

Distinct Populations of Sudden Unexpected Infant Death Based on Age

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abstract

OBJECTIVES: In most recent studies, authors combine all cases of sudden infant death syndrome, other deaths from ill-defined or unknown causes, and accidental suffocation and strangulation in bed as a single population to analyze sudden unexpected infant death (SUID). Our aim with this study is to determine if there are statistically different subcategories of SUID that are based on the age of death of an infant.

METHODS: In this retrospective, cross-sectional analysis, we analyzed the Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Data Set (2003–2013: 41 125 233 births and 37 624 SUIDs). Logistic regression models were developed to identify subpopulations of SUID cases by age of death, and we subsequently analyzed the effects of a set of covariates on each group.

RESULTS: Two groups were identified: sudden unexpected early neonatal deaths (SUENDs; days 0–6) and postperinatal SUIDs (days 7–364). These groups significantly differed in the distributions of assigned *International Classification of Diseases, 10th Revision* code, live birth order, marital status, age of mother, birth weight, and gestational length compared to postperinatal SUIDs (days 7–364). Maternal smoking during pregnancy was not a significant risk factor for deaths that occurred in the first 48 hours.

CONCLUSIONS: SUEND should be considered as a discrete entity from postperinatal SUID in future studies. These data could help improve the epidemiological understanding of SUEND and SUID and provide clues to a mechanistic understanding underlying the causes of death.



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WHAT'S KNOWN ON THIS SUBJECT: Authors in most recent studies analyzing sudden unexpected infant death (SUID) combine all cases of sudden infant death syndrome, other deaths from ill-defined or unknown causes, and accidental suffocation and strangulation in bed as a single population.

WHAT THIS STUDY ADDS: In this retrospective, cross-sectional analysis (41 125 233 births and 37 624 SUIDs) using advanced modeling techniques, we found that SUIDs in the first week of life are a separate entity from those occurring in the postperinatal period.

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Sudden unexpected infant death (SUID), as defined by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics, is a term that combines 3 cause-of-death categories of infants <1 year of age in the *International Classification of Diseases, 10th Revision* (ICD-10): sudden infant death syndrome (SIDS; R95), deaths from other ill-defined or unknown causes (R99), and accidental suffocation and strangulation in bed (W75). On rare occasion, researchers remove deaths occurring in the first week from the total SUID population in their reported results,¹⁻⁴ but most do not. Although SUID mortality has decreased overall in the United States since the mid-1990s, there has been little change in the number of deaths in the early neonatal period; thus, these deaths make up a larger percentage of total SUIDs.⁵

The initial days of human life carry considerable risk, with death in the first week of life representing 73% of all deaths in the neonatal period (<28 days) worldwide.⁶ Thus, this time window has been considered the most critical for a neonate. Although sudden unexpected postnatal collapse (SUPC) or sudden unexpected early neonatal deaths (SUENDs) are recognized as causes of early neonatal death (<7 days) in the United States, there is no standardized definition or ICD-10 cause-of-death entry code for either category.

SUPC includes both apparent life-threatening events and SUENDs occurring in apparently healthy or near-term infants within the first postnatal week. Infants with well-known risk factors, for example, prematurity, perinatal asphyxia, or congenital malformations, are generally excluded from these populations.¹ Approximately half of the infants that experience SUPC die, and half of the remaining survivors

suffer from long-term neurologic sequela.^{7,8}

Our aim with this study was to determine if there are statistically different subcategories of SUID that are based on the age of death of an infant, and if so, characterize the differences in risk factors associated with each group. These data could help improve the epidemiological understanding of SUID, SUEND, and their differentiation.

METHODS

A retrospective, cross-sectional study was conducted to assess the differences in SUID cases by the age of death by using data from the CDC Birth Cohort Linked Birth/Infant Death Data Set⁹ for births between 2003 and 2013. A SUID case ($n = 37\,624$) was defined as an infant (<365 days old) death with the following ICD-10 codes: R95 (SIDS), R99 (ill-defined and unknown cause), or W75 (accidental suffocation or strangulation in bed).

A set of logistic regression models were built comparing SUIDs at each age of death (by day) with the rest of SUIDs by using a set of covariates (smoking, mother's education, mother's race, mother's marital status, father's race, sex of infant, live birth order [LBO], prenatal care visits, birth weight, delivery method, and gestation). These were then analyzed to determine if there are statistically significant differences between each of these 2 groups of SUIDs. Each model was built by using a fixed size of 500 SUID cases that occurred on day X (0–364 days) and 37 124 controls. For this comparison, the control group include SUID patients who did not die on day X. To measure the difference between the SUID cases for each age of death subset versus the rest of SUID cases, the area under the receiver operating characteristic curve (AUC) for each model was used. The AUC quantifies

the overall ability of the model to discriminate between those SUID patients who died at a certain age of death versus the rest of the SUID patients. To measure the significance level of AUC, a permutation test was computed.

A second set of logistic regression models was built to compare the SUIDs at each age of death with all non-SUID live births (control; $n = 41\,125\,233$) from 2003 to 2013 and analyzed and computed the adjusted odds ratio (aOR) to understand the effects of the set of SUID covariates for each of the models at each age of death. Two additional logistic regression models were built to compute the aOR for SUEND (0–6 days; $n = 1260$) versus control and postperinatal SUID (7–364 days; $n = 36\,364$) populations versus control.

Finally, the trend of SUEND cases as a percent of total SUID cases from 1983 to 2016 was analyzed by using the CDC Birth/Infant Death Data Set (1983–2013)⁹ and CDC Wonder from 2013 to 2016.¹⁰ From 1983 to 1999, we used SUID *International Classification of Diseases, Ninth Revision* codes as described by Goldstein et al.¹¹

RESULTS

Out of a total of >41 million births in the United States between 2003 and 2013, our data set included 37 624 SUIDs (R95 + R99 + W75). Compared to the total SUID population, the only statistically different SUIDs occurred between days 0 to 6, deaths that will be referred to as SUEND throughout this study. These SUENDs could be individually distinguished from deaths that occurred between 7 and 364 days (postperinatal SUID) by the model with a 77.3% probability. This means that 2 deaths chosen at random, one that occurred in the first week and one that occurred between 7 and 364 days, could be individually

distinguished by the model ~77% of the time. Comparing 2 deaths that both occurred in the postperinatal period were statistically indistinguishable from one another in the model.

There were 1260 (3.3%) SUID cases that occurred between 0 and 6 days of life. The largest peak of SUIDs were on day 0 ($n = 591$; 1.6%; Fig 1). The incidence of SUEND revealed an exponential decay over the course of the first week. After this decay, a separate, more gradual peak spanning 1 to 4 months of age was observed.

The majority (67%) of SUENDs were classified in the CDC data set as R99, with a minority categorized as R95 (24%) and W75 (9%). In contrast, most postperinatal deaths were identified as R95 (55%), with fewer classified as R99 (28%) and W75 (17%). This difference was statistically significant ($P < .001$).

The SUEND rate, as a percentage of total births, has remained constant since 1983; therefore, as a percentage of all SUIDs, it has increased greater than twofold over the past 3 decades (Fig 2).

When compared to the first live birth, increasing LBO between the second and fifth children progressively increased the aOR for postperinatal deaths (Table 1). Conversely, for the SUEND population, the second and higher LBO revealed a lower risk compared to the first live birth. Approximately 43% of SUENDs that occurred within the first week were a mother's first live birth compared to only 29% for postperinatal SUID cases.

There was also a statistical difference for marital status (Table 1). The data revealed higher postperinatal SUID rates (aOR = 1.19; 95% confidence interval [CI] = 1.15–1.23; $P < .001$) for children of those that were unmarried at their child's birth. In contrast, being unmarried decreased

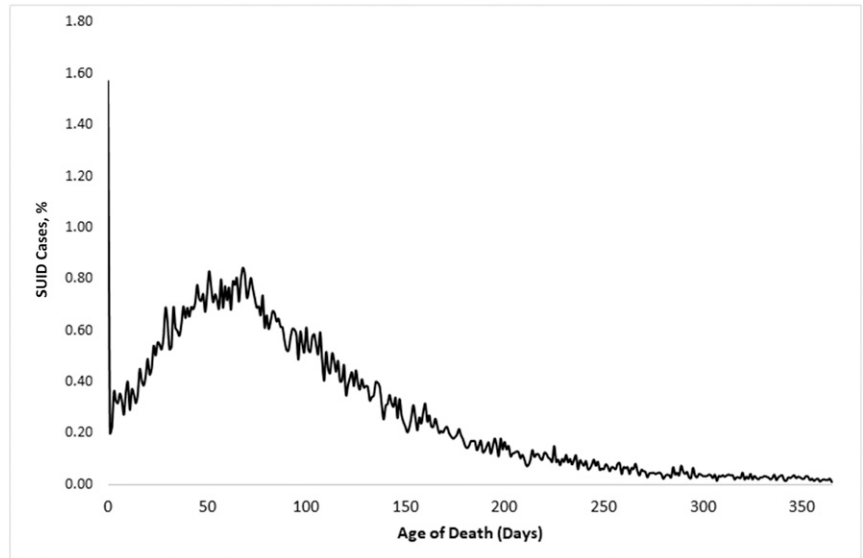


FIGURE 1

Distribution of SUID cases by age of death. There are 2 peaks in the distribution pattern of SUID cases by age of death. The first peaks on day 0 and decreases exponentially over the first week (SUEND). The second, smaller peak spans ~1 to 3 months of age (postperinatal SUID). After this second peak, the number of SUID cases gradually decreases across the remainder of the first year of life.

the risk of a SUEND (aOR = 0.72; 95% CI = 0.61–0.85; $P < .001$).

Compared with a baseline of mothers aged 25 to 29, younger mothers (ages 15–24) demonstrated statistically higher postperinatal SUID

rates but lower SUEND rates (Table 1). SUID and SUEND rates were both similarly lower for mothers >30 years old.

SUENDs exhibited 2 peaks in birth weight distribution pattern (Fig 3).

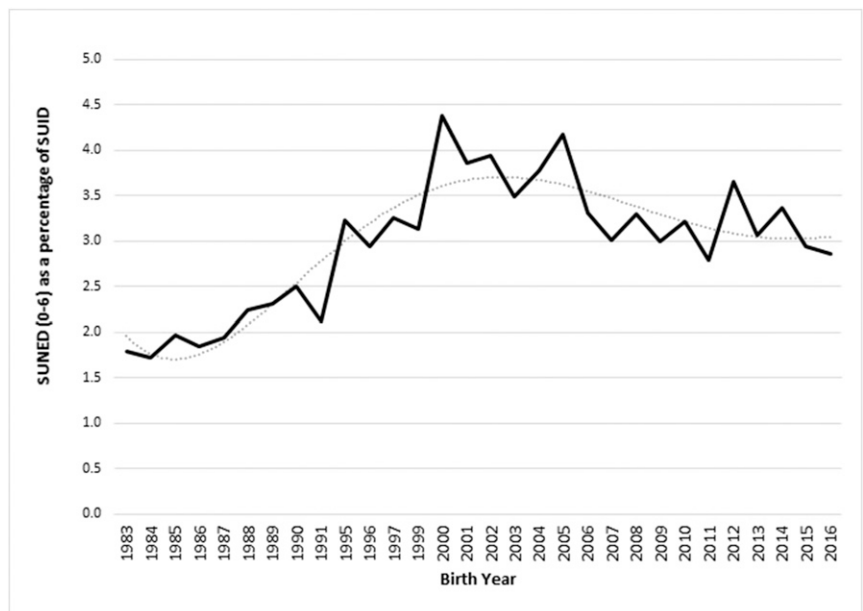


FIGURE 2

SUENDs as a percentage of total SUIDs. The rate of SUEND as a proportion of total SUID cases rose between 1983 and the early 2000s, and then has plateaued over the last couple of decades.

TABLE 1 Comparing Risk of Various Factors Between SUEND and Postperinatal SUID Populations

	Controls <i>n</i> = 41 125 233		SUEND, 0–6 d <i>n</i> = 1260			Postperinatal SUID, 7–364 d <i>n</i> = 36364			
	%	%	aOR	CI	<i>P</i>	%	aOR	CI	<i>P</i>
Maternal smoking in pregnancy									
No and unknown	91.7	—	Reference	—	—	71.5	Reference	—	—
Yes	8.3	23.3	1.44	1.20–1.72	<.001	28.5	2.20	2.12–2.28	<.001
LBO									
First live birth	39.8	43.5	Reference	—	—	29.1	Reference	—	—
Second live birth	31.7	22.1	0.34	0.29–0.40	<.001	31.0	1.16	1.13–1.20	<.001
Third live birth	16.6	14.2	0.44	0.36–0.53	<.001	20.5	1.61	1.55–1.67	<.001
Fourth live birth	6.8	9.0	0.61	0.47–0.79	<.001	10.3	2.05	1.94–2.16	<.001
Fifth live birth	2.6	3.2	0.45	0.29–0.71	.001	4.4	2.37	2.20–2.56	<.001
Marital status									
Married	60.8	41.0	Reference	—	—	33.4	Reference	—	—
Not married	39.2	59.0	0.72	0.61–0.85	<.001	66.6	1.19	1.15–1.23	<.001
Mother's age, y									
15–19	9.2	15.2	0.55	0.43–0.70	<.001	17.7	1.3	1.24–1.36	<.001
20–24	24.2	30.1	0.44	0.38–0.53	<.001	39.3	1.06	1.03–1.10	.001
25–29	28.1	24.7	Reference	—	—	24.5	Reference	—	—
30–34	23.9	18.0	0.58	0.47–0.70	<.001	12.2	0.5	0.48–0.52	<.001
35–39	11.8	8.0	0.52	0.39–0.71	<.001	5.0	0.41	0.38–0.44	<.001
Birth wt, g									
227–499	0.0	18.1	447.6	19.87–913.24	<.001	0.6	17.02	11.68–24.80	<.001
500–749	0.2	7.8	38.80	3.53–75.79	<.001	0.8	4.25	3.31–5.46	<.001
750–999	0.2	2.0	7.31	3.01–15.10	<.001	1.0	3.05	2.47–3.77	<.001
1000–1249	0.3	1.7	5.96	1.94–11.79	<.001	1.1	2.53	2.12–3.01	<.001
1250–1499	0.4	1.3	3.83	1.17–7.56	<.001	1.4	2.94	2.52–3.42	<.001
1500–1999	1.6	2.6	1.82	1.00–2.84	.009	4.8	2.13	1.96–2.32	<.001
2000–2499	5.1	7.9	1.29	0.57–1.65	.049	11.6	1.57	1.49–1.65	<.001
2500–2999	18.3	18.9	0.67	0.21–0.79	<.001	25.2	1.03	1.00–1.07	.047
3000–3499	39.1	23.7	Reference	—	—	33.4	Reference	—	—
3500–3999	26.9	11.1	0.26	0.15–0.32	<.001	16.0	0.56	0.54–0.58	<.001
4000–4499	6.8	2.3	0.23	0.24–0.34	<.001	3.3	0.5	0.47–0.53	<.001
4500–4999	1.0	0.7	0.53	0.00–1.20	.13	0.5	0.55	0.46–0.65	<.001
Not stated	0.0	1.7	33.21	1.00–99.98	<.001	0.1	6.39	3.29–12.42	<.001

List of aOR, CIs, and *P* values for factors that differ between SUEND and postperinatal SUID populations. LBOs are compared to the first live birth, mother's age is compared to ages 25 to 29 y, and birth weight is compared to 3000 to 3499 g. Controls are live births that survived to the first birthday. The reference category aOR is 1.00. —, not applicable.

The first peak corresponded to extremely low birth weights. A total of 19% of SUENDs that occurred between 0 to 6 days had a birth weight of <500 g and/or a gestational length of <28 weeks. The second peak in birth weight distribution for SUENDs overlapped with the peak for postperinatal SUIDs at 3000 to 3499 g. Both populations demonstrated higher rates of SUID for infants with low birth weight; however, the rates of SUEND were much greater than for postperinatal SUID (Table 1). Removing the infants with low birth weight from the population in our model and only analyzing infants with a birth weight of >1000 g

resulted in SUENDs that were still significantly different from postperinatal SUIDs. This significant difference was even stronger if we restricted the analysis to infants with a birth weight of >2500 g and >28 weeks' gestation (data not shown).

Smoking in pregnancy was a significant risk factor for SUEND but less than for postperinatal SUID (aOR = 1.44 vs 2.20, respectively). After covariate adjustment, maternal smoking was not a significant risk factor for deaths that occurred in the first 48 hours (aOR = 0.89; 95% CI = 0.65–1.22; *P* = .47). This was still true if we did not control for

birth weight and gestational length. Two covariates, marital status and the father's age, seem to explain this change in significance. After the first 48 hours, the risk of smoking sharply increased and peaked at approximately day 21 (aOR = 2.34; 95% CI = 1.79–2.89; *P* < .001; Fig 4), after which the risk slowly decreased and plateaued at an ~1.4-fold risk over the first 6 months. For infants born ≥2500 g and ≥28 weeks' gestation, only 13.2% mothers smoked in SUEND cases that occurred in the first 48 hours, whereas 27.8% of mothers smoked in postperinatal SUID cases.

