SUDDEN INFANT DEATH SYNDROME: MOVING FORWARD

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SUDDEN INFANT DEATH SYNDROME: MOVING FORWARD

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Editorial: Sudden infant death syndrome: Moving forward

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KEYWORDS

sudden infant death syndrome (SIDS), sudden unexpected death in infancy (SUDI), epidemiology, pathophysiology, intervention

Editorial on the Research Topic
Sudden Infant Death Syndrome: Moving Forward

Sudden unexpected death of infants (SUDI) remains a tragedy for hundreds of parents, siblings and families in 2022. It is still one of the leading causes of death between 28 and 360 days of age in high-income countries (1).

Infant mortality is a well-known key indicator of population health. It is strongly related to socio-economic development, quality of preventive and curative care. However, the incidence of SUDI differs greatly among western countries, with great heterogeneity and no evident explanations (2). In the 1990s, great hope was born with the description of the prone sleeping position as a main risk factor of SUDI. However, although the back-to-sleep campaign initially had spectacular impact in limiting death, since 2000, the incidence has stagnated at a too-high level. Some complementary risk factors have been reported since this period, with changeable factors (e.g., sleeping environment, tobacco exposure) as well as non-changeable factors (e.g., sex, prematurity). These different risk factors were combined in the triple risk hypothesis in 1994 (3).

Thirty years after the prone sleeping risk-factor discovery, it is now urgent to investigate new risk factors and understand the current pathophysiology of SUDI to find complementary prevention measures and build large programs to limit avoidable deaths.

In this Research Topic, we are pleased to gather multi-approach research papers with new perspectives and promising international collaborations. The publications provide new insights into epidemiological data and more specifically age-specific risk factors (Kanits et al.); breastfeeding and sleeping practices in The Netherlands, with a warning on a new increase in unsafe habits in the last decade (Kanits et al.); and the mis-opportunity of preventive care in the days before sudden infant death syndrome (SIDS). Indeed, more than 25% of SUDI cases had a healthcare encounter within 7 days of their death, and notably, all unsafe sleep behaviors had increased in frequency before and during the SUDI event as compared to routine (Salada and Badke). This is also a warning for the increased risk of SIDS when there is a combination

of maternal alcohol, tobacco, and recreation drug use and bed sharing (Hauck and Blackstone). We also published a literature review on the interventions for safer sleep practices showing that information-exchange personalized models are the most effective interventions (Ellis et al.). Concerning the pathophysiological mechanisms, anatomical characteristics such as ogival palate is frequently observed in SUDI, which suggests chronic obstruction as an additional risk factor (Ducloyer et al.) Also, at the molecular level, the serotoninergic system and maturation of histaminergic systems (Plancoulaine et al.) have been deciphered, with different subtypes of observed cardiorespiratory and arousal deficits (Haynes et al.). Another review reports that thermal stress can alter cardiovascular and respiratory functions and lead to life-threatening events (Bach and Libert). These functions could be explored with new tools to assess newborns' autonomous reactivity and identify children at high risk of SIDS (Patural et al.).

A multitude of questions still remain.

1) What pathophysiological mechanisms and pathways are involved?
2) Why are there such geographic variations in SUDI incidence?
3) What is the relative responsibility of genetics, infections, toxicological or drug exposure?
4) Why do so many infants still sleep in the prone position 30 years after back-to-sleep campaigns? What are the current breaks in guidelines' implementation and how can we improve their acceptability?
5) What place do biomarkers, medical software solutions, and health digital learning have in prediction and prevention?
6) What are the perspectives for consolidating and developing international registers and collaborative databases?

And many others …

SUDI today must be considered a priority Research Topic and involve physicians, scientists, teachers, childcare professionals and family associations altogether. SUDI should no longer be a fatality but rather become a preventable accident with evidence-based prevention measures shared by all child carers.

Author contributions

CG-L, PF, and SP contributed to the redaction of this editorial and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Risk and Preventive Factors for SUDI: Need We Adjust the Current Prevention Advice in a Low-Incidence Country

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Background: The incidence of Sudden Unexpected Death in Infancy (SUDI) is low in the Netherlands, with an incidence rate of 0.18 per 1,000 live births. Therefore, prevention advice may receive less attention, potentially leading to increasing incidence rates. It is currently unknown whether the risks for SUDI changed in the Netherlands, and if other risk factors might be present. The aim of this study was to examine the current risks and preventive factors for SUDI in Dutch infants, in order to determine if it is necessary to adapt the prevention advice toward the current needs.

Methods: A case-control study was conducted comparing SUDI cases aged <12 months from 2014–2020 in the Netherlands ($n = 47$), to a Dutch national survey control group from 2017 including infants <12 months of age ($n = 1,192$).

Results: Elevated risks for several well-known factors were observed, namely: duvet use (aOR = 8.6), mother smoked during pregnancy (aOR = 9.7), or after pregnancy (aOR = 5.4) and the prone sleeping position (aOR = 4.6). Reduced risks were observed for the well-known factors: room-sharing (aOR = 0.3), sleep sack use (aOR = 0.3), breastfeeding (aOR = 0.3), and the use of a pacifier (aOR = 0.4). For infants <4 months, the risk for SUDI was higher when bed-sharing (aOR = 3.3), and lower when room-sharing (aOR = 0.2) compared to older infants. For older infants, the sleep sack was found to be more protective (aOR = 0.2). A high risk for SUDI when bed-sharing was found when mother smoked, smoked during pregnancy, or if the infant did not receive any breastfeeding (respectively aOR = 17.7, aOR = 10.8, aOR = 9.2).

Conclusions: Internationally known factors related to the sudden unexpected death of infants were also found in this study. Relatively new findings are related to specific groups of infants, in which the strengths of these risk factors differed. In a low-incidence country like the Netherlands, renewed attention to the current prevention advice is needed. Furthermore, additional attention for prevention measures in low educated groups, and additional advice specifically targeting high-risk groups is recommended.

Keywords: SIDS (sudden infant death syndrome), SUDI (sudden unexpected death in infancy), incidence, risk factors, preventive factors, high-risk groups, prevention advice

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INTRODUCTION

Sudden Unexpected Death in Infancy (SUDI) is a broad term used to describe the sudden unexpected death of an infant without an apparent cause, which includes Sudden Infant Death Syndrome (SIDS). SIDS is "the sudden unexpected death of an apparently healthy infant under one year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy with ancillary testing, examination of the death scene, and review of the clinical history," and often occurs during an unobserved sleep period (1, 2). Taylor et al. (3), proposed a set of six codes from the International Classification of Diseases-10 (ICD-10), to encompass the majority of SUDI in eight high-income countries, to ensure better international comparison. This set includes SIDS (R95), and for example accidental suffocation or strangulation in bed (W75) and other ill-defined and unspecified causes (R99).

Both the incidence of SIDS and SUDI have largely declined in high-income countries since the 1980s, when the advice was given not to place infants to sleep prone (4). Between 2002 and 2010, low incidence rates were observed in the Netherlands (0.19 per 1,000 live born infants) (3). Nevertheless, 31 infants died suddenly and unexpectedly in 2019, of which 13 were classified as SIDS (5). The loss of a child is considered among the worst experiences in life, and the traumatic aspect of the unexpected death leads to great parental grief and psychological burden (6). Parents experience intense feelings of responsibility and failure in their role as parents, and most of these difficulties are under-recognized and unaddressed.

Various risk factors, as well as preventive factors for SUDI have been recognized internationally over the years (7). These findings have been incorporated in specific prevention programs, which have contributed greatly to the decrease in incidence. Risk factors can be divided in unavoidable and avoidable factors. Unavoidable risk factors are the infant's young age, male gender, being second or later born, and born small for gestational age and/or prematurely. Potentially avoidable risk factors include the prone and side sleeping position, unsafe bedding, parental smoking, and unsafe sleeping places, including bed-sharing. Preventive factors include breastfeeding, appropriate sleep sack use, consistent pacifier use, and room-sharing in a separate bed. These factors are incorporated in the Dutch guideline for the prevention of SUDI (8). The most recently updated prevention campaign in The Netherlands is that of The Dutch Consumer Safety Institute (Veiligheid NL), which focuses on "The four of Safe Sleeping": sleeping supine, in an own cot or crib, in a well-fitting sleep sack, and in an empty bed without soft materials (9).

SUDI prevention advice in the Netherlands is successively offered by the midwife, the maternity nurse and the preventive child healthcare physician and nurse, and is characterized by a continuous supply of information and care. The organization and approaches of youth healthcare (YHC) differ between countries (10). In the Netherlands, the YHC includes free governmentally established preventive care for all children 0–18 years of age, provided by professionals who monitor growth and development of children, and carry out the vaccination program. With regard to the first year of life, infants and their parent(s) have 6–8 consultations with the preventive child healthcare center (PCHC). PCHC attendance during the first year of life is high in the Netherlands. This preventive system, together with obstetric and maternity care, offers many opportunities to interact with parents about infant care practices.

Since the incidence of SUDI is low in the Netherlands, attention for prevention can fade among parents and (professional) caregivers, as well as in governmental organizations and (public) health professionals, potentially leading to increasing incidence rates. Furthermore, parental behavior changes over time, and new trends regarding infant care arise. In 2007, the original 1996 consensus statement on SIDS prevention was rewritten into a prevention guideline. This guideline was revised in 2009 and a multidisciplinary national cooperation agreement was written in 2017 to aid implementation. The main messages remained unchanged. Studies are needed to determine if it is necessary to adapt the prevention advice toward the current needs. Therefore, this study aimed to identify risk and preventive factors for SUDI and their prevalence in Dutch infants under 12 months of age in the period 2014–2020, and to explore these factors in high-risk groups.

MATERIALS AND METHODS

A case-control study was conducted comparing SUDI cases aged 0–12 months from 2014 to 2020 in the Netherlands, to a national survey control group from 2017.

