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Understanding the Relative Contributions of Prematurity and Congenital Anomalies to Neonatal Mortality

Ciaran S Phibbs, PhD^{1,2}, Molly Passarella³, Susan K Schmitt, PhD^{1,2}, Jeannette A Rogowski⁴, Scott A Lorch, MD, MSCE^{3,6}

¹Health Economics Resource Center and Center for Implementation to Innovation, Veterans Affairs Palo Alto Health Care System, Menlo Park, CA

²Perinatal Epidemiology and Health Outcomes Research Unit, Division of Neonatology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

³Center for Outcomes Research, Children's Hospital of Philadelphia, Philadelphia, PA.

⁴Department of Health Policy and Administration, The Pennsylvania State University

⁶Leonard Davis Institute of Health Economics, Wharton School, University of Pennsylvania, Philadelphia, PA

Abstract

Objective: To examine the relative contributions of preterm delivery and congenital anomalies to neonatal mortality.

Study Design: Retrospective analysis of 2009–2011 linked birth cohort-hospital discharge files for California, Missouri, Pennsylvania and South Carolina. Deaths were classified by gestational age and three definitions of congenital anomaly: any ICD-9 code for an anomaly, any anomaly with a significant mortality risk, and anomalies recorded on the death certificate.

Result: 59% of the deaths had an ICD-9 code for an anomaly, only 43% had a potentially fatal anomaly, and only 34% had a death certificate anomaly. Preterm infants (<37 weeks GA) accounted for 80% of deaths; those preterm infants without a potentially fatal anomaly diagnosis

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Corresponding Author: Ciaran S. Phibbs, PhD, HERC (152), VA Palo Alto Health Care System, 795 Willow Road, Menlo Park, CA 94025, cphibbs@stanford.edu, Phone: 650-493-5000 x22813, Fax: 650-617-2639.

Author Contributions:

CSP and SAL were co-PIs for the grant that provided funding, conceived of the idea for this study, designed the analysis, supervised the data analysis, interpreted the results, contributed to the framing of the manuscript, and contributed to the revisions to the manuscript. CSP drafted the initial version of the manuscript.

MP and SKS were the analysts that actually created the study datasets and conducted the analyses. They provided critical input into the design of the analyses and contributed to the revisions of the manuscript.

JAR helped refine the analysis plan and the interpretation of the results, and contributed to the framing of the manuscript and revisions of the manuscript.

All authors approved the final version of the manuscript before it was submitted.

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comprised 53% of all neonatal deaths. The share of preterm deaths with a potentially fatal anomaly decreases with GA.

Conclusion: Congenital anomalies are responsible for about 40% of neonatal deaths while preterm without anomalies are responsible for over 50%.

Introduction

Since 1960 there has been a dramatic reduction in neonatal mortality, falling from 18.7/1000 in 1960 to 3.85/1000 in 2017 (1, 2). Since the rate of premature delivery has remained essentially constant, almost all of this decline can be attributed to neonatal intensive care, as witnessed by the steady decline of birth weight (BW)-specific and gestational age (GA)-specific neonatal mortality (3, 4). For many years the National Vital Statistics Reports has listed congenital anomalies as the leading cause of infant death, with most of these deaths occurring in the neonatal period (5); in recent years congenital anomalies are the listed cause of death for about 30% of infant deaths (2). A closer examination of the leading causes of death shows that this is a somewhat misleading statistic as the prematurity-related deaths are distributed across several causes of death (e.g. disorders related to short gestation and low birthweight, respiratory distress syndrome, etc.), thus masking the true effect of premature birth on the neonatal mortality rate. In addition, many infants with anomalies deliver prematurely, and the relative contribution of each adjusting for the other on mortality has not been studied. As a result, true assessments of the relative impact of congenital anomalies and preterm birth on infant mortality have been difficult.

One reason for this lack of data is because previous studies relied on birth certificate data or infant discharge abstracts from the hospital of delivery. Such reliance leads to incomplete data. While birth certificate accurately provide population data on the rates of low weight and preterm delivery, congenital anomalies are very poorly identified on birth certificate (6). Data from patient discharge abstracts provide better, but not perfect information about the presence of congenital anomalies. However, rates of transfer are high among premature infants (7, 8) and in general, hospital discharge abstract data are not linked across transfers. We have previously noted that when transfers are linked there is a significant amount of disagreement between the diagnoses recorded at the birth hospital and the tertiary referral center (9), with the hypothesis that the diagnoses at the tertiary center are more accurate. A few states link birth certificates with infant discharge abstracts, including infant transfers, and death certificates. Such linked data provide a data source that can be used to better assess the relative contributions of prematurity and congenital anomalies on neonatal mortality, with all potential causes of death attributed to congenital anomalies or preterm birth regardless of the cause of death classification code.

The objective of this study was to use linked population-based data to examine the relative contributions of congenital anomalies and preterm delivery to neonatal mortality. We further examined how they overlap and how different ascertainment of congenital anomalies affected these estimates.

Subjects and Methods

We used linked Vital Statistics-Patient Discharge Data to obtain a population-based study cohort of all in-hospital deliveries from four states (California, Missouri, Pennsylvania, and South Carolina) for 2009, 2010, and 2011. As in prior work (10, 11), maternal and infant hospital discharge records were probabilistically linked with birth and infant death records to provide linked information for mother/baby pairs that were the same for all states. Data fields used in the match included date of admission and birth, hospital, maternal and infant residential ZIP code, race/ethnicity, gestational age, and insurance status. Approximately 95% of in-hospital birth records were successfully linked to maternal and infant hospital discharge abstract data (12). While these linkages are officially probabilistic, the vast majority (over 90% of mothers and almost 90% of infants) were unique matches; those that were not uniquely matched were assigned by probabilistic linkage and most of these were for uncomplicated term infants for whom the non-exact linkages have minimal effect on the analyses conducted for this study (12). Infant hospital discharge records included the delivery admission and subsequent transfers until the infant was initially discharged to home or died. This study was approved by the Institutional Review Boards at Stanford University, the Children's Hospital of Pennsylvania and the data agencies for the four states we obtained the data from (CA, MO, PA, SC). Part of both the DUAs and the ethics/IRB approvals from each of the states that provided data explicitly prohibit any sharing of the data; thus the data are not available from the authors and anyone wanting the data must go through the data approval process with each state in order to gain access to the data used for this study. The study was performed in accordance with the Declaration of Helsinki.

Cases were selected for infant deaths if the birth certificate was successfully linked to the infant delivery record. For GA, we used the best obstetric estimate of GA from the birth certificate. The GA value from the birth certificate was set to missing in cases indicating a live birth <22 weeks or a GA>45 weeks. Figure 1 outlines how the various criteria above affected the study sample. Of the 2,268,635 live births for 2009–2011 in California, Missouri, Pennsylvania and South Carolina, 2,143,033 (94.5%) were linked to infant discharge abstracts. Among these there were 5,806 infants who died in the hospital with a gestational age between 22 and 45 weeks. Of these, 5,534 were linked to a death certificate; the analyses were limited to those that were linked to a death certificate, which also allows the inclusion of infants with lethal conditions who were discharged home for comfort care.

We used three different definitions for a congenital anomaly. First, we considered if the infant had any ICD-9 code for a congenital anomaly (codes 740.00–759.99) recorded in the hospital discharge data. Second, we restricted the anomalies to those that had a significant association with mortality risk (see below), creating three groups, anomalies that can be lethal, non-lethal anomalies, and no anomalies. Third, we limited anomalies to those cases where the infant had a congenital anomaly listed as the immediate or underlying cause of death on the death certificate. In assigning diagnoses for congenital anomalies, if an infant was transferred to a higher level of NICU, then the diagnoses from the higher-level NICU overrode those from the lower-level NICU if they were inconsistent based on prior work (10).

We had previously identified which congenital anomalies were associated with an elevated mortality risk (10), but these data were from the 1990s. Since the mortality risks of specific anomalies could have changed, we repeated this process with the current data. We searched the California infant delivery and transfer hospital discharge records and created binary indicators for each ICD-9 anomaly code (740.0–759.9) and examined their prevalence. This part of the analysis was restricted to California because of a higher quality linkage of the transfers and the importance of being able to over-ride inconsistent birth hospital codes for infants who were transferred. Of the 409 ICD-9 congenital anomaly codes with at least one instance in the data, we excluded those where direct causal association with mortality is not biologically plausible. We also excluded those with initial univariable associations with mortality that were secondary to collinear associations with other more lethal abnormalities, such as polydactyly and congenital ocular and otic malformations, resulting in 205 specific ICD-9 codes with a potential association with mortality. Such exclusions yielded more stable estimates for the remaining abnormalities because of the elimination of these collinear anomalies. We then ran a logistic regression that included these indicators and also controlled for BW, GA, maternal race/ethnicity and education, type of insurance, and several indicators for delivery complications (e.g., premature rupture of membranes, prolapsed cord, oligohydramnios, placental hemorrhage, hemolytic disorders) that may also affect infant mortality. We carefully examined the results, in addition to retaining all codes that had a statistically significant association with mortality, we retained codes that represented rare conditions with meaningful mortality risk that were too rare to be statistically significant, such as the 9 codes for various locations and severity of meningomyelocele, and many “Not Elsewhere Classified” and Not Otherwise Specified” codes for similar conditions. The final result was 133 indicators for anomalies with a statistical association with mortality, which are labeled as “potentially lethal” anomalies. These were labelled as potentially lethal as many infants with these conditions survive; in aggregate there were 32,477 infants in these groups and the overall unadjusted mortality rate for these infants was 13.4%. We grouped these codes by organ system and their association with mortality. For example, the 5 cardiac groupings represent 37 diagnoses, grouped into 5 groups of increasing association with mortality. This yielded 31 groups across 13 organ systems. Appendix table A-1 shows the ICD-9 codes for each of these groups, the unadjusted mortality rate for each group, the adjusted odds ratio for mortality, and the statistical significance of the odds ratio. Only 2 of these groupings were ultimately not statistically significant but were retained in the model due to small sample size and meaningful clinical risk.

To account for the fact that advanced NICU care can prolong life past the 28-day definition of a neonatal death, we include deaths that occur after 28 days if the infant was continuously hospitalized. We classified each death by gestational age (<28 weeks (extremely preterm), 28–31 weeks, 32–36 weeks (moderate preterm), and \geq 37 weeks (not preterm)). We also created aggregated groups for very preterm (<32 weeks) and any preterm (<37 weeks). We then calculated the percentage of all deaths that occurred in each of these groups for all deaths and then for subgroups with and without our three definitions of congenital anomalies (any ICD-9 code for a congenital anomaly, those congenital anomalies associated with a measurable mortality risk (potentially lethal anomaly) and if a congenital anomaly was listed as one of the causes of death on the death certificate). The 1st and 3rd definitions serve

as a sensitivity analysis: the first definition overstates the share of deaths associated with congenital anomalies, as many of these anomalies are not associated with an elevated risk of death, while the third definition almost certainly under-estimates the share of deaths where a congenital anomaly was at least a contributing factor in the death given the limited number of ICD codes recorded on the death certificate. We also calculated the shares of deaths within each gestational age strata.

Results

We present two related tables to show how neonatal deaths are distributed across gestational age and congenital anomalies, and how these vary by our different definitions of congenital anomalies. Table 1 shows the share of all neonatal deaths in California, Missouri, Pennsylvania, and South Carolina for 2009–2011 that occurred in each gestational age/congenital anomaly cell. Table 2 has the same layout as Table 1, but presents a gestational age focused partition, showing within each gestational age group (row) the share of deaths for each of the different definitions of presence/absence of a congenital anomaly. Both tables are sorted into four sections. The first section is just column one, which reports all deaths. The second section, columns 2 and 3 sorts the deaths based on if the infant did or didn't have an ICD-9 congenital anomaly coded in the hospital discharge data. The third section, columns 4, 5, and 6, sorts that data by our definition of potentially lethal anomalies; column 4 are those deaths with an ICD-9 code for one of the anomalies we identified as potentially lethal; column 5 are those deaths with an ICD-9 code for those anomalies that we found had no association with mortality risk, and column 6 combines columns 3 and 5. The fourth section sorts the data by if the infant had an anomaly noted as a cause of death on the death certificate (column 7) or had no anomalies noted as a cause of death (column 8).

Column 1 of Table 1 shows the distribution of deaths by gestational age; of the 5,534 deaths in our sample, 80.0% were preterm (gestational age <37 weeks). Overall, 64.1% of the deaths were very preterm (<32 weeks) and 53.4% of the deaths were extremely preterm (<28 weeks). Columns 2 and 3 show the GA distribution of deaths for those cases where any ICD-9 code for a congenital anomaly was noted on the discharge abstracts (column 2) or where there was no such ICD-9 code (column 3), which corresponds to definition 1 in the methods. 58.6% of the deaths occurred in infants who had at least one ICD-9 diagnosis code for a congenital anomaly. Most of these were also preterm (41.8% of all deaths). Comparing columns 2 and 3 of Table 2 shows that the pattern varies markedly by gestational age; 63.8% of the deaths < 28 weeks had no anomaly coded, only 22.1% of the deaths between 28 and 31 weeks had an anomaly coded, and only 15.8% of the term deaths had no anomaly coded.

Given that many congenital anomalies have no effect on mortality, and many have low mortality risks, Columns 4 to 6 of both tables report these data where the definition of congenital anomalies are restricted to those which we determined to have at least some significant mortality risk as shown in supplemental Appendix 1. These columns are ordered; column 4 shows those infant deaths with one or more of these potentially lethal anomalies coded (these infants could also have other anomalies coded), column 5 shows those deaths that had ICD-9 anomalies codes that we found had no significant association with mortality or for which the association with mortality was not clinically plausible (the infants in

column 5 excludes those in column 4), and column 6 which combines those with non-lethal anomalies (column 5) and those with no anomaly coded (column 3). Considering the overall shares of deaths reported in Table 1 only 42.9% (column 4) of the deaths had an anomaly coded that could feasibly be associated with mortality. By definition, given that the overall mortality in the “potentially lethal” anomaly group is only 13.4% we know that the actual mortality attributable to congenital anomalies in this group is less than 42.9%. Column 5 shows the percentages of total deaths in each group where there was one or more ICD-9 anomaly codes that are not associated with any mortality risk; overall 15.7% of all deaths had one or more of these codes without having a code for a potentially lethal anomaly. With this definition of congenital anomalies, 52.6% of deaths were preterm without a potential lethal anomaly, and 49.7% were very preterm. Column 4 of Table 2 shows that only 14.9% of the deaths at < 28 weeks gestation had a potentially lethal anomaly and this share increases with gestational age to 60.4% for gestational ages between 28 and 31 weeks, 81.9% for infants between 32 and 36 weeks, and 77.4% for gestational ages >36 weeks.

Columns 7 and 8 report the data by whether a death had a congenital anomaly noted as a cause of death on the death certificate (column 7) or had no such indication (column 8). Table 1 shows that with this more restrictive definition only 34.4% of all deaths are attributed to a congenital anomaly, 59.5% of deaths were preterm without an anomaly, 55.0% were very preterm without an anomaly, and 48.9% of deaths were extremely preterm with no anomaly. Column 7 highlights that among the 34.4% of infants who have a congenital anomaly listed as one of the causes of death, over half (20.6%) were preterm; these are almost equally divided between moderate preterm (32–36 weeks) and very preterm (<32 weeks). Especially for the very preterm infants, their prematurity could have also contributed to their cause of death. Looking at Table 2, only 8.4% of the infant deaths <28 weeks gestation had a congenital anomaly noted on the death certificate, this rises to 43.2% for infant deaths 28–31 weeks, and is about 70% for larger infants.

As a sensitivity analysis for variation across states in mortality risk we repeated the analyses splitting the sample roughly in half, CA vs. MO, PA, SC, and found that the results were essentially the same for both subsamples.

Discussion

The goal of this study was to determine the relative contributions of preterm delivery and congenital anomalies to neonatal mortality, and how this varied by gestational age and the definition of anomalies. The coding of congenital anomalies was considered, contrasting anomalies that have plausible mortality risk versus not. Our results demonstrate that these coding differences matter in determining the role of congenital anomalies in neonatal mortality. We conclude that congenital anomalies are responsible for about 40% of neonatal deaths while preterm without congenital anomalies are responsible for over 50%.

Our results demonstrate that while a majority of neonatal deaths have a congenital anomaly coded in the discharge data (59%), over a third (37%) of the coded congenital anomalies are ICD codes for anomalies with no plausible mortality risk. If only those anomalies that have a significant association with mortality are considered, congenital anomalies are associated

with just over 40% of deaths, and about one third of these are also very preterm, so the cause of death could have been the extreme prematurity, not the anomaly. Among infants who die there is an overlap between preterm infants and infants with an anomaly that could be associated with death; for all three of our definitions of anomalies, a majority of these infants were preterm. When we consider the deaths where the coded anomaly was one not associated with any mortality risk, the vast majority (91%) of these infants were preterm, with most of them (85%) being extremely preterm. Thus, it is likely that in these infants, the cause of death was likely a sequelae of preterm birth. However, for these infants with minor anomalies, we cannot determine whether the anomaly contributed to the preterm delivery.

The identification of the ICD-9 codes for congenital anomalies that have a meaningful mortality risk is an important product of this study. There are over 400 individual ICD-9 codes for congenital anomalies which far exceeds what can be included in most statistical analyses. We identified a subset of 133 of these codes that are associated with meaningful mortality risk, and we further group those into 31 groups based on mortality risk across 13 organ systems. The provision of the full details of these groupings in the appendix will allow other investigators a to use our results in subsequent analyses.

There are limitations to our analyses, most importantly the identification of congenital anomalies and the age of the data. At the time this study was conducted more recent years of the linked files necessary to perform the analyses were not available. As newer linked data become available it will be important to repeat this analysis to see if there is any change over time in the prevalence of anomaly-related mortality, and to identify the ICD-10 congenital anomaly codes that are associated with mortality. It is well documented that the birth certificates miss a large share of congenital anomalies (6, 13). We addressed this bias by using the ICD codes from the hospital discharge data, but there are concerns about the coding of congenital anomalies the hospital discharge data as comparisons with birth defects monitoring programs find that the discharge data significantly over-identify congenital anomalies (13). It is suspected that some of this may be associated with both coding for rule-out diagnoses and diagnostic errors by non-specialists in lower level hospitals. We have attempted to minimize this bias by only considering the congenital anomalies from the higher-level hospital when an infant was transferred but some error likely remains in our identification of congenital anomalies. We suspect that this type of error is minimal in the most serious cases that are the ones that can cause death, which is supported by the high level of concurrence between our identification of anomalies associated with mortality and those listed as the cause of death list on the death certificates. A further complication is that the ICD codes only list the presence of a congenital anomaly, with no indication of the severity and many anomalies have wide ranges in their severity. This lack of severity coding explains why a large share of the anomalies that we identified as having an association with mortality have relatively low absolute mortality rate; the average unadjusted mortality rate across all of the anomalies we identified was only 13.4%.

In summary, research using congenital anomaly data must cautiously consider data that are used to attribute deaths to congenital anomalies. Depending on the coding of anomalies, among preterm infant deaths, the no anomaly group prevalence increases from 47% when all ICD-9 anomaly codes are considered to 66% when only potential lethal anomalies

are considered and 74% for death certificate anomalies. Both the change and the overall rate of deaths without a congenital anomaly were much lower for term infants, 16%, 23%, and 31%, respectively. Use of congenital anomaly data is complicated by the fact that a large share of preterm infants have one or more congenital anomalies coded. We provide information for researchers on alternate coding options and their implications for quantifying the contributions of congenital anomalies and prematurity to neonatal mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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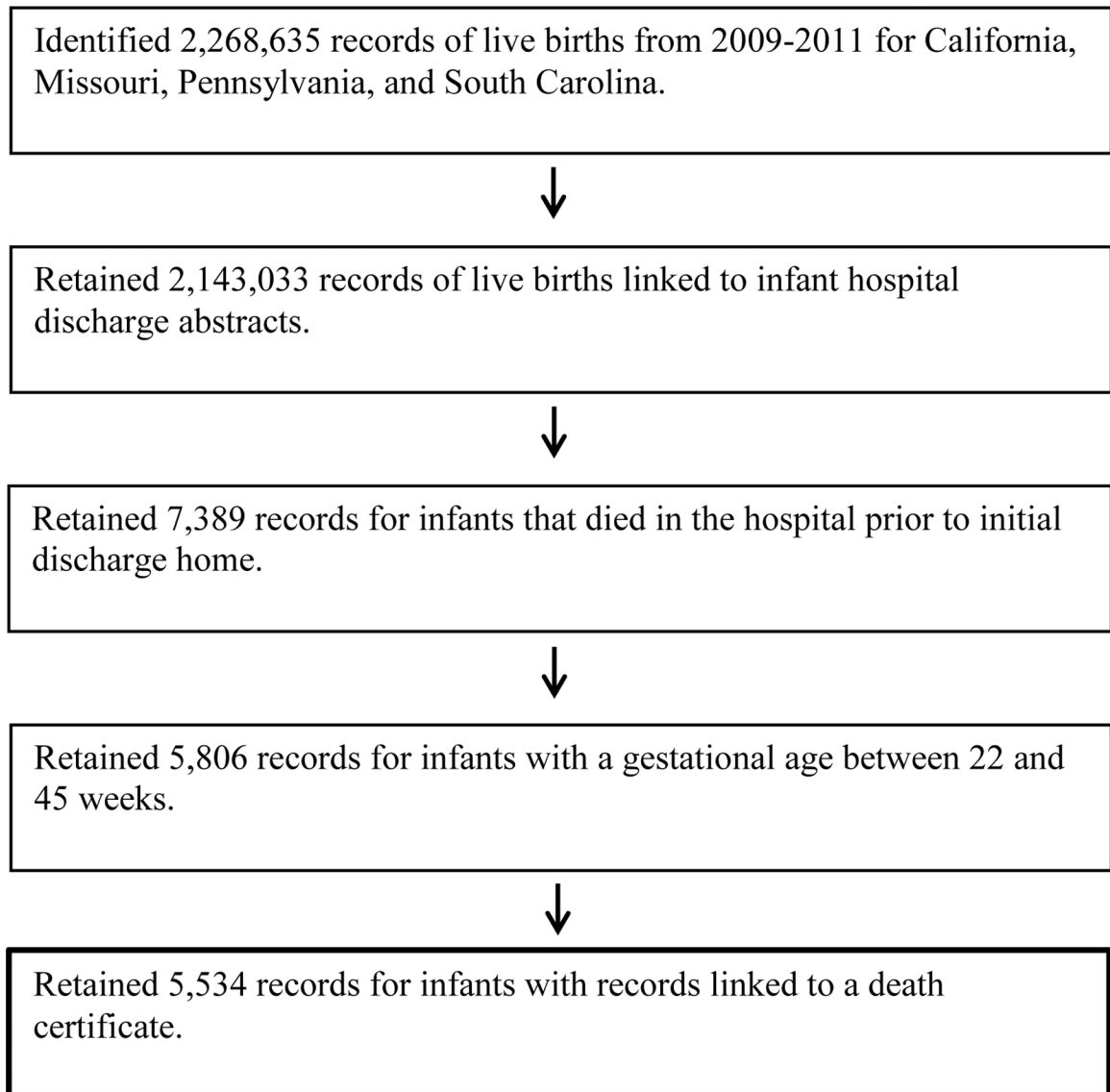