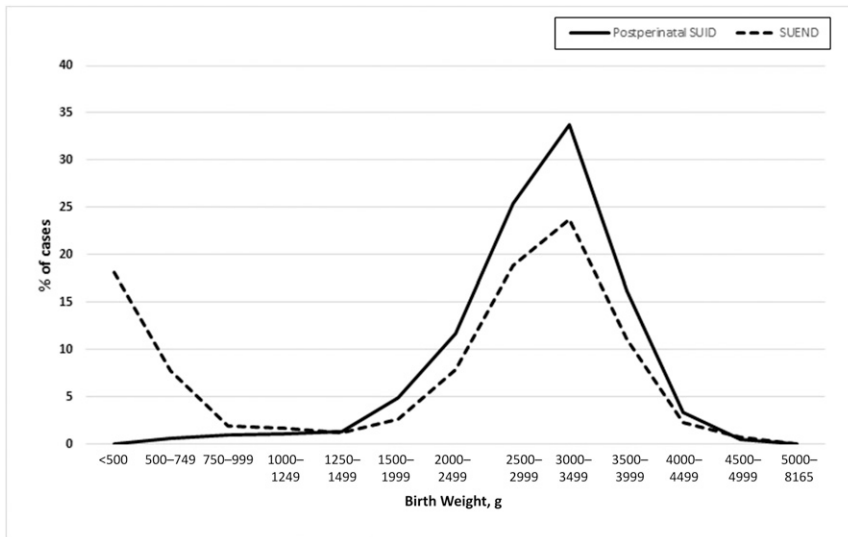


FIGURE 3 Birth weight distribution of SUEND versus postperinatal SUID. SUEND cases have 2 peaks in birth weight distribution. The first coincides with light weight births. The second overlaps with the only peak in the distribution of postperinatal SUID cases at approximately average birth weight (3000 g).

DISCUSSION

Over the last 20 years, SIDS rates have slowly decreased; however, overall SUID rates have remained relatively constant.¹² This is in part because of “diagnostic transfer” or “diagnostic shift.”¹³ There is a fair amount of subjectivity in interpreting a death scene and much disagreement among pathologists when deciding whether findings within the death scene were factors in the death.¹⁴ Many medical examiners and coroners have shifted to labeling a death that would have once been called SIDS as “undetermined” or “asphyxia” in cases of shared sleeping surface.¹⁵ Thus, it is difficult to evaluate SIDS without also including unknown causes and accidental suffocation¹⁶ and is the reason why we and others (CDC and American Academy of Pediatrics) include all 3 causes of death in the SUID category.

For the better part of a century, it has been well known from epidemiological and autopsy findings that sudden unexpected and unexplained death in infants followed a consistent age distribution: they rarely occurred in the first month,

and the majority occurred in the first 6 months.¹⁷ The focus of SIDS and SUID research ever since has primarily been focused on these deaths.

The vast majority of deaths that occur in the early neonatal time period are due to explained causes such as complications during delivery, congenital malformations, or preterm birth. In fact, this is why a few studies, particularly those following the sudden unexpected death in infants definition (which is the same as SUID) developed from the Confidential Enquiry into Stillbirths and Deaths in Infancy studies in the United Kingdom,¹⁸ restrict study populations of SUIDs to only include deaths between 7 and 364 days.¹⁻⁴ There is a small percentage of neonatal deaths that remain unexplained, and most recent studies, especially in the United States, tend to combine all SUIDs between 0 and 364 days as a single population.

In this study, we took a computational modeling approach to determine if there were distinct age of death populations within the total SUID population while controlling for a set

of various demographic, socioeconomic, and delivery factors. The model compared all children who died at a certain age (eg, day 0) with every other child that died of SUID (eg, days 1–364). This technique allowed us to determine if there were statistically separate groups without any preconceived age boundaries. The model revealed that deaths that occurred in the first week (0–6 days; SUEND) were statistically distinct from all other SUIDs (7–364 days; postperinatal SUID) and could distinguish between the 2 populations with >77% accuracy. Importantly, deaths that occurred in the postperinatal period were statistically indistinguishable from each other, suggesting that these deaths are indeed a single group. To our knowledge, this is the first study to systematically reveal that SUEND and postperinatal SUIDs are statistically distinct entities.

Our data confirm similar reports that the first day of life carries the largest risk of death for SUID cases.¹⁹ The peak of sudden unexpected deaths on day 0 and subsequent exponential decrease over the first week is similar to other non-SUID infant deaths, for example, preterm newborns (ICD-10: P07.3).

The percent distribution of stillbirths by gestational age has not changed since 2006.²⁰ Approximately one-quarter of stillbirths (≥ 20 weeks’ gestation) in the United States are unexplained²¹ in large part because of a failure to complete a full investigation.²² It has been suggested that the pathogenesis underlying unexpected deaths in late-term stillbirth, early neonatal death, and SIDS lies on a continuum and that the origin of SIDS is prenatal.^{23,24} However, the differences in risk factors between our SUEND and postperinatal SUID populations suggest that underlying mechanisms are separate and do not lie on a continuum.

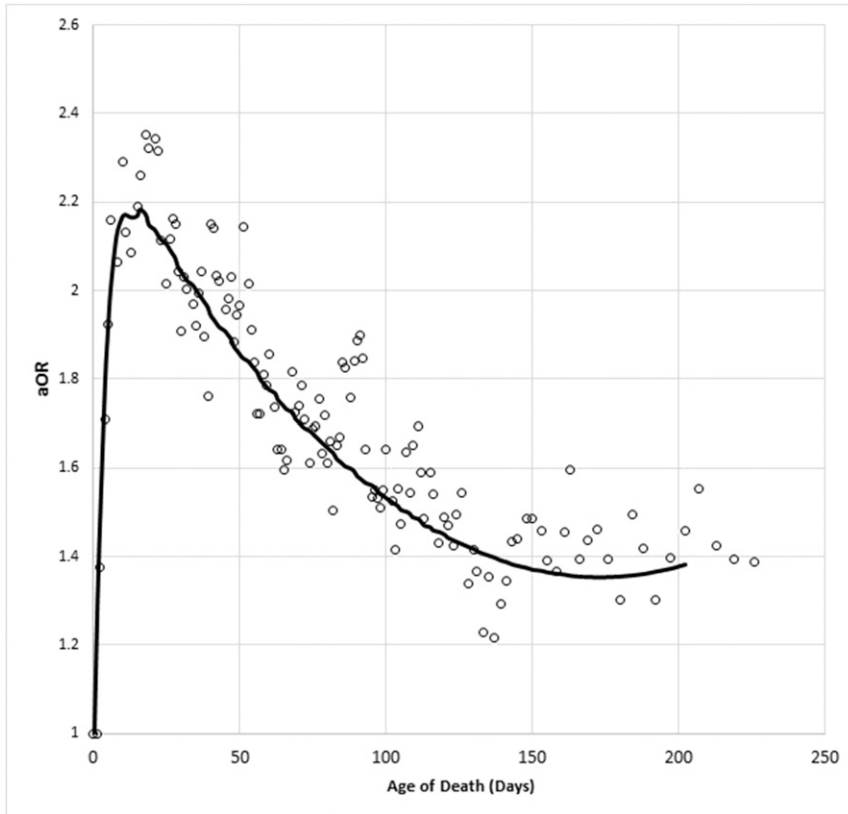


FIGURE 4

Maternal smoking and the risk of SUID by age of death. After controlling for other factors including birth weight and gestation, there is no increased risk of maternal smoking for deaths that occur in the first 48 hours. However, the aOR steeply increases on day 3, peaks around day 21, and gradually decreases and plateaus at ~1.4-fold risk over the first 6 months.

Estimates of the prevalence of SUPC in a presumed healthy infant after birth vary widely across literature sources. This is in part because of varying definitions and inclusion and exclusion criteria⁷ as well as nonuniformity in coding the death of infants after a resuscitation attempt. If a SUPC death was not classified as an R95 or R99, the death would not be captured in this study. An agreement over a dedicated cause-of-death code in the ICD-10 has not been established⁷; however, it would facilitate research as well as focus education and preventive efforts.

The second peak in age of death distribution takes place over 1 to 4 months, overlapping the known critical developmental window for SUIDs.²⁵ These 2 peaks exhibit different time functions in distinct

periods of development likely indicating separate underlying causes of death.

The prone position is a major risk factor of SUID and led to the launch of the Back to Sleep campaign, which educated parents and caregivers to place infants in a supine position to sleep.²⁶ This led to a decrease in overall SUID rates; however, it did not decrease SUEND rates. In fact, SUEND rates have remained relatively constant since 1983 and have only increased or held steady as a percentage of total SUIDs over the last 30 years. The SUPC (a subset of SUEND) of an apparently healthy infant has been associated with initial, unsupervised breastfeeding, the prone position, primiparity, bed-sharing, and distractions.⁸ Unfortunately, a limitation of this

study is that the data set lacks these postnatal risk factors. These would be important and interesting additional behavioral variables with which to compare and contrast SUEND and postperinatal SUIDs in future studies.

A major strength of this study is the large, national sample size. We analyzed every birth in the United States between 2004 and 2013 (>41 million), which included every SUID case (>37 000). Our data reveal that SUENDs (0–6 days) and postperinatal SUIDs (7–364 days) differ significantly in distributions of LBO, marital status, mother's age, birth weight, and gestational age, which are all established risk factors for SIDS and SUIDs.

The risk of postperinatal SUID increased with increasing LBO compared to a control group. This trend for SUIDs has been previously reported²⁷ and is similar to that of infant mortality overall; the death rate for higher-order births is generally associated with older maternal age, multiple births, and lower socioeconomic status.²⁸ In contrast, the likelihood of a SUEND occurring was lower for a mother's second versus first live birth. It is currently unknown why the trends are opposite, but it is yet another clue that the underlying physiologic causes of death are different between these 2 groups. Of note, there were more SUENDs, proportionally, than postperinatal SUIDs for a mother's first live birth.

Interestingly, there was a difference in risk between SUEND and postperinatal SUID regarding marital status. Infants of mothers that were married at birth had a lower risk of postperinatal SUID but a higher risk of SUEND. Conversely, those that were unmarried had a higher risk of postperinatal SUID and lower rates of SUEND. This can possibly be explained by age because younger mothers (ages 15–24), who are more likely to be unmarried, also exhibited

lower SUEND rates. It has been well documented in several countries that risk factors for SIDS include younger mothers and single mothers²⁹⁻³¹; however, to our knowledge, it was previously unknown that these risk factors were specific to postperinatal SUID cases and are actually protective factors for SUEND cases.

Furthermore, the 2 groups showed different birth weight and gestational age distributions. The first SUEND peak corresponded to extremely low birth weights. In these cases, it may have been more appropriate to classify the cause of death as resulting from “disorders related to short gestation and low birth weight” (ICD-10 code P07). The second peak in birth weight distribution for SUENDs overlaps with the only peak for postperinatal SUIDs at 3000 to 3499 g. Importantly, even if we remove infants with low birth weight from our model (>2500 g and >28 weeks’ gestation), SUEND and postperinatal SUIDs are still significantly different.

Maternal cigarette smoking during pregnancy is the greatest modifiable risk factor for SUID, and in fact, any amount of smoking more than doubles the risk.³² Surprisingly, smoking does not play a significant

role in SUENDs that occur in the first 48 hours. The developmental window within which physiologic mechanisms lead to an increased risk of SUID due to smoking starts several days after birth, peaks at ~3 weeks, and eventually plateaus at a constant, elevated risk. Although we have not been able to explain this finding, this time function could provide clues to the underlying mechanisms of action of cigarette exposure.

The evidence presented here suggests that SUENDs have a distinct epidemiological pattern compared to the more typical postperinatal SUIDs. Risk factors for SUEND include lower LBO, being married, and low birth weight. In contrast, risk factors for postperinatal SUID include higher LBO, being a single mother, being a young mother, and maternal smoking during pregnancy. On the basis of these differences in risk factors and developmental windows, we propose that SUIDs that occur in the first week of life are a distinct etiology and should consistently be considered separately from postperinatal SUID cases. Considering these 2 populations discretely may help uncover independent underlying physiological mechanisms and/or

genetic causes underlying SUEND and SUPC versus postperinatal SUIDs.

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ABBREVIATIONS

aOR:	adjusted odds ratio
AUC:	area under the receiver operating characteristic curve
CDC:	Centers for Disease Control and Prevention
CI:	confidence interval
ICD-10:	<i>International Classification of Diseases, 10th Revision</i>
LBO:	live birth order
SIDS:	sudden infant death syndrome
SUEND:	sudden unexpected early neonatal death
SUID:	sudden unexpected infant death
SUPC:	sudden unexpected postnatal collapse

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