Data Collection

The case group consisted of SUDI cases aged 0–12 months who died in the period 2014 up to 2020 in the Netherlands, and were reported to the SUDI Expert Group of the Dutch Pediatric Society. The Expert Group consists of a group of pediatricians, pathologists, a pediatric cardiologist, pediatric physiotherapist, youth health doctor/epidemiologist, biologist, and a psychotherapist, who review the reported SUDI cases. Classification of these cases is based on the Avon clinico-pathological system (11). Upon consent of the parents, the pediatricians visit the families of reported SUDI cases a few weeks after their loss, and fill in an extensive questionnaire together with the parents. The Expert Group has registered these data in a database since 1996.

Data of an unmatched control group were retrieved from a Dutch national survey on safe sleeping conditions in 2017 (12). For this survey, parents with an infant under 12 months old were asked to fill in an online survey via a link on a flier that was distributed among 139 PCHCs. To also include a representative number of respondents with lower socioeconomic status (SES), 21 PCHCs in areas of low SES were selected to also conduct paper questionnaires. Furthermore, via online media, parents were asked to fill in the online survey.

Previous approval process allow for the use of this de-identified data from both cases and controls.

Data Assessment

For all cases and controls, the mother's migration background was defined by the country she was born in, and categorized as either Dutch or non-Dutch. The mother's education level, as indicator of SES, was defined by the highest educational level attained, categorized as low, middle, or high, based on the division used in the Netherlands (13).

Unavoidable risk factors for SUDI, including infant age in months, gender, birth rank and birthweight, were assessed among cases and controls. Birth rank indicates either the first, second, or third or later born infant of the mother. Birthweight was dichotomized into under 2,500 grams (low), or 2,500 grams or higher (normal). Avoidable risk factors and preventive factors for SUDI that were assessed included: sleeping position, bed-sharing, room-sharing, duvet use, sleep sack use (wearable blanket), pacifier use, breastfeeding and maternal smoking both during and after pregnancy.

Sleeping position, i.e., placed to sleep in the prone, side or supine position, was assessed for last night (controls), or last time before death (SUDI cases). Bed-sharing was defined as sleeping with one or both parents in bed for most of the last night (controls), and sharing the sleep-surface with one or both parents when the infant was found dead (SUDI cases). The type of bedding, including a duvet and sleep sack, the infant was covered with last night was assessed for controls, and for cases it was the type of bedding when found deceased. Room-sharing for controls was assessed by the sleeping place where the infant slept most of last night, including sleeping in the parents' bedroom in an own crib or cot, or in a co-sleeper. For the cases this was assessed by the infant sleeping in the parents' bedroom, but not bed-sharing, during the last sleep. Pacifier use was assessed regarding the usual way the infant was placed to sleep for both cases and controls. Infant feeding type and smoking of the mother were assessed at the time of filling out the questionnaire for controls, whereas for the SUDI cases this was around time of death. Breastfeeding included both exclusive breastfeeding, and breastfeeding supplemented with formula feeding. Lastly, maternal smoking during pregnancy was asked for both cases and controls.

Data-Analysis

As the control population comprised a relatively high number of highly educated parents, data of the 2017 survey were weighted according to the education level distribution of women aged 25–45 in 2017, as retrieved from the Central Bureau of Statistics Netherlands (14). This resulted in the following weighting factors: 0.936 for low education level; 1.292 for medium education level; and 0.867 for high education level.

Firstly, background characteristics of SUDI cases and their weighted survey controls were generated. Secondly, prevalence of risk and preventive factors among both cases and controls were presented. With Logistic Regression analyses, Odds Ratios (ORs) with 95% Confidence Intervals (CI) were calculated. Adjusted ORs (aORs) were calculated to correct for potential confounding of non-modifiable factors related to SUDI risk (age, gender, birthweight and birth rank). Data on aORs, combined with the prevalence of the risk factor or inverse prevalence of the preventive factor among SUDI cases, were used to calculate the Population Attributable Fraction (PAF) with the formula: $\boldsymbol{PAF = \frac{(OR-1)}{OR} \times prevalence}$. By explaining the theoretical percentage of SUDI cases in the total population that could be attributed to the specific risk or preventive factor, the PAF provides an estimation of the relative impact on SUDI incidence that could be achieved if the risk were reduced or eliminated, while all other factors remained constant. Specific groups of infants are known to be at higher risk of SUDI when exposed to certain risk factors, and the current prevention advice might need specification for these groups. Therefore, stratified risks (ORs and aORs with 95% CIs) were calculated for infants <4 months and ≥ 4 months, and for infants with low and normal/high birthweight. Furthermore, the risk of bed-sharing was separately explored over various strata, as it is still unclear whether specific groups are at higher risk of SUDI when bed-sharing compared to others.

RESULTS

Between 2014 and 2020, 56 SUDI cases were reported to the Expert Group. Nine cases were excluded because of: missing date of birth (13); over 12 months of age (4); a cause of death was subsequently found (15). Therefore, 47 SUDI cases were included in this study.

Parents of 1,209 infants participated in the national survey on safe sleeping in 2017. After weighing for education level, 1,192 controls could be used for analyses. Characteristics of the 47 cases and 1,192 weighted controls are presented in **Table 1**. Mean age of controls was slightly older than that of cases. Furthermore, cases were more often boys, second or later born and born with low birthweight. Mothers of cases were more often non-Dutch, and lower educated compared to the mothers of controls.

Table 2 shows ORs and PAFs for risk and preventive factors for SUDI. All studied risk factors were found to have a higher prevalence among SUDI cases compared to controls in univariate analyses, except for the factor placed in the side sleeping position. No significantly elevated risk was found for bed-sharing in the total group. The risk of SUDI for an infant placed to sleep in the prone position was 4.6 (2.1–10.3) times as high as the risk for infants placed supine. Data suggest that around 21% (PAF% = 21.4) of the SUDI cases could possibly have been prevented if these infants had been placed supine. As over one third of mothers of SUDI cases smoked either during or after pregnancy, and aORs were respectively 9.7 (4.6–20.4) and 5.4 (2.6–11.4), high PAFs of respectively 31.3 and 28.4% were found.

All studied potential preventive factors were found to have lower prevalence among SUDI cases compared to controls. Combining ORs with the prevalence of not performing the preventive behavior resulted in varying PAFs. The highest PAF was found for room-sharing, where, if all infants had slept in the parents' bedroom, but not in the parental bed, potentially 57% of cases could have been prevented [aOR room-sharing 0.3 (0.1–0.6)]. The lowest PAF was found for infants usually not placed to sleep with a pacifier, where the PAF was almost 34%. Infants

TABLE 1 | Characteristics of cases and controls.

		Cases *n* = 47		Controls *n* = 1,192	
Age^		3.4 ± 2.7		5.1 ± 3.4	
Gender	Boy	28	(59.6%)	586	(49.2%)
	Girl	19	(40.4%)	605	(50.8%)
Birth rank	First	14	(32.5%)	658	(55.2%)
	Second	21	(47.5%)	375	(31.5%)
	Third or more	9	(20.0%)	159	(13.3%)
Birthweight	≥2,500 g	38	(80.9%)	1,143	(95.9%)
	<2,500 g	9	(19.1%)	49	(4.1%)
Migration background mother	Dutch	34	(77.3%)	1,032	(87.0%)
	Non-Dutch	10	(22.7%)	154	(13.0%)
Education level mother	Low	6	(15.0%)	157	(13.2%)
	Middle	19	(47.5%)	443	(37.2%)
	High	15	(37.5%)	591	(49.6%)

Frequency and percentage of population with non-missing data for respective factors are presented. Controls are weighed for maternal education level.
^Age is presented as mean ± standard deviation.

TABLE 2 | Prevalence in cases and controls of known risk and preventive factors for SUDI, Odds Ratio (OR), both crude and adjusted, and the Population Attributable Fraction (PAF) for the aOR.

	Cases *n* = 47	Controls *n* = 1,192	OR	Adjusted OR*	PAF (%)
Risk factors					
Position placed to sleep *prone vs supine*	12 (27.3%)	105 (8.9%)	3.9 (1.9–7.8)	4.6 (2.1–10.3)	21.4
side vs supine	3 (6.8%)	99 (8.4%)	1.0 (0.3–3.4)	1.0 (0.3–3.4)	-
Bed-sharing *yes vs no*	7 (16.3%)	118 (10.0%)	1.8 (0.8–4.0)	2.0 (0.8–4.7)	8.2
Duvet *yes vs no*	10 (24.4%)	55 (4.6%)	6.6 (3.1–14.2)	8.6 (3.7–20.2)	21.6
Mother smoked during pregnancy *yes vs no*	15 (34.9%)	47 (3.9%)	13.1 (6.5–26.1)	9.7 (4.6–20.4)	31.3
Mother smokes after pregnancy *yes vs no*	15 (34.9%)	78 (6.6%)	7.6 (3.9–14.8)	5.4 (2.6–11.4)	28.4
Preventive factors					
Sleep sack *yes vs no*	9 (24.3%)	657 (55.1%)	0.3 (0.1-0.6)	0.3 (0.1-0.7)	52.0
Breastfeeding *exclusive/mixed vs none*	12 (26.7%)	494 (41.6%)	0.5 (0.3-1.0)	0.3 (0.2-0.7)	48.9
Room-sharing, not bed *yes vs no*	10 (21.7%)	362 (30.6%)	0.6 (0.3–1.3)	0.3 (0.1–0.6)	57.1
Usually pacifier *yes vs no*	17 (43.6%)	699 (58.7%)	0.5 (0.3–1.0)	0.4 (0.2–0.8)	33.8

**Adjusted for infant age, gender, birthweight and birth rank. Due to adjustment, a maximum of two extra missing cases was present per factor.*

usually provided with a pacifier when placed to sleep had 0.4 (0.2–0.8) times the risk of SUDI compared to those without. Infants sleeping in a sleep sack or receiving any breastfeeding had 0.3 times the risk of SUDI (95% CI 0.1–0.7 and 0.2–0.7 respectively) compared to infants who did not.

To explore risk factors (placed prone, bed-sharing, duvet) and preventive factors (sleep sack, room-sharing, pacifier) in specific groups of infants for which the current prevention advice may require specification, stratified analyses were performed and results are summarized in **Table 3**. For infants under the age of 4 months, the risk of SUDI when placed in the prone position was 6.9 (2.0–23.9) times as high as when placed supine, and 12.6 (0.9–168.3) times as high for infants with a birthweight under 2,500 grams. While there was no strong evidence for an

increased risk of SUDI when bed-sharing for the total group, a high risk was found for infants under the age of 4 months [aOR = 3.3 (1.1–9.3)], for infants who did not receive any breastfeeding [aOR = 9.2 (3.0–28.6)], and for infants whose mother smoked after pregnancy [aOR = 17.7 (1.9–162.8)] or during pregnancy [aOR = 10.8 (1.4–81.3)] (**Supplementary Table 1**). Furthermore, a high risk for duvet use was observed in both the younger infants, and those with low birthweight. The preventive effect of a sleep sack was found to be greater among infants 4 months of age and older [aOR = 0.2 (0.1–0.6)], compared to infants aged under 4 months [aOR = 0.5 (0.1–2.0)]. These infants under the age of 4 months also had 0.2 (0.0–0.5) times the risk of SUDI when room-sharing, which was lower than 0.6 (0.2–2.2) times the risk for the older infants.

DISCUSSION

In the current study, risk and preventive factors for SUDI and their prevalence in Dutch infants under 12 months of age were identified for the period 2014–2020. Significantly elevated risks were found for infants placed under a duvet, infants whose mother smoked pre- and/or postnatally, and infants placed in the prone sleeping position. Significantly reduced risks were found for room-sharing, sleeping in a sleep sack, breastfeeding, and the usual use of a pacifier. These are internationally known factors related to the sudden unexpected death of infants (7, 16–20).

Relatively new is that the strengths of these risk factors differed among specific groups of infants. A high risk of SUDI was found for infants under 4 months of age when placed prone, bed-sharing or placed under a duvet. In these young infants, room-sharing with parent(s) greatly reduced the risk. Infants aged 4 months and older benefit most from the preventive effect of a sleep sack. For infants born with low birthweight (under 2,500 grams), sleeping in the supine position is particularly important as they are at higher risk for SUDI when placed prone. For the total group of infants, there was no strong evidence for an increased risk of SUDI when bed-sharing. However, a significantly high risk was found for young infants, infants whose mother currently smokes, or smoked during pregnancy, and infants not receiving any breastfeeding.

Besides ongoing attention for the current prevention advice, additional focus should be on risk factors with the most impact on the population risk of SUDI, assessed by the PAF which is a combination of the OR and the prevalence of the risk factor. According to the results of this study, several SUDI cases could possibly have been prevented by room-sharing of parent(s) and infant, and by placing the infant to sleep in a sleep sack. Therefore, additional attention is necessary regarding room-sharing, especially with infants under 4 months of age, and the use of a sleep sack, especially for infants over 4 months of age.

Compared to an earlier Dutch study in the period 1996–2001 (21), the magnitude of risk increasing and preventive factors in the current study varies, but with overlapping confidence intervals. In terms of preventive factors, in the current study a stronger preventive effect was seen for sleeping in a sleep sack (aOR 0.3 vs. 0.7), for breastfeeding (aOR 0.3 vs. 0.5), and for pacifier use (aOR 0.6 vs. 1.0), compared to the earlier study. Data on room-sharing were not reported by De Jonge et al. (21). In the Netherlands, the use of sleep sacks and pacifiers has increased over the past decades, as can be observed from the data of the control populations (21). In terms of risk factors, now a higher risk of SUDI was found compared to the earlier study for sleeping prone (aOR 4.6 vs. 3.0), placed under a duvet (aOR 8.6 vs. 3.9), and smoking after pregnancy (aOR 5.4 vs. 2.7). The estimated risks for bed-sharing were comparable. No notable differences in the prevalence of prone sleeping and bed-sharing between the control populations of both studies were observed, but the use of a duvet and smoking of parents were much lower in 2017 compared to the earlier study (21).

The association between bed-sharing and SUDI is subject of international debate. Although there was no strong evidence of an increased risk of SUDI for the total group in the current study when bed-sharing, the risk was estimated to be extremely high in different sub-groups, and therefore still of major concern. The prevalence of bed-sharing in the parents' bed increased in the period 2002-2017 in the Netherlands (12, 22). This is especially of concern for infants under 4 months, where the associated risk of SUDI is higher, and the prevalence of bed-sharing was 9.1% in 2017. The risk of bed-sharing was also higher for infants whose mother smoked. Similar results were found in a case-control study combining individual data from a European, Scottish, New Zealand, Irish and German database (23). The same study also showed an increased risk of SUDI when bed-sharing with a parent who used alcohol or drugs (23). As this information was lacking in the current study, we weren't able to confirm this. Furthermore, the risk of bed-sharing in the current study was increased among formula fed infants. There was no significant risk associated with bed-sharing among breastfed infant, but numbers are very small. In the Netherlands, breastfeeding prevalence is higher among high educated mothers (90% at birth, and 51% at 5 months after birth) compared to low educated parents (69% at birth, 33% at 5 months after birth) (24). Also, smoking is more prevalent among low educated people (age 25–44: men 55%, women 40%) compared to high educated people (age 25–44: men 17%, women 13%) (15). This indicates a cumulation of risk factors (no breastfeeding and smoking) in lower educated parents, and thereby an increased risk when bed-sharing, making this an important target group for specific SUDI prevention strategies.

Most factors found in this study point in the direction of accidental suffocation, or accidental asphyxia contributing to the sudden death of an infant. Physiological studies indicate that facial obstruction in infants by e.g., soft bedding or lying face straight down, may lead to complete upper airway obstruction and/or accidental suffocation by rebreathing, and/or overheating (25). In these cases, it might be assumed that the airway-protective components of the infant's arousal response failed (26). It is known that maternal smoking impairs infant arousal processes (27), and higher arousal thresholds are also found among preterm born infants, infants sleeping prone, infants that

TABLE 3 | Prevalence in cases and controls of known risk and preventive factors for SUDI, stratified for age and birthweight, and the Odds Ratio (OR), both crude and adjusted in these strata.

	Cases	Controls	OR	Adjusted OR*
Risk factors				
Position placed to sleep *prone vs supine*	12 (27.3%)	105 (8.9%)	3.9 (1.9–7.8)	4.6 (2.1–10.3)
Age <4 mo	5 (21.7%)	23 (4.8%)	6.0 (2.0–17.9)	6.9 (2.0–23.9)
Age ≥4 mo	7 (33.3%)	82 (11.6%)	3.4 (1.4–8.8)	3.5 (1.2–10.3)
Birthweight <2,500 gr	2 (22.2%)	3 (6.3%)	4.1 (0.6–28.3)	12.6 (0.9–168.3)
Birthweight ≥2,500 gr	10 (28.6%)	101 (8.9%)	4.0 (1.9–8.7)	4.3 (1.8–10.1)
Bed-sharing *yes vs no*	7 (16.3%)	118 (10.0%)	1.8 (0.8–4.0)	2.0 (0.8–4.7)
Age <4 mo	6 (26.1%)	44 (9.1%)	3.5 (1.3–9.4)	3.3 (1.1–9.3)
Age ≥4 mo	1 (5.0%)	75 (10.6%)	0.4 (0.1–3.4)	0.5 (0.1–4.2)
Birthweight <2,500 gr	1 (11.1%)	3 (6.2%)	1.9 (0.2–20.4)	1.4 (0.1–21.9)
Birthweight ≥2,500 gr	6 (17.6%)	115 (10.2%)	1.9 (0.8–4.7)	2.0 (0.8–5.0)
Duvet *yes vs no*	10 (24.4%)	55 (4.6%)	6.6 (3.1–14.2)	8.6 (3.7–20.2)
Age <4 mo	7 (30.4%)	12 (2.5%)	16.6 (5.8–47.5)	17.6 (5.3–57.8)
Age ≥4 mo	3 (16.7%)	43 (6.1%)	3.1 (0.9–11.2)	5.6 (1.4–22.4)
Birthweight <2,500 gr	3 (42.9%)	2 (4.1%)	16.2 (2.1–122.6)	386.5 (2.0–74,013.4)
Birthweight ≥2,500 gr	7 (20.6%)	53 (4.6%)	5.3 (2.2–12.8)	7.1 (2.8–18.1)
Preventive factors				
Sleep sack *yes vs no*	9 (24.3%)	657 (55.1%)	0.3 (0.1–0.6)	0.3 (0.1–0.7)
Age <4 mo	3 (15.8%)	141 (29.2%)	0.5 (0.1–1.6)	0.5 (0.1–2.0)
Age ≥4 mo	6 (33.3%)	516 (72.7%)	0.2 (0.1–0.5)	0.2 (0.1–0.6)
Birthweight <2,500 gr	0 (0.0%)	26 (54.2%)	-	-
Birthweight ≥2,500 gr	9 (29.0%)	631 (55.2%)	0.3 (0.2–0.7)	0.4 (0.2–1.0)
Room-sharing, not bed *yes vs no*	10 (21.7%)	362 (30.6%)	0.6 (0.3–1.3)	0.3 (0.1–0.6)
Age <4 mo	6 (25.0%)	246 (51.5%)	0.3 (0.1–0.8)	0.2 (0.0–0.5)
Age ≥4 mo	4 (18.2%)	116 (16.5%)	1.1 (0.4–3.4)	0.6 (0.2–2.2)
Birthweight <2,500 gr	5 (55.6%)	14 (29.0%)	3.1 (0.7–13.1)	1.3 (0.2–7.6)
Birthweight ≥2,500 gr	5 (13.5%)	348 (30.7%)	0.4 (0.1–0.9)	0.2 (0.1–0.5)
Usually pacifier *yes vs no*	17 (43.6%)	699 (58.7%)	0.5 (0.3–1.0)	0.4 (0.2–0.8)
Age <4 mo	9 (45.0%)	303 (62.9%)	0.5 (0.2–1.2)	0.4 (0.1–1.0)
Age ≥4 mo	8 (42.1%)	396 (55.9%)	0.6 (0.2–1.4)	0.4 (0.1–1.0)
Birthweight <2,500 gr	3 (50.0%)	31 (63.3%)	0.6 (0.0.1–3.2)	0.4 (0.0–2.8)
Birthweight ≥2,500 gr	14 (42.4%)	669 (58.5%)	0.5 (0.3–1.1)	0.4 (0.2–0.8)

**Adjusted for infant age, gender, birthweight and birth rank. N cases: total = 47, <4 mo = 25 (53.2%), ≥4 mo = 22 (46.8%), <2,500 gr = 9 (19.1%), ≥2,500 gr = 38 (80.9%) N controls: total = 1,192, <4 mo = 482 (40.5%), ≥4 mo = 710 (59.5%), <2,500 gr = 49 (4.1%), ≥2,500 gr = 1,143 (95.9%).*

are too warm/overheated and among formula-fed infants (28). Some SUDI cases while bed-sharing might be designated as accidental suffocation in bed (29). For infants under 4 months of age, this can be the case as they lack motor skills to escape potential threats in the parents' bed, when for example being covered with soft bedding (29). Well-developed upper airway muscle tone might contribute to the prevention of airway obstruction in hazardous situations, which might be stimulated by breastfeeding and pacifier sucking (30–32). Furthermore, overlaying when sharing a surface can obstruct the airways either directly, or by inadvertent pressure on the infant's lower jaw (33).

The prone sleeping position is a well-known risk factor for SUDI. Studies also identified a similar risk of the side sleep position, likely because many infants who are placed on their side can roll to the prone position, or lay with their face against (soft) bed material. Nevertheless, no elevated risk for infants being placed in the side position compared to the supine position was found in the current study. Infants with a birthweight under 2,500 gram, i.e., those born small for gestational age and/or prematurely are at higher risk when sleeping prone. The AAP guideline advises to "keep hospitalized preterm infants predominantly in the supine position, at least from 32 weeks

gestational age onwards, so that they become acclimated to supine sleeping before discharge" (16). It would be insightful to gather data if this guideline is adhered to in the Netherlands. If not, it offers opportunity for extra targeted prevention through neonatal and newborn units.

Both the use of a pacifier, and the use of a sleep sack can reduce the risk of SUDI, which may be reflected by the same mechanism of preventing infants from turning to the prone position in their cot or crib. Around the age of 5 months, most infants start rolling from the supine to the prone position, but may still have problems rolling back. This can explain the lower risk of SUDI among infants over 4 months old placed in a sleep sack, compared to younger infants: a sleep sack can delay turning over to the prone position as it hampers the infant slightly, especially in using their legs as a fulcrum to turn (34). Consistent use of a pacifier may soothe the infant and support falling asleep, whereby turning prone might be inhibited. It is also suggested that pacifier sucking improves airway stabilization, and thereby contribute to the prevention of SUDI (35). It should be noted that it is important that the pacifier is used consistently with every sleep (36).

Strengths and Limitations

A strength of this study is that we were able to assess multiple risk and preventive factors for SUDI among both cases and controls. The Dutch practice of having SUDI cases and their families visited at home by an Expert group pediatrician who interviews the parents and conducts an extensive questionnaire, has resulted in detailed information of the included cases. The 2017 survey used for the control population included comparable questions, which allowed for a good comparison between the groups. The control population was a good representative of the general Dutch population, however, slightly more first born infants and less infants with a non-Dutch mother were included (12).

A limitation of this study is that the size of the case group is rather small. This is mainly due to the low incidence of SUDI in the Netherlands. Furthermore, SUDI cases are only reported to the SUDI expert group when parents give their consent to a visit of one of the members. As not all parents provide consent, not all SUDI cases in the Netherlands are reported to the SUDI Expert group. Underreporting seems especially to be the case for non-Dutch parents who have lost their child, what may have led to an underrepresentation of this group among the cases. The small size of the case group means that, when exploring subgroups of infants and risk factors for SUDI among these groups, there might not be enough power to show statistically significant results.

CONCLUSION

While the risk of SUDI in the Netherlands is still low, the current study shows several factors that significantly increase this risk. Therefore, focus on "the four of safe sleeping" factors in the current primary prevention should be maintained. This implies that renewed attention by midwives, maternity nurses and preventive child healthcare physicians and nurses is needed for these infant care factors. Besides, a cumulation of risk factors in low educated parents can be observed, indicating a need for additional attention for prevention measures in this group. A new selective prevention campaign regarding bed-sharing should be initiated in the PCHCs, focusing on parents of infants under 4 months of age, parents who smoke, and those who formula feed their infant. The use modern, picture driven prevention information material is recommended to reach as many groups in society as possible.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Granted permission is required to access datasets. Requests to access these datasets should be directed to https://easy.dans.knaw.nl/ui/datasets/id/easy-dataset:110196 for survey datasets, and requests for SUDI cases data should be submitted to the NODOK science committee, which can be arranged *via* the fourth author: a.engelberts@zuyderland.nl.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception, design, and interpretations of the work. FK performed the analyses of the data. All authors assisted in preparing the article, critically assessed the final version, and agree to be accountable for the accuracy and integrity of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.758048/full#supplementary-material

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Renewed Attention Needed for Prevention of Sudden Unexpected Death in Infancy in the Netherlands

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Background: The incidence of sudden unexpected death in infancy (SUDI), which includes sudden infant death syndrome (SIDS), has declined in developed countries since the 1980s, including the Netherlands. To identify improvement opportunities in SUDI prevention, we monitored the adherence of parents to the prevention advice on infant care habits over the past 20 years, especially in relation to the SUDI incidence over time. Potential changes in parental adherence between the latest surveys are of specific interest, as these indicate where current focus is needed.

Methods: Description of the prevalence of infant care factors related to the risk of SUDI, assessed from five Dutch national surveys from 1999 to 2017 among parents of infants under 12 months, and analysis of the potential differences in these prevalences between the two latest surveys in 2010/11 and 2017 with a z-test.

Results: Supine sleeping position decreased from the highest prevalence of 92% in 2010/11, to 83% in 2017. Sleep sack use has increased to 55%, the highest prevalence up to now. Avoiding a duvet has remained reasonably stable since 2002/03 and now 95% of parents do not use a duvet. The prevalence of room-sharing, without sharing the bed, increased from 14% in 1999 to the highest prevalence in 2017 (31%). However, also bed-sharing almost doubled from 5.6% in 2010/11 to 10% in 2017. Breastfeeding decreased between 1999 and 2010/11, but increased from 34% in 2010/11 to 42% in 2017. An increased prevalence of mothers who abstained from smoking during pregnancy, as well as both parents not smoking, was observed, although mostly higher educated parents showed this beneficial behavior.

Discussion and Conclusion: Much has already been achieved first by decreasing prone sleeping since the 80's, and subsequently promoting supine as the safest sleep position. The decrease in duvet use and smoking, and an increase in breastfeeding have also had impact. Indications of a recent decreased prevalence of the supine sleeping position and higher prevalence of bed-sharing might relate to the slightly increasing SUDI incidence in the Netherlands. Renewed attention for prevention of SUDI and specific advice targeting high-risk groups is needed. Modern, picture driven information *via* internet is recommended.

Keywords: SUDI (sudden unexpected death in infancy), SIDS (sudden infant death syndrome), prevention, safe sleeping, advice, parental behavior, surveys

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INTRODUCTION

Sudden infant death syndrome (SIDS), also known as cot death, is defined as "the sudden unexpected death of an apparently healthy infant under 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy with ancillary testing, examination of the death scene, and review of the clinical history" as suggested at the 3rd International Congress on Unexplained Deaths in Infants and Children (1, 2). Because of the differences in diagnosis and classification between countries, scientists now advocate the use of the term Sudden Unexpected Death in Infancy (SUDI), which includes SIDS (3). The comprehensive set of diagnostic categories used to define SUDI are specified in the footnote of **Figure 1**.

Both the incidence of SIDS and SUDI have declined in developed countries since the 1980s, as in the Netherlands, when the advice was given to place infants to sleep in the supine position (5, 6). Between 2002 and 2010, low incidence rates were found in the Netherlands (0.19 per 1,000 live births) (3). In the Netherlands, the SUDI rate has followed a trend similar to the SIDS rate over the years, and is slightly increasing again since 2017 (**Figure 1**). In 2019, 31 infants died suddenly and unexpectedly, of which 13 were classified as SIDS (4). The death of a seemingly healthy infant without an apparent cause, and without any warning, has an immense impact on parents, family and friends, causing them great grief (7).

The decline in SIDS and SUDI incidence in the Netherlands is attributable to ongoing prevention based on knowledge of risk factors (8), and the prevalence of these factors in the population. From 1987 onwards, 11 safe sleeping surveys were distributed in the Netherlands with time intervals varying from 1 to 7 years (9–18). Monitoring infant care practices by repeated national surveys is part of the SUDI prevention and provides input for preventive messages, including adjustments to existing messages.

In **Figure 1**, addition of SUDI prevention advice over time is visualized. This led to the latest Dutch guidelines for the prevention of SIDS and SUDI including the advice to always place an infant to sleep in the supine position, to make sure the

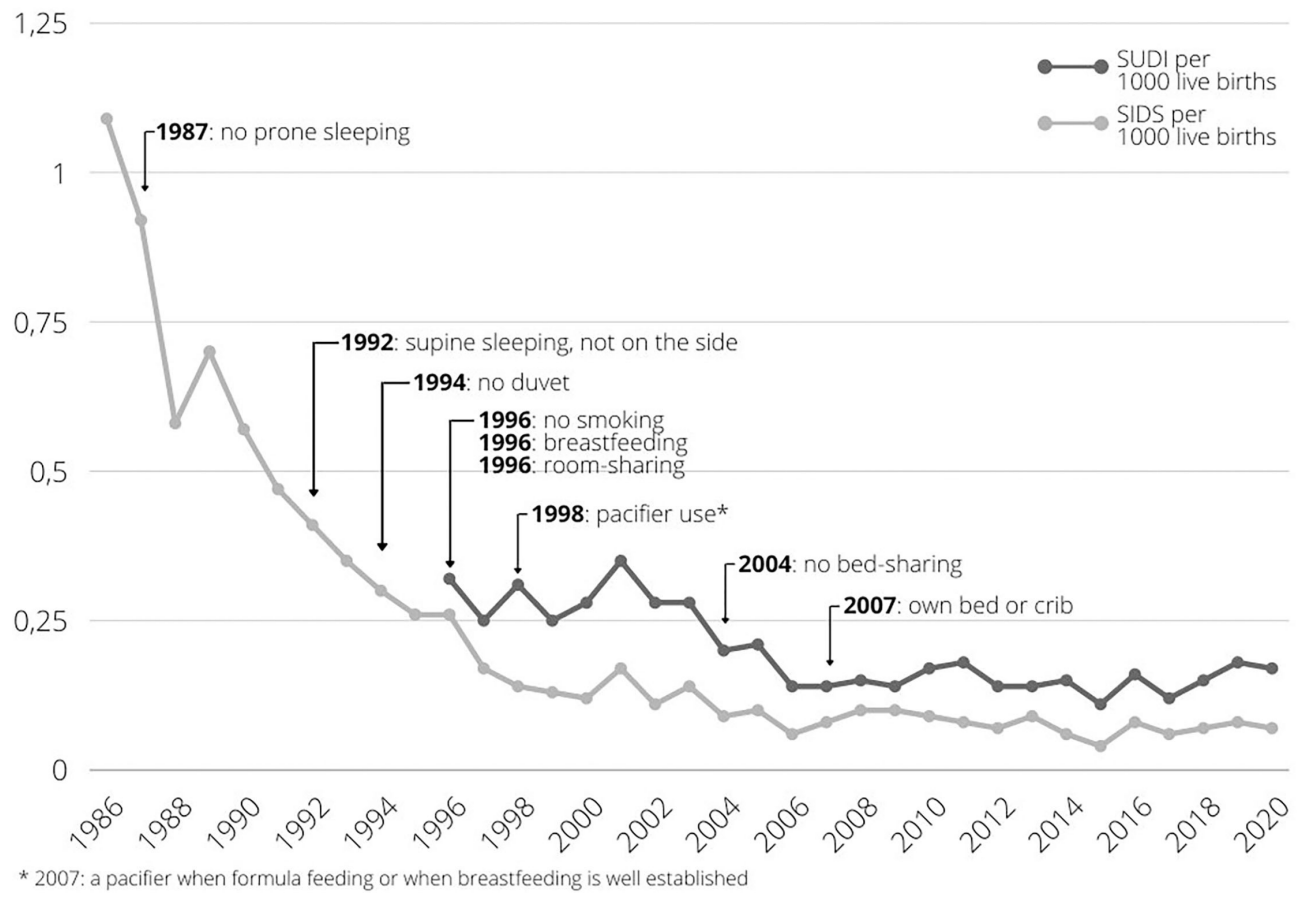

FIGURE 1 | SUDI and SIDS incidence in the Netherlands from 1986 to 2019, with addition of prevention advice elements over time. Data retrieved from Central Bureau for Statistics Netherlands (4). SIDS incidence represents cases coded as R95 in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). SUDI incidence represents cases coded as R95, and R96: other sudden death, cause unknown, R98 unattended death, R99: other ill-defined and unspecified causes of mortality, W75: accidental suffocation and strangulation in bed, W78: inhalation of gastric contents, W79: inhalation and ingestion of food, causing obstruction of respiratory tract in the ICD-10, as suggested by Taylor et al. (3).

infant is not too warm when in bed, not to smoke during and after pregnancy, to place the infant to sleep in a safe sleeping environment and to provide a safe situation when the infant is awake (8). This includes placing an infant to sleep in an own bed or crib in the parents' bedroom the first 6 months, not to bed-shareat least up to 4 months of age, and up to 6 months when one of the parents smokes. Additionally, breastfeeding is recommended. Based on this guideline, the Dutch Consumer Safety Institute (VeiligheidNL) currently promotes four major safe sleeping messages: place the infant to sleep on its back, in its own bed or cot, in an empty bed or cot, and in a well-fitting sleep sack (19). These advices are communicated to parents *via* midwives, maternity caregivers and child healthcare centers.

Especially since the incidence of SUDI is low, attention for prevention advice can weaken for both parents and (professional) caregivers, as well as governmental organizations and (public) health professionals, with increasing incidence rates as a result. Furthermore, popular infant care trends like sharing a sleep surface with an infant, shared on the internet and shown in magazines, may also influence the behavior of parents. A major part of the images online and in magazines do not adhere to the infant safe sleeping guidelines (20, 21). When the prevalence of behavior contrary to safe sleeping advice increases over time, a rise in SUDI incidence might also be expected. To identify improvement opportunities in SUDI prevention, it is important to monitor the adherence of parents to the advice, especially in relation to the SUDI incidence over time. Therefore, the aim of this study was to describe the prevalence of parental behavior recommended in the national infant safe sleeping guidelines. Potential changes in parental adherence between the latest surveys (2010/11 and 2017) are of specific interest, as these indicate where current focus in prevention is needed.

This resulted in the following research question: How can the development of infant care behavior of parents over the past 20 years in the Netherlands be described, and what are the differences in the prevalence of these behaviors between 2010/11 and 2017?

MATERIALS AND METHODS

Design

This descriptive study based on successive independent samples including five latest cross-sectional studies, describes the prevalence of infant care factors related to the risk of SUDI, assessed from Dutch national surveys from 1999 to 2017, and analyses the differences in prevalence between the two latest surveys in 2010/11 and 2017.

Data Collection

Data of five Dutch safe sleeping surveys were used, each of them representing sleeping conditions prevalences of a sample of the general population. These surveys were consecutively conducted by the Dutch organization for applied scientific research (TNO) in 1999 (N = 2,534), 2002/03 (N = 2,869) and 2010/11 (N = 1,956), the National Cot Death Working group (LWW) of the Dutch Pediatric Society (NVK) in 2005 (N = 1,399) and the University of Twente in 2017 (N = 1,209). Original data of these surveys were used, except for 1999, where only published results were available.

Survey administration differed slightly between the five successive surveys. For all surveys, Child Health Care (CHC) organizations in the Netherlands were asked to contribute by selecting all, or a random sample of CHC centers in their working area. Details of data collection are described in **Table 1**.

In 1999 and 2005, selected centers were asked to fill out the questionnaires together with parents. In 2010/11, centers were asked to distribute 20–40 questionnaires to parents who could return the questionnaire either directly or by post.

In 2002/03, questions regarding safe sleeping conditions were included in another survey that distributed questionnaires which were returned by post.

For the last survey in 2017, flyers with a link to an online survey were distributed among CHC centers and, the link to the survey was distributed *via* online media. Additionally, 21 centers in low socioeconomic status areas were selected to conduct in person questionnaires with the help of a research assistant directly at the CHC center.

Data Assessment

The adherence to the Dutch guidelines for the prevention of SIDS and SUDI (8, 19) was assessed with multiple choice surveys. The questions varied only slightly among surveys; differences are indicated in **Table 1**. The exact questions used in the surveys are summarized in **Supplementary Table 1**.

Population

Population characteristics of the five survey populations of infants are described in **Table 2**. Mothers of infants in the 2017 survey were more often highly educated compared to the other surveys with available data on education level. As this survey was distributed online, instead of directly filled in at the CHC center, a representative distribution of the education levels of the mothers was not guaranteed. Therefore, the data of the 2017 survey were weighted according to the education level distribution of women aged 25–45 in 2017, retrieved from Statistics Netherlands, with the following weighting factors: 0.936 for low education level; 1.292 for medium education level; and 0.867 for high education level.

Age categories were defined as: 0–3 months, 4–6 months, 7–12 months of age, corresponding to the current age-specific prevention advice. The population sizes per category are presented in **Table 2**. As the survey of 2002/03 was only intended for parents of infants under 7 months of age, the last age category of this survey was excluded.

Data Analysis

Prevalence of risk reducing behavior, according to the current Dutch SUDI prevention advice, was described for all surveys. Because infant care practices, as well as SIDS and SUDI prevention advice, are different per age of the infant, data were presented separately per age category. Age specific messages are included in the tables. For parental smoking, data were presented

TABLE 1 | Summary method of data ascertainment and differences in questionnaires.

	1999	2002/2003	2005	2010/2011	2017
Number of participating CHC organizations	39	50	23	17	17
Number of participating CHC centers	170	246	101	na	139
Distribution of questionnaires	To 15 consecutive parents visiting each center	Implemented in "Milk feeding of infants" survey each center To all parents visiting each center	To 15 consecutive parents visiting each center	To 20–40 consecutive parents visiting each center	Flyers with link to online questionnaire 21 CHC centers in low SES areas selected to conduct paper questionnaires directly Link also distributed online
Questionnaires send/received (%)	na/2,845 (na)	4,860/2,913 (60%)	na/1,490 (na)	3,048/2,014 (66%)	9,000*/1,289 (14%)
Who filled in questionnaire?	Research assistant with parent(s)	Parent(s) and sent back by post	Research assistant with parent(s)	Parent(s) in waiting room or at home and sent back by post	Parents online Research assistant with parent(s) on paper
Population for analysis	2,534	2,869	1,399	1,956	1,209
Age infants	<10 months	<7 months	<10 months	<12 months	<12 months
Differences questionnaires Sleep position	Last 4 weeks	Last night	Last 4 weeks	Last 4 weeks	Last night
Bedding	Last night	Usually at night	Last night	Last night	Last night
Pacifier	In general	In general	na	In general	Last 4 weeks

**Flyers with link to online questionnaire.*
na, not available.

TABLE 2 | Characteristics of the five survey populations.

	1999 ***N* = 2,534**		2002/2003 ***N* = 2,787**		2005 ***N* = 1,399**		2010/2011 ***N* = 1,955**		2017[$] ***N* = 1,192**	
Age (months)*	4.6 ± 2.5		2.7 ± 1.5		4.4 ± 2.6		4.8 ± 2.8		5.1 ± 3.4	
0–3 months	1,024	(40.5)	1,926	(67.1)	616	(44.0)	876	(44.9)	482	(40.5)
4–6 months	884	(34.8)	861	(30.0)	425	(30.4)	601	(30.7)	315	(26.4)
7–11 months	626	(24.7)	–	–	358	(25.6)	478	(24.5)	395	(33.1)
Male gender	1,297	(51.2)	2,342	(50.3)	747	(53.7)	981	(50.2)	586	(49.2)
Birthweight ≥2,500	2,311	(94.4)	2,630	(95.0)	na		1,796	(94.7)	1,143	(95.9)
Firstborn	1,203	(47.6)	1,366	(49.0)	628	(45.1)	1,011	(51.7)	658	(55.2)
Dutch nationality mother	na		2,623	(94.3)	na		1,727	(90.3)	1,032	(87.0)
Education level mother										
Low	na		842	(30.6)	na		372	(19.6)	157	(13.2)
Medium	na		957	(34.7)	na		613	(32.2)	443	(37.2)
High	na		957	(34.7)	na		915	(48.2)	591	(49.6)

*Values are described as mean ± SD, or **N** (%).*
Percentages are based on the sample of the population with available data for the concerned characteristic.
**The survey in 2002/03 only included infants up to 6 months of age, and the surveys of 1999 and 2005 infants up to 9 months of age.*
[$]Data of the 2017 survey were weighted according to the education level of women aged 25–45 in 2017 in the Netherlands (22). The total population included 1,209 infants, infants with missing data for mother's education level were excluded.
na, not available.

separately per education level of the mother. Since for the 1999 survey only published results were available, not all categories could be assessed.

A potential difference in prevalence between the 2010/11 and 2017 surveys for the reported risk reducing behaviors was tested with a z-test with $\alpha < 0.05$.

RESULTS

The prevalence of risk reducing behaviors by parents of infants up to 12 months of age in the five consecutive surveys are reported in **Tables 3**–**8**. Significant differences between the last two surveys are indicated in the tables.

Sleep Position

The prevalence of the supine sleeping position fluctuated between 1999 and 2010/11 in the total group as well as the separate age categories (**Table 3**). In 2017, a significantly lower prevalence was observed in all age categories compared to 2010/11. On average, around 83% of the infants were being placed supine in 2017, whereas this was 92% in 2010/11.

Sleep Conditions

Not using a duvet increased from 82% in 1999 to 95% in 2017, with no difference between 2010/11 and 2017 (**Table 4**). The use of a sleep sack fluctuated over time in all age categories. However, its prevalence increased significantly from 2010/11 (48%) to 2017 (55%), in particular among infants aged between 4 and 12 months, leading to the highest use of a sleep sack in the 2017 survey.

The use of a pacifier was lowest in 1999 (**Table 5**). In 2017, over 50% of infants in all age categories were usually placed to sleep with a pacifier, with the highest prevalence in the lowest age categories. Significantly higher usage in 2017 was observed in infants under 4 months of age compared to 2010/11.

The prevalence of infants sleeping in a room with their parents and not sharing the bed, increased in all age categories (**Table 6**). The highest prevalence was found in 2017, when over 30% of the infants shared a room with the parents, and not the bed. For infants 0–3 months old this was over 50%. The difference between 2010/11 and 2017 was significant for all age categories. However, also the prevalence of infants sleeping in their parents' bed increased to 10% in 2017, with over 9% of 0–3 month old infants not sleeping in their own bed or cot during the night (**Supplementary Table 2**).

Breastfeeding

The prevalence of breastfeeding fluctuated over the surveys and decreased with age as seen in **Table 7**. In 1999, almost 90% of the infants received any breast milk, either exclusive or in combination with formula milk, the highest prevalence of all surveys. In 2017, infants were more often exclusively breastfed compared to 2010/11 in all age categories.

Smoking

An increase in mothers who abstained from smoking during pregnancy was observed between 2002/03 and 2017, across all education levels (**Table 8**). Simultaneously, the prevalence of both parents not smoking postpartum increased. Differences in smoking prevalence between education levels of the mothers were observed.

TABLE 3 | Prevalence of supine sleep position in the five survey populations, including prevalence per age category.

	1999 *N* = 2,534[$]		2002/2003 *N* = 2,780[$]		2005 *N* = 1,250[$]		2010/2011 *N* = 1,709[$]		2017 *N* = 1,181[$]		2017 compared with 2010/2011	
	n	% (95%-CI)	*n*	% (95%-CI)	*n*	% (95%-CI)	*n*	% (95%-CI)	*n*	% (95%-CI)	*z*-statistic	*p*-value
Supine sleeping	1,957	90.1 (89.7–92.1)	2,375	85.4 (84.1–86.7)	1,124	89.9 (88.2–91.6)	1,577	92.3 (91.0–93.6)	977	82.7 (80.5–84.9)	−7.92	0.000
0–3 months	709	88.8 (86.7–91.0)	1,607	83.7 (82.0–85.4)	489	88.9 (86.3–91.5)	684	92.7 (90.8–94.6)	415	87.0 (84.0–90.0)	−3.29	0.001
4–6 months	734	92.1 (90.2–94.0)	768	89.3 (87.2–91.4)	357	92.0 (89.3–94.7)	516	93.1 (91.0–95.2)	272	86.3 (82.5–90.1)	−3.26	0.001
7–11 months	514	92.1 (89.9–94.4)	na	na	278	89.1 (85.6–92.6)	377	90.4 (87.6–93.2)	290	74.6 (70.3–78.9)	−6.11	0.000

The supine position is advised for all infants, at least until the infant can turn prone and back (often around 6 months of age).

[$]Percentages are based on the sample of the population with available data for sleeping position. When sleeping position was assessed over the last four weeks, varying sleeping positions were reported for some infants, and these are not included (1999: 381, 2005: 149, 2010/11: 246).

na, not available.

TABLE 4 | Prevalence of a sleep sack and not using a duvet in the five survey populations, including prevalence per age category.

	1999 *N* = 2,534[$]		2002/2003* *N* = 2,787[$]		2005 *N* = 1,399[$]		2010/2011 *N* = 1,955[$]		2017 *N* = 1,192[$]		2017 compared with 2010/2011	
	n	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	**z-statistic**	***p*-value**
No duvet	2,079	82.0 (80.5–83.5)	2,592	93.0 (92.1–93.9)	1,307	93.4 (92.1–94.7)	1,873	95.9 (95.0–96.8)	1,136	95.4 (94.2–96.6)	−0.67	0.502
0–3 months	876	85.5 (83.3–87.7)	1,802	93.6 (92.5–94.7)	588	95.5 (93.9–97.1)	850	97.1 (96.0–98.2)	470	97.4 (96.0–98.8)	0.32	0.748
4–6 months	714	80.8 (78.2–83.4)	790	91.8 (90.0–93.6)	389	91.5 (88.8–94.2)	577	96.0 (94.4–97.6)	302	95.7 (93.5–97.9)	−0.22	0.828
7–11 months	489	78.1 (74.9–81.3)	na	na	330	92.2 (89.4–95.0)	446	93.5 (91.3–95.7)	365	92.6 (90.0–95.2)	−0.52	0.602
Sleep sack	1,150	45.5 (43.6–47.4)	1,245	44.7 (42.9–46.5)	570	40.7 (38.1–43.3)	933	47.8 (45.6–50.0)	657	55.1 (52.3–57.9)	3.97	0.000
0–3 months	272	26.6 (23.9–29.3)	674	35.0 (32.9–37.1)	140	22.7 (19.4–26.0)	291	33.3 (30.2–36.4)	141	29.2 (25.2–33.2)	−1.55	0.121
4–6 months	474	53.6 (50.3–56.9)	571	66.3 (63.1–69.5)	213	50.1 (45.3–54.9)	346	57.6 (53.6–61.6)	219	69.5 (64.4–74.6)	3.52	0.000
7–11 months	404	64.5 (60.8–68.2)	na	na	217	60.6 (55.5–65.7)	296	62.1 (57.7–66.3)	297	75.3 (69.1–77.9)	4.16	0.000

A sleep sack can be used from birth on, but is especially advised when the infants starts turning (often around 3–6 months). A duvet is discouraged up to 2 years of age.
[$]*Percentages are based on the sample of the population with available data for bedding.*
**2002/03 survey assessed usual bedding at night.*
na, not available.

TABLE 5 | Prevalence of pacifier use when infants were placed to sleep in the five survey populations, including prevalence per age category.

	1999 *N* = 2,462[$]		2002/2003 *N* = 2,781[$]		2005 *N* = 1,399[$]		2010/2011 *N* = 1,945[$]		2017 *N* = 1,192[$]		2017 compared with 2010/2011	
	n	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	**z-statistic**	***p*-value**
Pacifier	1,001	40.7 (38.8–42.6)	2,040	73.4 (71.8–75.0)	na	na	1,088	56.0 (53.7–58.1)	699	58.7 (55.9–61.5)	1.48	0.138
0–3 months	331	33.4 (30.5–36.3)	1,499	78.0 (76.1–79.9)	na	na	490	56.2 (52.9–59.5)	303	62.8 (58.5–67.1)	2.36	0.018
4–6 months	364	42.6 (39.3–45.9)	541	62.9 (59.7–66.1)	na	na	342	57.2 (53.2–61.2)	189	60.0 (54.6–65.4)	0.82	0.415
7–11 months	306	49.8 (45.9–53.7)	na	na	na	na	256	54.0 (49.4–58.4)	207	52.4 (47.7–57.5)	−0.47	0.638

A pacifier is advised when breastfeeding is well established (often around 1 month of age).
[$]*Percentages are based on the sample of the population with available data for pacifier use.*
na, not available.

TABLE 6 | Prevalence of room-sharing during sleep in the five survey populations, including prevalence per age category.

	1999 *N* = 2,534[$]		2002/2003 *N* = 2,770[$]		2005 *N* = 1,395[$]		2010/2011 *N* = 1,803[$]		2017 *N* = 1,185[$]		2017 compared with 2010/2011	
	n	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	**z-statistic**	***p*-value**
Room-sharing not bed	369	14.6 (13.2–16.0)	640	23.1 (21.5–24.7)	253	18.1 (16.1–20.1)	307	17.0 (15.3–18.7)	362	30.6 (28.0–33.2)	8.72	0.000
0–3 months	222	21.7 (19.2–24.2)	516	27.0 (25.0–29.0)	140	22.8 (19.5–26.1)	211	27.2 (24.1–30.3)	246	51.5 (47.0–56.0)	8.68	0.000
4–6 months	107	12.1 (10.0–14.2)	124	14.5 (12.1–16.9)	84	19.8 (16.0–23.6)	67	11.9 (9.2–14.6)	65	20.6 (16.1–25.1)	3.46	0.001
7–11 months	40	6.4 (4.5–8.3)	na	na	29	8.1 (5.3–10.9)	29	6.2 (4.0–8.4)	52	13.1 (9.8–16.4)	3.46	0.001

Room-sharing is advised up to 6 months of age, and bed-sharing discouraged until 4 months, or 6 months when parent(s) smoke.
[$]Percentages are based on the sample of the population with available data for sleeping place.
na, not available.

TABLE 7 | Prevalence of feeding type in the five survey populations, including prevalence per age category.

	1999 *N* = 2,534[$]		2002/2003 *N* = 2,785[$]		2005 *N* = 1,389[$]		2010/2011 *N* = 1,797[$]		2017 *N* = 1,179[$]		2017 compared with 2010/2011	
	n	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	***n***	**% (95%-CI)**	**z-statistic**	***p*-value**
Exclusive breastfeeding	501	19.8 (18.2–21.4)	1,001	35.9 (34.1–37.7)	409	29.4 (27.0–31.8)	422	23.5 (21.6–25.4)	370	31.4 (28.8–34.0)	4.77	0.000
0–3 months	334	32.6 (29.7–35.5)	778	40.4 (38.2– 42.6)	267	43.7 (39.8–47.6)	285	35.0 (31.8–38.2)	220	45.8 (41.4–50.2)	3.85	0.000
4–6 months	130	14.7 (12.4–17.0)	223	25.9 (23.0–28.8)	106	25.1 (21.0–29.2)	103	18.6 (15.5–21.7)	78	25.0 (20.2–29.8)	2.22	0.026
7–11 months	37	5.9 (4.1–7.7)	na	na	36	10.1 (7.0–13.2)	34	7.9 (5.5–10.3)	72	18.8 (14.9–22.7)	4.61	0.000
Mixed breast/formula feeding	1,751	69.1 (67.3–71.0)	380	13.6 (12.4–14.9)	149	10.7 (9.1–12.3)	191	10.6 (9.2–12.0)	124	10.5 (8.8–12.2)	−0.09	0.931
0–3 months	556	54.3 (51.2–57.4)	249	12.9 (11.4–14.4)	57	9.3 (7.0–11.6)	98	12.0 (9.8–14.2)	52	10.8 (8.0–13.6)	−0.65	0.514
4–6 months	652	73.8 (70.9–76.7)	131	15.2 (12.8–17.6)	51	12.1 (9.0–15.2)	60	10.8 (8.3–13.3)	35	11.2 (7.7–14.7)	0.18	0.856
7–11 months	543	86.7 (84.0–89.4)	na	na	41	11.5 (8.2–14.8)	33	7.7 (5.3–10.1)	37	9.6 (6.7–12.5)	0.97	0.334

Breastfeeding is advised up to 6 months of age.
[$]Percentages are based on the sample of the population with available data for type of feeding.
na = not available.

TABLE 8 | Prevalence of not smoking by both parents of the infants, and not smoking of mother during pregnancy in the five survey populations, including prevalence per education level of the mother.

	1999		2002/2003		2005		2010/2011		2017		2017 compared with 2010/2011	
	N = 2,507[$]		*N* = 2,787[$]		*N* = 1,399[$]		*N* = 1,955[$]		*N* = 1,192[$]			
	n	% (95%CI)	*n*	% (95%CI)	*n*	% (95%CI)	*n*	% (95%CI)	*n*	% (95%CI)	*z*-statistic	*p*-value
Mother did not smoke during pregnancy	na	na	2,394	85.9 (84.6–87.2)	na	na	na	na	1,144	96.1 (95.0–97.2)	na	na
Low education	na	na	651	78.7 (75.9–81.5)	na	na	na	na	136	86.8 (81.5–92.1)	na	na
Middle education	na	na	833	87.5 (85.4–89.6)	na	na	na	na	424	95.6 (93.7–97.5)	na	na
High education	na	na	888	93.4 (91.8–95.0)	na	na	na	na	584	98.8 (97.9–99.7)	na	na
Both parents do not smoke*	1,537	61.3 (59.4–63.2)	1,859	69.3 (67.6–71.0)	887	63.8 (61.3–66.3)	1,338	74.6 (72.7–76.5)	902	77.9 (75.4–80.2)	2.05	0.041
Low education	na	na	474	59.2 (55.9–62.5)	na	na	183	54.3 (49.2–59.4)	95	62.3 (54.4–69.6)	1.65	0.098
Middle education	na	na	623	67.7 (64.7–70.7)	na	na	401	70.5 (66.9–74.1)	297	69.7 (65.4–74.0)	–0.27	0.785
High education	na	na	747	79.8 (77.3–82.3)	na	na	743	85.7 (83.4–88.0)	511	87.9 (85.3–90.5)	1.20	0.229

[$]Percentages are based on the sample of the population with available data for smoking of parent(s). Subcategories are only based on the sample of the population with available data for both education level of the mother and smoking of parents.

na, not available.

DISCUSSION

The aim of this study was to describe the prevalence of parental behavior recommended in the Dutch infant safe sleeping guidelines and analyze potential changes in prevalence between the latest surveys to identify where current focus is needed. The prevalence of infant sleep position fluctuated over the surveys. Significantly less infants were placed in the supine position in 2017 compared to 2010/11, with more infants sleeping prone or on the side in 2017. More infants were placed to sleep in a sleep sack in 2017 compared to 2010/11. The highest prevalence of room-sharing, but not bed-sharing was found in 2017, however also an increase in bed-sharing was observed. Although parents are advised to room-share for the first 6 months of life, this message seems to be one of the most difficult to adhere to. Type of milk feeding varied per survey, with more infants being breastfed exclusively in all age categories in 2017. An increase in mothers who abstained from smoking during pregnancy, and both parents not smoking in general was observed, although mostly in higher educated parents.

SUDI prevention strategies in the Netherlands has proved to be effective, resulting in a decreasing SUDI incidence and increasing prevalence of most preventive infant care factors over time. However, as visualized in **Figure 1**, from 2017 on, the SUDI incidence seems to increase again. It is unknown if this reflects yearly fluctuation, or an actual increase. Indications of a lower prevalence of the supine sleeping position and higher prevalence of bed-sharing in 2017, compared to the prior survey, might relate to this potentially increased SUDI incidence. Renewed attention for the current prevention advice is therefore needed.

The incidence of SIDS/SUDI is very low in the Netherlands, which makes it of interest to see if our infant care habits are comparable to other countries. Although the prevalence of infants placed to sleep in the supine position decreased in our study, it is still comparable to Ireland (23) and Australia (24). In Scandinavian countries, only just over 60% of infants were always placed supine (25, 26). Room-sharing is more prevalent in these countries compared to the Netherlands, i.e., 60% in Norway (25), and 54% in Sweden (26). However, also bed-sharing is a very common, perhaps cultural, behavior in Norway and Sweden. While an increased prevalence of bed-sharing in the Netherlands was observed (10% in 2017), the prevalence was 63% in Norway, and in Sweden 43% among infants 3 months of age, and 33% at 6 months (25, 26). In both countries so-called baby nests are a popular sleep surface when bed-sharing. There are concerns about safety of these baby nests (27), but although we advise against them as a sleep surface, they seem to become more popular. Their use needs to be assessed in following surveys. Accurate data about infant care habits are not widely available for countries. It is therefore not possible to hypothesize on their influence on differences in incidence, especially as SIDS seems to be such a multifactorial occurrence.

An infant being placed to sleep in the prone position was associated with a three times higher risk of SUDI compared to the supine position among infants up to 9 months in the Netherlands between 1996 and 2001 (28). Internationally, 2 to 13 times higher risks were found (29). With the lower prevalence of the supine

position in this study in 2017, more infants were placed to sleep in the prone (8.9%) and side position (8.4%) compared to earlier surveys. Especially in the lowest age categories, where the SUDI risk is highest, the prevalence of the prone position more than doubled. This can be of great concern in relation to the increased SUDI incidence.

Since the advice in 2004 to room-share with an infant the first 6 months, and not share the sleep surface the first 4 months, infants were more often placed to sleep in the parents' bedroom while not sharing the same bed. These infants have a lower risk of SUDI (30, 31). Nevertheless, the prevalence of so-called room-sharing was only 31% in 2017, and 51% among infants aged under 4 months. The prevalence of bed-sharing was also much lower in 2010/11 compared to the survey in 2005. Nevertheless, in 2017 this prevalence was again at a comparable level to 2005. Bed-sharing of a parent with the infant increases the risk of SUDI, and it is believed that a soft mattress, a duvet, pillows, the risk of overheating and the risk of overlaying can potentially contribute to this increased risk (8, 29). The risk of bed-sharing increases when parents smoke, drink alcohol, use drugs or are extremely tired (30). The Dutch prevention advice focuses on encouraging placing the infant to sleep in its own bed or cot. This prevalence decreased but was still 90% in 2017. However, the higher prevalence of bed-sharing in 2017, comparable to that in 2005, is of great concern. New sleeping practices, such as 'clip-on beds' or co-sleepers, become more popular and monitoring of their safety seems warranted.

The prevalence of smoking, both during and after pregnancy, greatly decreased over the past twenty years. Nevertheless, low and middle educated groups are lagging behind in this trend (32). Smoking during pregnancy and after birth both need ongoing attention, which in the Netherlands is covered in the national prevention agreement of the Dutch Government (33).