Figure 1:
Flow Diagram of the Derivation of the Study Sample

Table 1:

Shares of Neonatal Deaths in Each Gestational Age/Anomalies Group with and without Congenital Anomalies.

	1	2	3	4	5	6	7	8
Gestational Age	All deaths	Any Anomaly	No Anomaly	Lethal Anomaly	Non-Lethal Anomaly	No Lethal Anomaly	Death Certificate Anomaly	No Death Certificate Anomaly
<28 weeks	53.4%	19.4%	34.1%	8.0%	11.4%	45.5%	4.5%	48.9%
28–31 weeks	10.7%	8.3%	2.4%	6.5%	1.9%	4.2%	4.6%	6.1%
<32 weeks	64.1%	27.7%	36.4%	14.4%	13.3%	49.7%	9.1%	55.0%
32–36 weeks	15.9%	14.1%	1.8%	13.0%	1.0%	2.9%	11.5%	4.4%
<37 weeks	80.0%	41.8%	38.3%	27.4%	14.3%	52.6%	20.6%	59.5%
not preterm	20.0%	16.8%	3.2%	15.4%	1.4%	4.5%	13.8%	6.2%
All		58.6%	41.4%	42.9%	15.7%	57.1%	34.4%	65.6%

Data based on all in-hospital neonatal deaths in California, Missouri, Pennsylvania, and South Carolina, 2009–2011.

Table 2:

Share of Deaths within a Gestational Age Group for Each of the Different Definitions of Congenital Anomalies

	1	2	3	4	5	6	7	8
Gestational Age	All deaths	Any Anomaly	No Anomaly	Lethal Anomaly	Non-Lethal Anomaly	No Lethal Anomaly	Death Certificate Anomaly	No Death Certificate Anomaly
<28 weeks	2,955	36.2%	63.8%	14.9%	21.3%	85.1%	8.4%	91.6%
28–31 weeks	592	77.9%	22.1%	60.4%	17.5%	39.6%	43.2%	56.8%
<32 weeks	3,547	43.2%	56.8%	22.5%	20.7%	77.5%	14.2%	85.8%
32–36 weeks	880	88.4%	11.6%	81.9%	6.5%	18.1%	72.0%	28.0%
<37 weeks	4,427	52.2%	47.8%	34.3%	17.9%	65.7%	25.7%	74.3%
not preterm	1,107	84.2%	15.8%	77.4%	6.8%	22.6%	69.1%	30.9%
All	5,534	58.6%	41.4%	42.9%	15.7%	57.1%	34.4%	65.6%

Data based on all in-hospital neonatal deaths in California, Missouri, Pennsylvania, and South Carolina, 2009–2011.