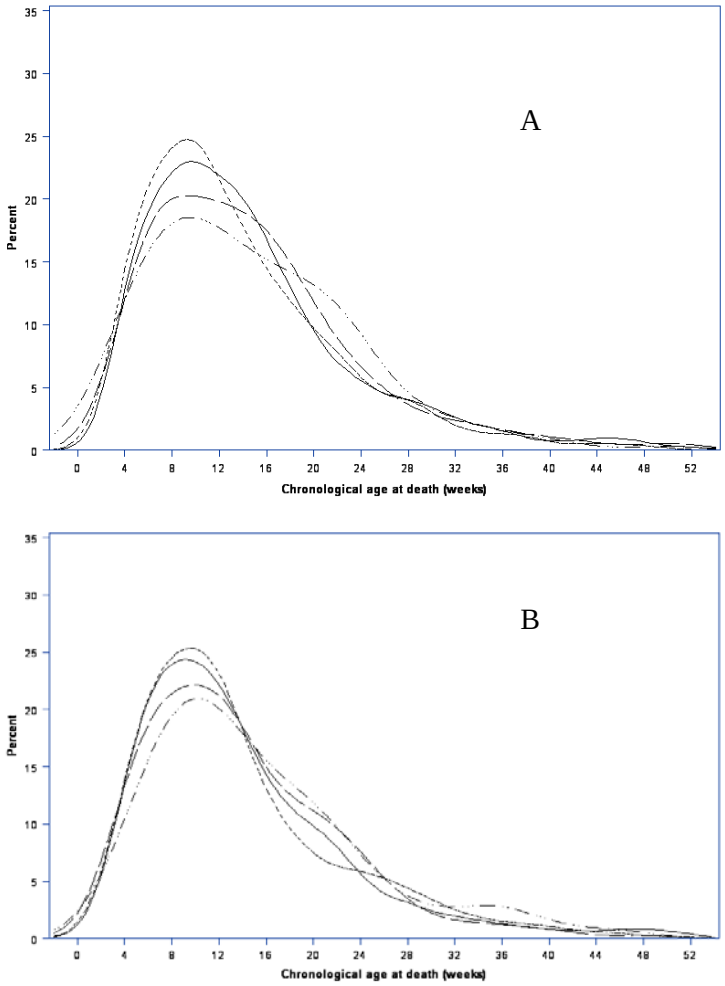

Figure 2. Chronological age at death distributions among gestational age at birth groups in SIDS infants, stratified by race; A. Non-Hispanic white B. Non-Hispanic black; Solid line: 39-41 weeks; Dotted line: 37-38 weeks; Long dashed line: 33-36 weeks; Dashed and Dotted line: 28-33 weeks.

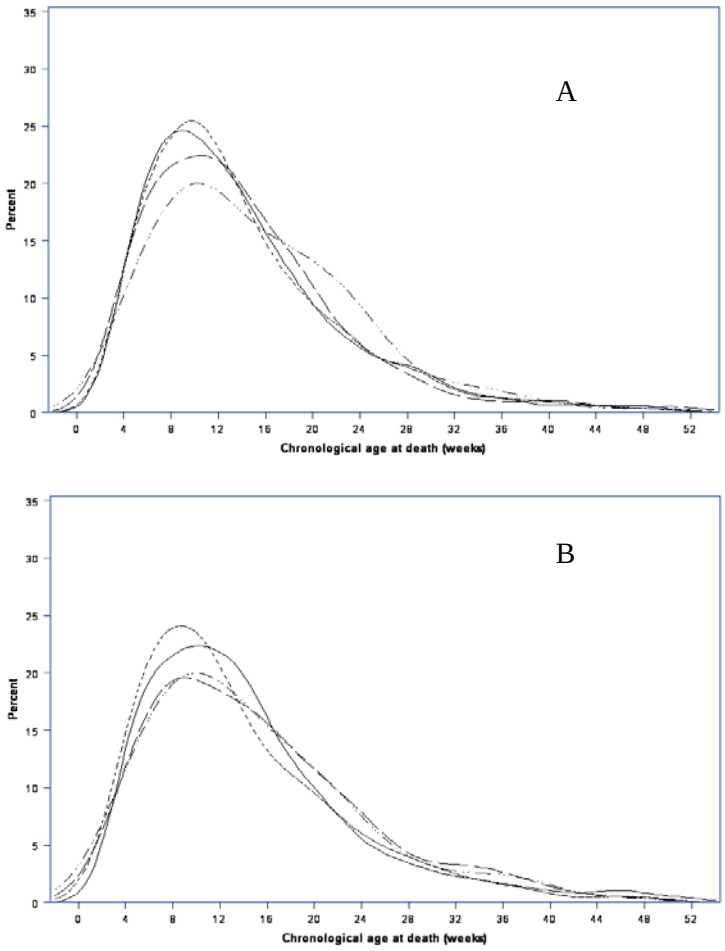

Figure 3. Chronological age at death distributions among gestational age at birth groups in SIDS infants, stratified by sex; A. Male; B. Female; Solid line: 39-41 weeks; Dotted line: 37-38 weeks; Long dashed line: 33-36 weeks; Dashed and Dotted line: 28-33 weeks.

APPENDIX

EMORY UNIVERSITY

Institutional Review Board

June 10, 2011

RE: Determination: No IRB Review Required
Title: Analysis of Corrected Age at Death Distributions for Term and Pre-Term Infants
PI: Rebecca Ludvigsen

Dear Ms. Ludvigsen:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "human subject research" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will be conducting a secondary data analysis of de identified data sets.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Andrea Goosen, MPH
Research Protocol Analyst
This letter has been digitally signed

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu