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All sudden unexplained infant respiratory deaths may result from the same underlying mechanism

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ABSTRACT

The Sudden Infant Death Syndrome (SIDS) was defined in 1969 by Beckwith as sudden death of an infant or young child, unexpected by medical history, remaining unexplained after thorough autopsy/death-scene investigation. Recently researchers have used the general terms Sudden Unexplained Death in Infancy (SUDI) and Sudden Unexpected Infant Death (SUID) as "umbrella-terms" covering unexplained deaths (SIDS); sudden deaths for which SIDS risk factors present but insufficient cause is found; and sudden deaths for which sufficient cause is found. A characteristic feature of such deaths is that, 24-hours before death (or unexpected collapse that led to death), the caregivers were unaware that the baby was at increased risk of dying. The explainable cases include deaths from several recognized causes including infection, metabolic conditions, accidental and non-accidental injury, and various genetic or cardiac conditions as well as "Accidental Suffocation and Strangulation in Bed (ASSB)." SIDS is characterized by a ~50% male excess common to all respiratory infant deaths and a 4-parameter lognormal age distribution - thought to be unique and SIDS main distinguishing characteristic. In this article we model these data for age and/or gender distributions of SUDI/SUID and SIDS reported from the U.K., U.S., Norway and Germany. When pooled together with SIDS, these explained SUDI/SUID data on infant ages and gender have the same distributions as SIDS, indicating that the final mode of death for all SUDI or SUID may be a consequence of different paths to the same biological phenomena as for SIDS, though the mechanism of death remains unclear.

Keywords:
SIDS, SUDI, SUID, SRD, ASSB, 4-parameter Lognormal

INTRODUCTION

The death of any infant is tragic and such a death that is truly unexpected, sudden, and unexplained, creates an even greater psychological burden on the infant's parents who were not aware that the infant was at imminent risk of dying [1]. The effort to divide such cases called Sudden Unexpected Infant Deaths (SUID) [2,3] or Sudden Unexplained Death in Infancy (SUDI) [4,5] into categories of unexplainable cases as Sudden Infant Death Syndrome (SIDS) and potentially explainable cases has been made to aid researchers, and also to provide an explanation, if possible, for the parents to alleviate their terrible uncertainty and suffering of their loss. For example, the U.S. Centers for Disease Control and Prevention (CDC) [2] divides those SUID previously defined as SIDS by Beckwith [6], into inexplicable SIDS, Accidental Suffocation and Strangulation in Bed (ASSB) and Causes Unknown (UNK).

Total SIDS (Beckwith definition [6]) are characterized by a 4-parameter lognormal age distribution, also known as the Johnson S_B distribution [7], that has been called unique amongst all causes of infant death [8-10]. Mage and Donner [10] have shown, by Cramér's Theorem [11,12], if total SIDS ages are lognormally distributed and to be divided into independent groups of inexplicable SIDS and explicable SUDI or ASSB/UNK, then these new groupings *must* have the same original 4-parameter lognormal transform distribution as the total SIDS distribution. This leads to the paradox that the new categories of explicable SIDS, such as ASSB and UNK, if different and independent phenomena, must also have the same 4-parameter lognormal distributions as inexplicable SIDS. Because this is virtually impossible if they are truly independent phenomena, inexplicable SIDS and explicable SUDI or SUID must be the result of the same physiological terminal-state that can be achieved by either presently unknown and unexplainable physiological defects as well as known and explainable defects that can be found at autopsy and death scene investigation. We show that evidence of this commonality was first published in 1982 [13] but a misinterpretation hid it in two published papers [14,15]. Byard said it succinctly: "It is also likely that the aetiology of SIDS is heterogeneous and it is likely that the term SIDS is not so much a diagnosis but a term covering a variety of mechanisms which result in a common lethal outcome" [16]. We propose here to show that this is truly the case.

We present datasets of SIDS/SUDI/SUID and show that they all have similar 4-parameter lognormal age distributions and ~50% male excess gender distributions. This will be demonstrated to mean that explainable SUDI and SUID are a distinction from SIDS without a difference in terminal

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mechanism though the nature and specific characteristics of the different triggers of the processes leading to death remains unclear - perhaps by a chance superposition of different risk factors unexpectedly acting suddenly and simultaneously, like a *'rogue wave'*, sometimes with identifiable potentially lethal conditions and illness.

MATERIALS AND METHODS

We base our modeling on published datasets, shown in Table 1, available in the medical literature, and unpublished SIDS and explainable SUDI/SUID age-at-death datasets received as personal communications from some of our coauthors. Because SIDS is a diagnosis by exclusion, these SIDS datasets may contain false positive cases (e.g., undiagnosed infanticide by gentle suffocation) and omit false negative cases (e.g., a non-lethal low-grade respiratory infection cited as cause of death).

The 4-parameter lognormal (S_B) transform of these ages is $y = \mathrm{Log}[(m-a)/(b-m)] = \mu + \sigma z$, where: m is age in months, z is a standard normal deviate, μ and σ are median and standard deviation of y, and a = -0.31 month and b = 41.2 months, are the 3rd and 4th parameters, respectively [9]. For the data shown in Table 1, $y = \mathrm{Log}[(m + 0.31)/(41.2 - m)]$ is plotted against the probability corresponding to the normal inverse (z) of their cumulative distribution function (CDF) at month m, where CDF = $[\sum n(m)] / N$, and $z = 0$ @ CDF = 0.50.

SIDS age data are usually limited to the range between 7 days and 1 year of life by convention because of the difficulty of neonatal autopsy under 7 days and the difficulty of separating out the relatively rarer SIDS above 1 year from the more common causes of death above 1 year. As described previously [9,10], we use a linear semi-log extrapolation of SIDS ages from 4 to 12 months out to 41.2 months to estimate the missing data removed by truncation of the distribution at 1 year. The upper limit of 41.2 months for SIDS used herein was determined independently by maximum likelihood estimation [9].

We note that the users of age in units of integer month-of-life-attained often do not define how many days constitute a month of life, and this introduces an error as four 12-month years contain (4 x 365 + 1)/48 = 30.44 days/month. The exact value of 30.44 days/month is used by us throughout our analysis to convert days to months where possible. Table 2, as an example, shows how the Australian Bureau of Statistics (ABS) and U.S. CDC

Table 1. Number (n) of SIDS and SUDI at monthly age (m*) analyzed at plotting position $y = \mathrm{Log}[(m + 0.31)/(41.2 - m)]$.

Data [Ref]	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m	11 m	12 m	13-41m**	Total N
y	-1.487	-1.230	-1.062	-0.936	-0.834	-0.747	-0.670	-0.602	-0.539	-0.481	-0.427	-0.375	-	-
SIDS [10]	1,649	5,233	6,053	4,900	3,147	1,966	1,336	925	643	386	247	160	315	26,960
SRD C&G [13]	1,113	3,347	4,236	3,460	2,158	1,342	952	676	513	377	318	259	567	19,318
SIDS 1(a) O&M [17]	308	971	1,105	953	640	397	288	191	134	86	54	36	77	5,240
SIDS 1(b) O&M [17]	62	197	215	186	130	79	71	55	33	17	11	8	15	1,079
SIDS 1(b) OPCS [18]	25	119	128	127	84	75	40	34	33	11	8	6	13	703
SIDS +SUDI CESDI [19]	51	64	76	56	38	29	18	20	14	12	11	8	31	428
SIDS +SUDI SWISS [20]	26	26	18	8	7	7	4	2	3	5	0	2	8	116
SIDS +SUDI GeSID [21]	29	63	86	75	55	32	27	27	17	19	16	10	43	499
ASSB [22]	200	334	276	179	104	81	45	56	32	23	12	14	30	1,386
SRD Philadelphia	87	142	161	92	73	38	30	21	8	4	6	8	11	681
Total N	**3,550**	**10,496**	**12,354**	**10,036**	**6,436**	**4,046**	**2,811**	**2,007**	**1,430**	**940**	**683**	**511**	**1,110**	**56,410**

* Months may be defined differently by different authors without explanation.
** Estimated by semi-logarithm extrapolation of numbers at ages 4 - 12 months to 41 months.

Table 2. Examples of different definitions of days to reach a full month of life completed as used by U.S. Centers for Disease Control (CDC) and Australian Bureau of Statistics (ABS) compared to exact number of days with correction for leap year.

Month	1	2	3	4	5	6	7	8	9	10	11	12
Exact	30.44	60.88	91.31	127.75	152.19	182.63	213.06	243.50	273.94	304.38	334.82	365.25
CDC*	28	63	91	126	154	182	210	245	273	301	336	364
ABS**	31	60	90	120	150	180	210	240	270	300	330	360

* personal communication: weeks converted to months, Kimberley D. Peters, U.S. CDC, February 2, 1998.
** personal communication: days converted to months, Louise Ellis, SIDS and Kids, Australia, October 5, 2010.

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differently convert ages recorded in days and weeks which are defined (24 hours = 1 day; 7 days = 1 week), into months which are not defined (28-31 days = 1 calendar month).

Finally we note that the Beckwith definition of SIDS [6] has been revised since 1969 and different countries, and even different pathologists within a country, may use different definitions. Furthermore, many articles on SIDS do not even specify which definitions of SIDS were applied to their data [23]. Given that objective statistical testing assumes that variances are due to only sampling error and that individual observations of age and cause of death are made without such experimental errors, we rely on the subjective graphical goodness-of-fit to support our conclusions.

RESULTS AND DISCUSSION

1. Sudden Respiratory Death (SRD) at home and in hospital:

In 1982, Carpenter and Gardner [13] reported on the ages, genders and causes of all respiratory infant deaths between 7 days and 1 year of life, in England and Wales, between 1965 and 1976. According to the authors "Attention was primarily focused on home deaths, that is, excluding deaths occurring in hospital, which are certified by a coroner as due to respiratory or unknown causes [See Table 3]." Between 1969 and 1976, 11,792[1] cases were called Sudden Respiratory Deaths (SRD). This period spans the first published definition of SIDS in 1970 by Beckwith [6], so the numbers of SIDS cases were estimated as "about 70%" (about 8,300) of the total SRD. Their study also reported 3,939 infant respiratory deaths in hospital certified by coroner and 2,766 infant respiratory deaths at home or in hospital certified by an attending doctor in the same period, implying that both those classes of death were not unexpected (i.e., not meeting Beckwith's definition of SIDS) as the infant was being treated for some unspecified symptoms of illness at the time of death.

Table 3 of Carpenter and Gardner's report shows the age and gender totals of SRD at home for years 1965-1976. They also provided the monthly data by personal communication which expanded the monthly intervals 7-9 and 10-12 months in their Table 3. We estimated the numbers of cases under 7 days by curvilinear extrapolation to -0.31 month and the numbers of such respiratory cases beyond 1-year out to 41.2 months by semilog extrapolation of the monthly totals between 4 and 12 months by the procedure previously described [10].

Figure 1 is a probability plot of the SRD data in Table 1 showing that they have the same 4-parameter lognormal distribution as for SIDS. Not shown in Table 1 are 189 SRD and 345 SRD reported in the second and third weeks of life, respectively, and 96 SRD not reported but estimated in the first week of life - corresponding to the three leftmost plotted data points. The median

[1] Table 1 shows the age distribution of these sudden respiratory deaths. The 1965-1976 SRD age data within the original SMPS 45 Table 3 contained two transposition errors (1,032 instead of 1,302 and 583 instead of 538). Burch and Chesters describe these corrected SRD data as "cot deaths" in their 1984 Lancet letter [14] and as SIDS in their 1988 Medical Science Research article [15] - not noting that only approximately 70% of the SRD were likely to have been SIDS. The corrected total numbers of all SRD in SMPS No. 45 Table 3 were 11,212 males and 7,443 females, with male fraction of 0.601 - as expected by Mage and Donner's X-linkage model [24,25] built independently of these data. The male fraction of respiratory hospital deaths certified by coroner 1969-1976 was 2,375 male/3,939 total = 0.603 indicating these deaths may also have been the same phenomenon as the SRD deaths.

$\mu = -1.00$ and $\sigma = 0.316$ are only a few percent different from those for SIDS with $\mu = -1.05$ and $\sigma = 0.290$ [10]. This remarkable similarity is noteworthy because it implies that non-SIDS unexpected sudden infant respiratory home-deaths not only have the same gender distribution as SIDS but they also have the same age distribution as SIDS as required by Cramér's Theorem [11,12]. Therefore these deaths *must* be due to the same underlying process leading to death as SIDS.

Burch and Chesters [14,15] treated these SRD as "crib deaths" or "SIDS." They noted that the male and female SRD age distributions were "strikingly similar" to those of Australian and U.S. SIDS. However, they modeled the SRD and SIDS ages as a Weibull distribution (not a normal transform) that doesn't invoke Cramér's Theorem. A finding that the ~30% of a normal-transform non-SIDS age distribution has the same normal-transform age distribution as the ~70% SIDS could have pointed them towards discovering these causes of death were apparently the same.

2. Secondary SIDS (Osmond and Murphy [17]).

In *BMJ* 1972 [26], Emery and Weatherall made the following proposal concerning Cot Deaths: "We recommend that the information 'sudden death'

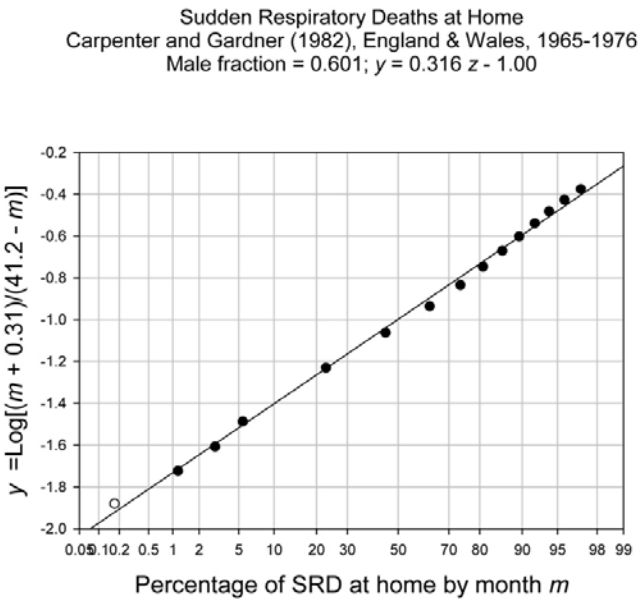

Figure 1. Carpenter and Gardner, Home SRD ages, certified by coroner.

Table 3. Categories of infant sudden respiratory deaths at home (SRD), by International Classification of Diseases (ICD) codes, included in definition of SRD certified by coroner [13].

Cause of Home Sudden Respiratory Death (SRD)	ICD, 7th Revision	ICD, 8th Revision
All respiratory deaths	470-572.2	460 - 519.9
Allergy associated with respiratory system	240, 241	
Pneumonia of newborn	763.0, 763.5	
Sudden death, cause unknown (SIDS)	795.2	795
Accidental mechanical suffocation and inhalation	E921, E924, E925	E911, E913.0, E913.9

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should be put on a death certificate but that it be entered as secondary information [1(b)] to that [non-SIDS] cause [1(a)] which the pathologist considers most likely after all aspects of the case have been considered." These category 1(b) deaths that were called "secondary SIDS" were reported by Osmond and Murphy [17] for the years 1979-1983 in England and Wales as shown in Table 1.

Figure 2 is a probability plot of these data, showing both primary and secondary SIDS have the same slope (σ = 0.295) and virtually the same median (μ = -1.03 and -1.01, respectively). Along with the male fraction of 0.603 similar to that of 0.601 for all sudden respiratory deaths (SRD) in the previous section, the same age distribution means that these primary and secondary SIDS deaths are again a consequence of the same phenomenon.

3. Secondary SIDS, England and Wales, 1986-1992, OPCS Monitor DH3 93/2 23 September 1993, HMSO, London, and Personal Communication 1994 [18].

The U.K. Office of Population Censuses and Surveys (OPCS) reported secondary SIDS in England and Wales, 1986-1992 for 702 cases with gender specified in 690 cases with male fraction of 0.646. The age distribution is shown in Table 1. Figure 3 is the probability plot of these ages showing the same 4-parameter lognormal distribution as SIDS with μ = -0.979 and σ = 0.286 compared to μ = -1.05 and σ = 0.290 for SIDS. The causes of death for these cases are given by OPCS as: Acute bronchitis and bronchiolitis; pneumonia; other respiratory diseases; congenital anomalies; perinatal conditions; injury and poisoning; otitis; mastoiditis; intestinal infection; other infections; bacterial and parasitic diseases; other unspecified causes.

4. Reclassified SIDS from Norway, 1976-1988, Øyen *et al.* [27].

Øyen *et al.* [27] report a thorough detailed study of all possible SIDS cases in Norway during the period 1976-1988. A team of pathologists examined all pathological evidence from such cases and divided them into three groups: Original SIDS [Primary 1(a)]; Reclassified as SIDS [Secondary 1(b)]; and Non-SIDS. The 'reclassified as SIDS' cohort consisted of 567 SIDS-like deaths with previous causes of death assigned to: Aspiration and suffocation; Minor findings of lower respiratory infection; and Nonlethal congenital effects, similar to the causes cited previously by OPCS for the 1986 - 1992 Secondary SIDS [18]. The male fractions of the Original SIDS (0.601) and Reclassified as SIDS (0.610) were virtually the same. The age distributions of the Original and Reclassified SIDS were not provided in the 1994 paper but Øyen (personal communication, 2011) described the age distributions of Original SIDS and Reclassified SIDS as similar, which would match the other cases reported in this paper.

5. SIDS and explained SUDI in England. The CESDI and SWISS studies. [1,19,20]

Leach *et al.* [19] studied SIDS and explained SUDI in 5 areas of England for approximately 3 years, from February 1993 through March 1996 in the National Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI). There were 325 SIDS and 72 explained SUDI, all restricted to ages 7 to 364 days. Those 72 explained SUDI deaths were caused by: congenital anomaly; accident; non-accident injury; metabolic disorder; aspiration of gastric contents; bowel obstruction; bronchopulmonary dysplasia;

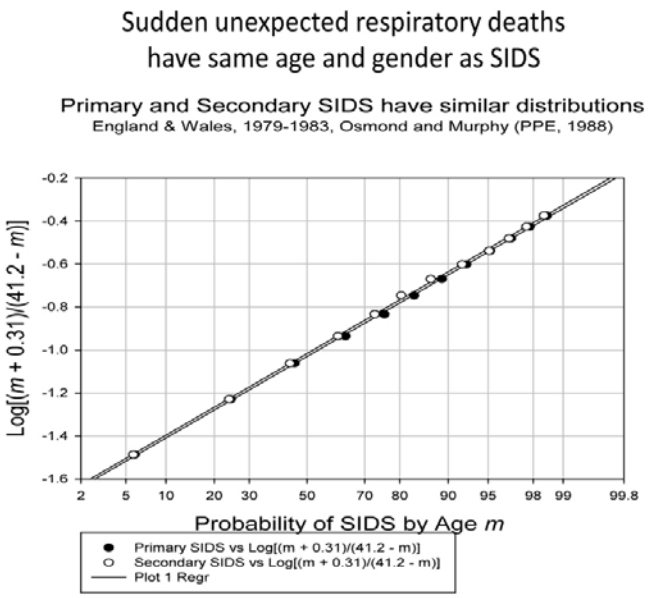

Figure 2. Osmond and Murphy, Primary and secondary SIDS.

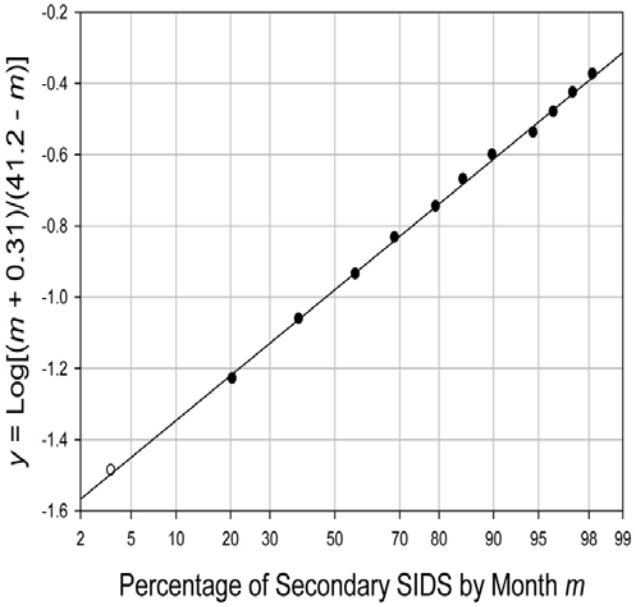

Figure 3. OPCS Monitor, Secondary SIDS.

cardiomyopathy; craniocleidodysostosis; intussusception; and malrotation with volvulus. The combined set of both SIDS and explained SUDI had a male fraction of 249/397 = 0.623, as expected for SIDS.

The age histogram of the CESDI SIDS and explained SUDI data in Table 1 are shown in Figure 4a separately and combined as published in 28-day intervals. Figure 4b shows these data plotted at these thirteen 28-day intervals (not listed in Table 1). Figure 5a shows all 397 CESDI data plotted individually. Four SIDS <7 days are estimated and 31 unreported cases over 1-year are predicted by semilog extrapolation as described above, so N = 432. Note, as

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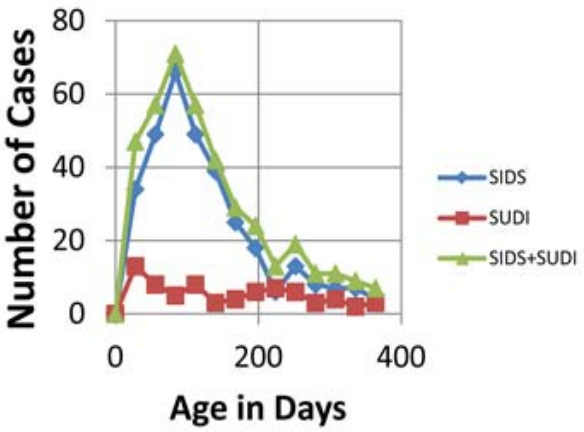

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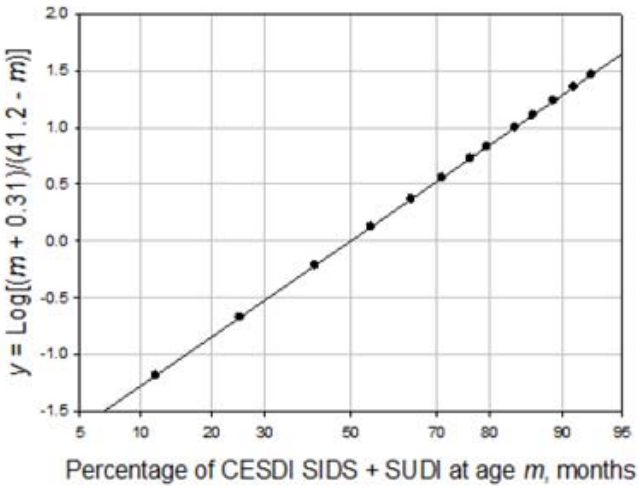
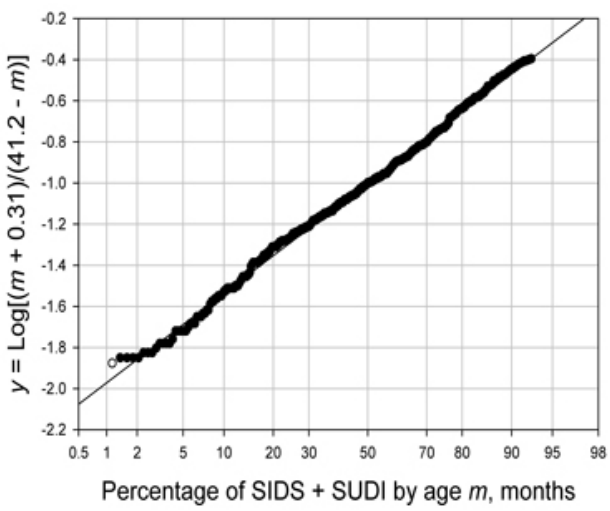


Figure 4. Leach *et al.*, CESDI Histogram and CESDI Probability plot.

a



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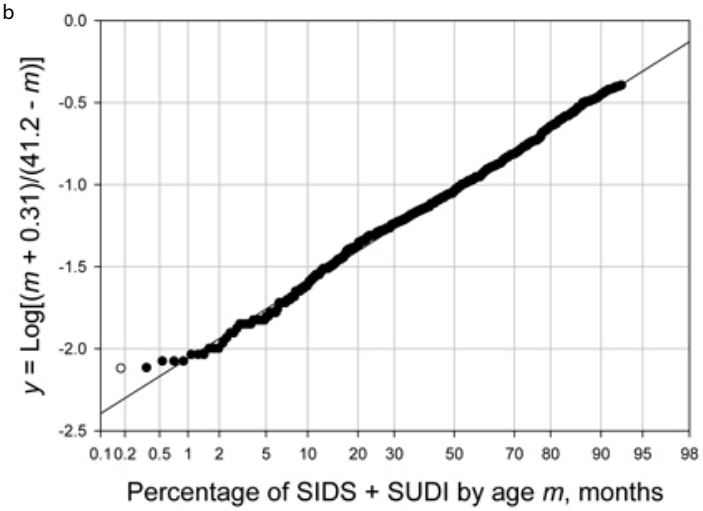

Figure 5. Leach *et al.*, CESDI SIDS+SUDI, daily ages and CESDI + SWISS, SIDS + SUDI, daily ages.

expected, that the slope and intercept from the 13 points spaced at 28 day intervals in Figure **4b** are virtually the same as when all 397 data points are plotted in Figure **5a**.

Sidebotham *et al.* [20] conducted the later South West Infant Sleep Study (SWISS) and reported SIDS and explained-SUDI in an English region. These data are also shown in Table 1 and in Figure **5b** where they are combined with the CESDI study data for N = 539 SIDS + explained-SUDI individually plotted. Almost all the points fall on the straight line with $\mu = -1.03$ and $\sigma = 0.441$. Here the median is the same as SIDS but the slope is ~50% higher than $\sigma = 0.290$ for SIDS.

6. The German SIDS Study (GeSID), SIDS and SUDI data [21].

The GeSID is a comprehensive multi-region study of 456[2] infant deaths, 1998 - 2001, with ages restricted to the 7 to 365 day interval. "All cases were classified into one of 4 categories using defined criteria: 7.3% of the children were assigned to category 1 (no pathological findings: SIDS); 61.1% to category 2 (minor findings: SIDS+); 20.4% to category 3 (severe findings: SIDS++); and 11.2% to category 4 (findings which explained the death: non-SIDS)." Table 1 shows the combined age distribution of all 4 categories by month of life. Figure **6a** shows the Log-probability plot of these data where 43 SIDS over 1 years were estimated by semilog extrapolation of ages 4 to 12 months out to 41 months.

Figure **6b** shows the same data but with all 456 observations plotted per above. Note the median remains constant and the slope changes by about 4%. We note that because of the truncation of the age data at 7 days the lowest points' deviation from the line is maximal so they provide inordinate weight to the regression line (also in Figure **5b**). If 2 cases under 7 days were assumed to have been truncated from the dataset, this would increase the rank of the lowest recorded datum point from 1/499 (0.2%) to 3/501 (0.6%) and this would shift that point to the right, almost onto the regression line.

[2] The article [21] reported on 455 SIDS or SUDI cases with three controls each. One case with 2 controls was not included in that analysis but it's age was available and included in the 456 reported here.

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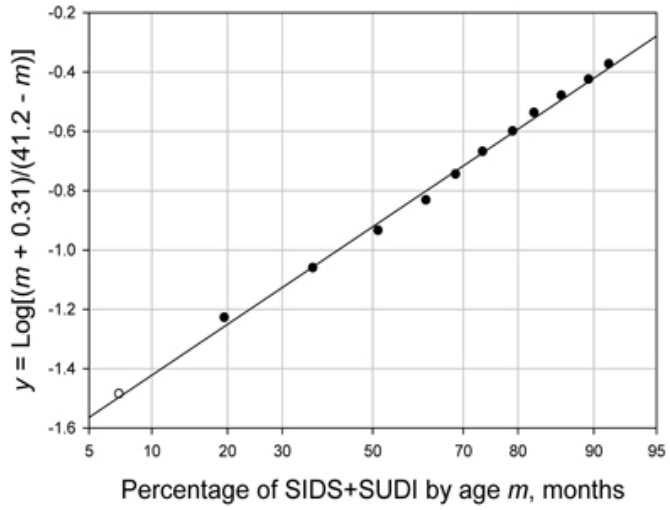

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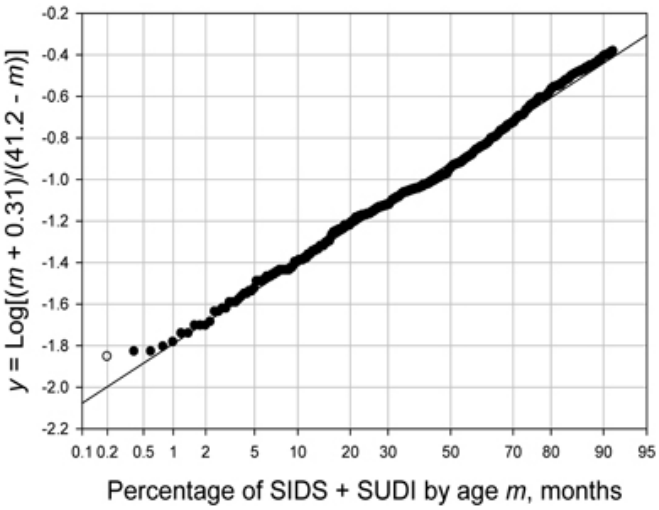

Figure 6. GeSID SIDS + SUDI, monthly ages and GeSID SIDS + SUDI, daily ages.

7. SUID and ASSB data. Shapiro-Mendoza *et al.* [22]

The U.S. CDC [2,3,22] presents the Beckwith-definition SIDS [6] as a subset of SUID. They then divide those cases previously called SIDS [6] into three classes: SIDS; Accidental suffocation and strangulation in bed (ASSB); and Unknown causes (UNK) where an autopsy or a death scene investigation is missing. The ASSB designation appears to be developed to account for the higher risk of the prone sleep position and the belief that "positional asphyxiation" may be a better descriptor than SIDS for such a prone death. Shapiro-Mendoza *et al.* [22] reported the 1,356 ASSB ages at death shown in Table 1 for the U.S. years 2002-2004.

Figure 7 shows the probability plot of these data and its similarity to that for SIDS. The ASSB data have the same age distribution as Beckwith's SIDS, with slope different by 20% and median different by 7%. They have a similar but lower male fraction = 0.573, corresponding to a higher U.S. Black fraction than found in the predominantly White German and U.K. SIDS cohorts [28], indicating that these ASSB and SIDS deaths may also have a similar terminal process.

8. Sudden Respiratory Infant Deaths - Philadelphia, PA, USA, 1995-2009

The Philadelphia, PA, Department of Public Health, Medical Examiner's Office, is responsible for determining cause-of-death for all suspicious, unattended or sudden deaths of children. With IRB approval, de-identified records of all infant/child deaths younger than 7-years of age were examined in two periods, 1995-2002 N = 603 and 2003-2009 N = 578, for cause of death, excluding several non-Philadelphia cases. These two periods spanned the period when the diagnoses of SIDS began to change and SUID, SUDI, positional asphyxia, acute encephalopathy and 'undetermined' began to be accepted as alternatives to SIDS. As shown in Table 4, the numbers of SIDS decreased from 80% to 30% of all infant SRD but the average numbers of SRD remained approximately constant at about 44/year over the 15 year period. The ICD codes for these causes of deaths are determined independently by the Pennsylvania Department of Health before transmitting the records to the U.S. CDC, and these ICD codes are not considered here.

A total of 710 cases with ages between birth (m = 0) and 41.2 months (Table 4) were identified in which the cause of death was judged by us to be primarily respiratory and not due to cardiac causes, trauma or homicide. These cases are similar to, but not the same, as the Sudden Respiratory Death (SRD) as defined by Carpenter and Gardner (1982), discussed above.

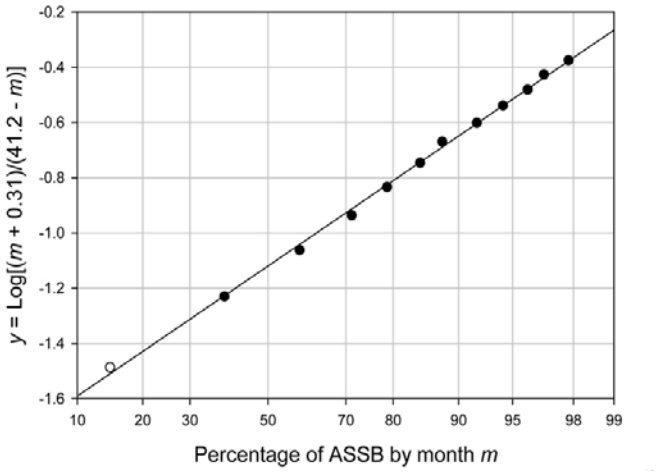

Figure 7. Shapiro-Mendoza, *et al.*, ASSB monthly ages.

Table 4. Autopsied Causes of Sudden Respiratory Infant Deaths in Philadelphia, PA, 1995-2009 N = 670 under 1-year of life (387 male, 283 female, male fraction = 0.578).

Causes of Infant Death in Philadelphia, PA (0 - 41.2 months)	1995 - 2002	2003 - 2009
Sudden Infant Death Syndrome	296	96
Acute Encephalopathy	5	98
Cerebral Anoxia	7	15
Positional Asphyxia	7	11
Undetermined or Unexpected	5	62
Asphyxia, Bronchopneumonia, Pneumonia, Suffocation, CoSleeping, Overlying, Near-miss SIDS, Near-miss Drowning, Airway obstruction, etc.	48 (17 > 1 yr)	60 (23 > 1 yr)
Totals	**368**	**342**

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As indicated in Table 4, 670 SRD cases were under 1-year and 40 cases were over 1 year but less than 41.2 months, the predicted upper age for SIDS based on the Johnson S_B model of ages, as described above [9]. Figure 8 is the Johnson S_B model applied to all 670 <1 year data points but with the semilog-extrapolation procedure in the Methods section predicting 11 observations greater than 1 year consistent with the SRD less than one year shown in Table 1. We consider the 40 cases of potential SRD > 1 year to be a combination of these 11 SRD and 29 non-SRD typical of children > 1-yr. The effect of decreasing the estimated number of SIDS-related cases above 1-year from 40 to 11 is to increase the proportion of SRD under 1-year from 670/710 = 0.944 to 670/681 = 0.983.

The data of Figure 8 are very well fit by the S_B model $y = \text{Log}[(m + 0.31)/(41.2 - m)] = 0.332\ z - 1.12$ which is virtually the same as for the ASSB data reported by Shapiro-Mendoza *et al.* [22] of $y = 0.367\ z - 1.12$ as shown just above in Figure 7. Therefore these different causes of death shown in Table 4 appear to be subsets of SIDS reached by different pathways such as ASSB.

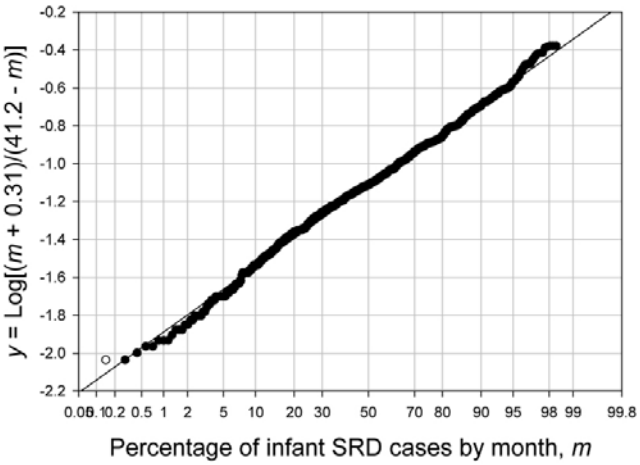

Figure 8. Philadelphia, PA, SRD data, extrapolated > 1 yr.

CONCLUSION

We have reported here datasets of eight studies of infants' deaths that had in common the observation that the deaths were sudden and unexpected (SUDI/SUID) in which either no cause of death could be found (SIDS) or in which a possible cause could be found, with different descriptions such as SRD, SIDS [1(b)], SIDS+, ASSB, Anoxic encephalopathy, Unknown, or explained SUDI. These cases are shown to all be fitted well by a left-censored 4-parameter lognormal distribution (Johnson S_B) bounded between the censor point at birth ($m = 0$) and 41.2 months of life, as $y = \text{Log}[(m + 0.31)/(41.2 - m)]$, normally transformed for uncensored y to be bounded from $-\infty$ to $+\infty$.

We interpret this confluence of SIDS and other classes of sudden unexpected infant deaths as them all being end products of the same terminal process. The infant dies suddenly as a consequence of a process as yet undetermined, brought about by genetic and physiological susceptibility interacting with environmental risk factors and other disease states [9,10,24,25,28]. Whilst it is likely that an important part of the terminal process is acute hypoxic/ischaemic encephalopathy from respiratory or circulatory failure or both, the importance of this analysis is that there is a characteristic age-related vulnerability leading to this lethal process as a consequence of a number of different contributory factors. In different infants the contribution from different factors will be different. In some infants the lethal pathway may be triggered by a confluence of several individually relatively subtle environmental factors (e.g. sleeping position, thermal stress, exposure to tobacco smoke) whilst in other infants the lethal process requires the presence of more easily identifiable contributory factors such as viral or bacterial infections. This hypothesis is in line with the conceptual model, developed by the late John L. Emery [29] shown as Figure 9 (used with permission), that displays the interconnected factors that alone or in combination might lead to that fatal cerebral anoxia. When the same transient but fatal anoxia is caused by numerous factors, each too weak individually to be the explanation by itself, we call it SIDS [i.e., the straws on the proverbial camel's back] - but when one observable factor (e.g., Emery's "hypersensitivity and asthma" and Carpenter and Gardner's "allergy associated with respiratory system" [13]) appears strong enough to create the identical transient anoxia we may give it as the corresponding ICD cause of death.

In the same way that automobile accidents may cause death by different mechanisms (exsanguinations, decapitations, fires, heart attacks, respiratory failures, etc.) an ICD code for a motor vehicle accident is given as the underlying cause, not as the proximate mechanistic cause. In the cases of SUDI and SUID, both at home and in hospital, the underlying cause in each case may be the genetic inability to withstand a transient acute hypoxic/ischaemic encephalopathy requiring a dominant X-linked gene product or enzyme [see Figure 9] that allows anaerobic oxygenation to protect the cardio-respiratory control neurons of the brainstem [24,25] - not the proximate mechanistic cause that brought the infant to that unfortunate terminal event. In terms of public health, the sub-classifications of SIDS discussed here, such as positional asphyxia, may be useful to distinguish the cases of SIDS that could have been prevented by educating the parents to minimize the modifiable risk factors, or treat conditions such as severe physiological anemia, believed to be involved in the causation of the terminal crisis [30].

In conclusion we agree with Byard and have shown that he was quite likely correct when he stated that "SIDS is not so much a diagnosis but a term covering a variety of mechanisms which result in a common lethal outcome" [16].

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Dr. Clive Osmond, MRC Southampton, kindly made available to us as a personal communication, the age and gender by month of life achieved of the Primary SIDS and Secondary SIDS (SUDI) analyzed by Osmond and Murphy in *Pediatric and Perinatal Epidemiology*, 1988 [17]. Dr. Peter S. Blair made available to us the SIDS and SUDI age and gender data for the CESDI and SWISS studies reported here [19,20]. The late Dr. John L. Emery and Academic Press gave us permission to adapt the published Figure of Dr. Emery's SIDS model [29] to the situation we described. We are also grateful to HMSO for the usage of the Crown Copyright materials provided by Drs. Robert Carpenter and Angela Gardner on Sudden Respiratory Deaths (SIDS + SUDI) in England and Wales, 1965-1977 [13], and those found in OPCS Monitor DH3 93/2, 23 September 1993 [18].

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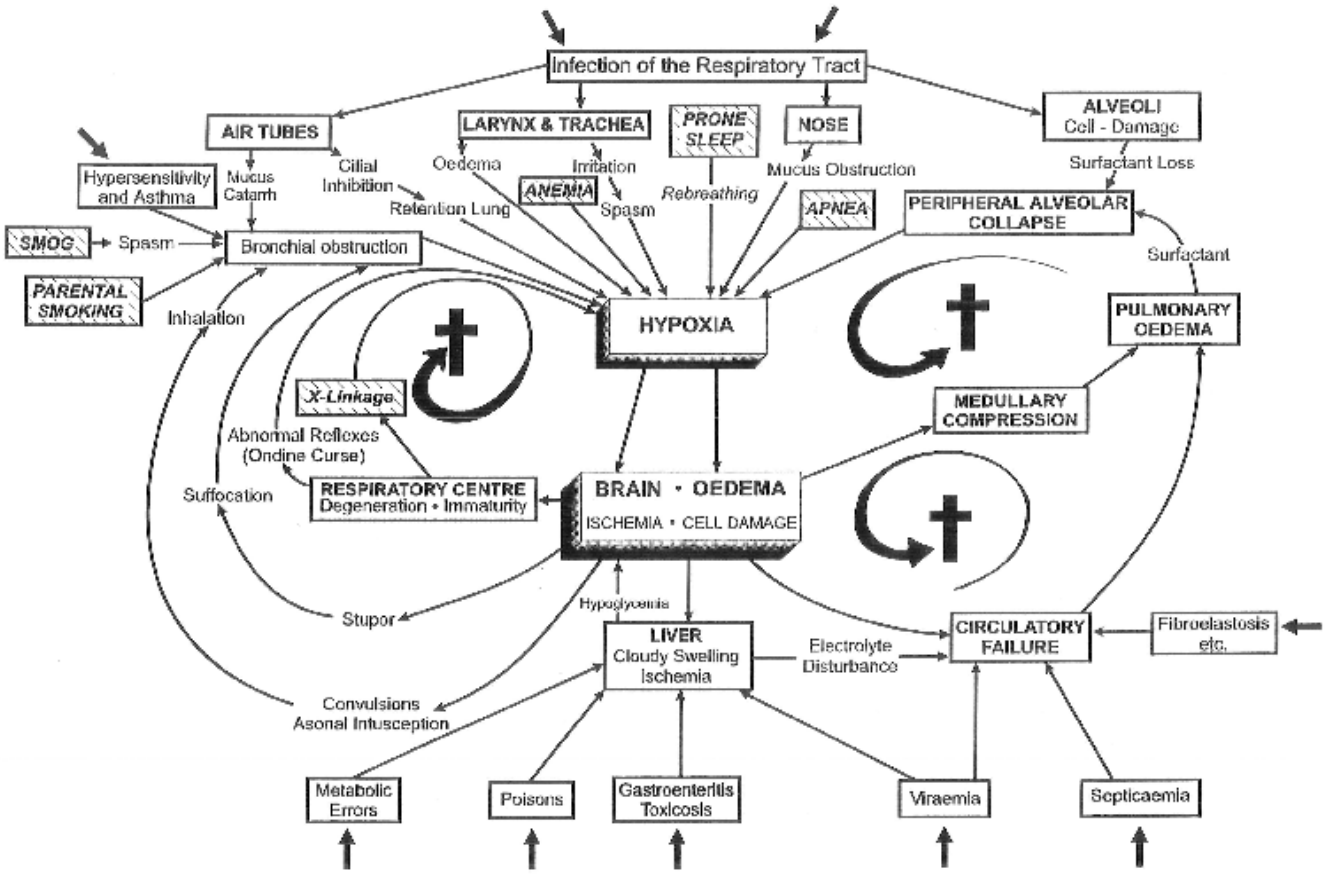

Figure 9. John L. Emery's Conceptual Model for SIDS as modified.

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