In addition, promoting breastfeeding could contribute to the prevention of SUDI. Breastfeeding could improve in the Netherlands as currently, 69% of the infants receive breastfeeding directly after birth, while at 3 months of age this is only 31%, and this decreases to 19% at 6 months of age (34). Breastfeeding is especially lower among mothers with middle or low education levels. These national numbers have decreased compared to earlier reports (34). In this study however, the prevalence of breastfeeding fluctuated over time, but in 2017 more infants were exclusively breastfed compared to 2010/11 in all age categories. Specific advice targeting middle and low educated parents is needed.

Many governmental institutions promote safe sleeping of infants and thereby contribute to the prevention of SUDI. Preventive youth healthcare is organized differently in different countries, nevertheless, there are many similarities between European countries (35). In the Netherlands, during the first week postpartum, maternity caregivers visit a family on a daily basis, where they provide information and help out with infant care. Furthermore, parents visit the CHC center with their infant about eight times during the first year of life for regular check-ups and to receive information. Despite these valuable channels for communicating the safe sleeping advice, we don't seem to take the current power and influence of the internet into account sufficiently. Many pictures contradict the safe sleeping advice on popular websites, in blogs, in ads, and on social media (20, 21). These pictures influence the behavior of young parents. An intervention providing videos *via* social media was shown to be effective in improving adherence to infant safe sleep practices by changing maternal attitudes and perceived social norms (36, 37). Therefore, it is important to anticipate, and provide more modern, outreaching, picture driven information to reach all young parents, next to all evidence based and well described information on (governmental) institutions' websites. Currently in the Netherlands, a group of parents of SUDI infants closely work together with professionals to take action and tackle inadequate information *via* Instagram.

Strengths and Limitations

The periodical collection of data on sleep related infant care habits in the Netherlands is unique. With data on the last five surveys over the past 20 years, we were able to monitor prevalences of parental behavior recommended in the national infant safe sleeping guidelines. Parents from different regions in the Netherlands participated in these surveys, ensuring a representative sample of the Dutch population. The surveys were distributed among CHC centers in slightly different, but comparable ways. The last survey used an online questionnaire, where an equal distribution of education levels could not be guaranteed, for which we corrected in this study. Although not validated, most surveys used similar questionnaires, making comparison between them possible. The main difference was in the assessment of the sleeping position of the infant either last night or over the past 4 weeks but, it is not to be expected that this has had major influence on the results. Some bias could have occurred however, due to these differences in questions, and due to the administration difference of online, postal and in person questionnaires. Lastly, parents who filled out the questionnaires were aware of the goal of the survey, namely to monitor safe sleeping of infants. Therefore, it cannot be ruled out that parents may have provided socially desirable answers, and that the actual behavior is less favorable. However, no differences in social desirability are to be expected between the surveys as execution of the studies was similar.

CONCLUSION

In a low SUDI incidence country as the Netherlands, attention for prevention advice can weaken for both parents and (professional) caregivers, as well as governmental organizations and (public) health professionals. The possible small increase in SUDI incidence over the last years and a lower prevalence of some risk reducing behaviors in the latest survey, show the importance of renewed attention for the prevention of SUDI. Attention could specifically be aimed at sleeping in the supine position and in an own bed or cot, combined with ongoing attention for the prevention of smoking, especially among lower socioeconomic status groups. Modern, picture driven information *via* social media and the internet could be considered.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

FK, ML'H, MB-B, AE, and EF made substantial contributions to the conception, design, and interpretations of the work. FK performed the analyses of the data. All authors assisted in preparing the article, critically assessed the final version, and agree to be accountable for the accuracy and integrity of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.757530/full#supplementary-material

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Medullary Serotonergic Binding Deficits and Hippocampal Abnormalities in Sudden Infant Death Syndrome: One or Two Entities?

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Sudden infant death syndrome (SIDS) is understood as a syndrome that presents with the common phenotype of sudden death but involves heterogenous biological causes. Many pathological findings have been consistently reported in SIDS, notably in areas of the brain known to play a role in autonomic control and arousal. Our laboratory has reported abnormalities in SIDS cases in medullary serotonin (5-HT) receptor $_{1A}$ and within the dentate gyrus of the hippocampus. Unknown, however, is whether the medullary and hippocampal abnormalities coexist in the same SIDS cases, supporting a biological relationship of one abnormality with the other. In this study, we begin with an analysis of medullary 5-HT$_{1A}$ binding, as determined by receptor ligand autoradiography, in a combined cohort of published and unpublished SIDS (n = 86) and control (n = 22) cases. We report 5-HT$_{1A}$ binding abnormalities consistent with previously reported data, including lower age-adjusted mean binding in SIDS and age vs. diagnosis interactions. Utilizing this combined cohort of cases, we identified 41 SIDS cases with overlapping medullary 5-HT$_{1A}$ binding data and hippocampal assessment and statistically addressed the relationship between abnormalities at each site. Within this SIDS analytic cohort, we defined abnormal (low) medullary 5-HT$_{1A}$ binding as within the lowest quartile of binding adjusted for age and we examined three specific hippocampal findings previously identified as significantly more prevalent in SIDS compared to controls (granular cell bilamination, clusters of immature cells in the subgranular layer, and single ectopic cells in the molecular layer of the dentate gyrus). Our data did not find a strong statistical relationship between low medullary 5-HT$_{1A}$ binding and the presence of any of the

hippocampal abnormalities examined. It did, however, identify a subset of SIDS (∼25%) with both low medullary 5-HT_{1A} binding and hippocampal abnormalities. The subset of SIDS cases with both low medullary 5-HT_{1A} binding and single ectopic cells in the molecular layer was associated with prenatal smoking ($p = 0.02$), suggesting a role for the exposure in development of the two abnormalities. Overall, our data present novel information on the relationship between neuropathogical abnormalities in SIDS and support the heterogenous nature and overall complexity of SIDS pathogenesis.

Keywords: medulla, temporal lobe epilepsy, seizure, arousal, dentate gyrus

INTRODUCTION

The sudden and unexpected death of an apparently healthy infant during a sleep period has long been recognized as a medical entity requiring investigation, but its cause remains unknown. Since the middle of the twentieth century, various definitions have been proposed for this phenomenon. It has usually been labeled as a "syndrome," which is a set of medical signs and symptoms that correlate strongly with each other without an established unifying cause. The use of the word syndrome is distinct from "disease," which is utilized when the cause or mechanism of the signs and symptoms is known, either by diagnostic laboratory findings, or pathognomonic clinical and/or autopsy findings. The typical phenotype of sudden infant death syndrome (SIDS) is the unique age distribution with a peak at 2–4 postnatal months, occurrence of death associated with a sleep period, socioeconomic disadvantage, and male predominance. SIDS is a diagnosis of exclusion and its differential diagnosis is broad and heterogeneous, including various causes that may be found on autopsy, e.g., inborn errors of metabolism, congenital heart disease.

Over the last two decades, our group has provided substantial evidence using neurochemical techniques that a subset of SIDS infants is characterized by serotonergic brainstem pathology in regions of the medulla oblongata involved in cardiorespiratory control and arousal. These abnormalities include serotonin (5-HT) receptor binding abnormalities (1–5), a decrease in 5-HT levels and tryptophan hydroxylase 2 (TPH2) (5), the key regulatory enzyme in 5-HT production, and an increase in serotonergic cells with an immature-like phenotype (4). Among these, the most robust and reproducible serotonergic abnormality identified in the brainstem to date is a deficiency in binding to the 5-HT_{1A} receptor (4, 5), a receptor which functions as a presynaptic auto-receptor on 5-HT neurons and a heteroreceptor on postsynaptic 5-HT neurons and non-5-HT neurons (6). This binding deficiency has been identified by us with tissue receptor autoradiography in two independent published datasets of SIDS cases compared to non-SIDS controls (4, 5) and confirmed by other laboratories with different techniques (7). Most recently, our laboratory reported a novel anatomic finding from light microscope studies in the hippocampus of ∼40% of SIDS cases (8). Hippocampal abnormalities, including abnormalities of the dentate gyrus (DG), have been reported in other cohorts of SIDS and sudden unexpected death in childhood (SUDC) (9–15), suggesting hippocampal involvement across a spectrum of ages. The hippocampal abnormalities identified in SIDS and SUDC, specifically granular cell bilamination of the DG, had been reported in patients with temporal lobe epilepsy (TLE) (16–19), suggesting a seizure-related mechanism of sudden death in SIDS and SUDC, a hypothesis postulated by others (20, 21). Shown in **Figure 1** are examples of medullary 5-HT_{1A} binding and the hippocampal features analyzed here. While hippocampal pathology in SIDS suggests an involvement of sleep-related fatal seizures, brainstem serotonergic abnormalities suggest brainstem-mediated central cardiorespiratory dysfunction during sleep.

Biologically, hippocampal development and the brainstem serotonergic system are related through the trophic actions of 5-HT during development (22–25). Pathologically, they are related through 5-HT-mediated cardiorespiratory dysfunction during seizures and seizure-induced impairment in serotonergic brainstem function (21, 26). Functionally, medullary 5-HT and limbic sites including the hippocampus are considered to be interconnected "nodes" and comprise an integrated central homeostatic network that regulates responses to stress (27). Given the links between the hippocampus, brainstem 5-HT and serotonergic dysfunction during seizures, we postulated that the hippocampal abnormalities identified in a subset of SIDS infants are related to the brainstem serotonergic abnormalities identified in SIDS infants. This is based on the fact that SIDS infants with hippocampal abnormalities seem to share clinical presentations (sudden and unexpected death), demographics, and general autopsy findings with SIDS infants with medullary 5-HT_{1A} abnormalities. While these common features suggest one pathological process, whether they represent two separate diseases is unknown. Whether hippocampal abnormalities coexist with brainstem serotonergic abnormalities in the same infant is also unknown. In this study we hypothesized that the medullary 5-HT_{1A} binding abnormality is found in SIDS infants with hippocampal structural abnormalities, suggesting a dependence between the two lesions and providing evidence for a single entity with a combined hippocampal-brainstem phenotype.

Prior to our analysis of the relationship between medullary and hippocampal abnormalities in SIDS, we expanded upon our reported medullary 5-HT_{1A} findings to show 5-HT_{1A} binding deficiencies in a combined published and unpublished cohort of SIDS and controls. Subsequently, in order to investigate the

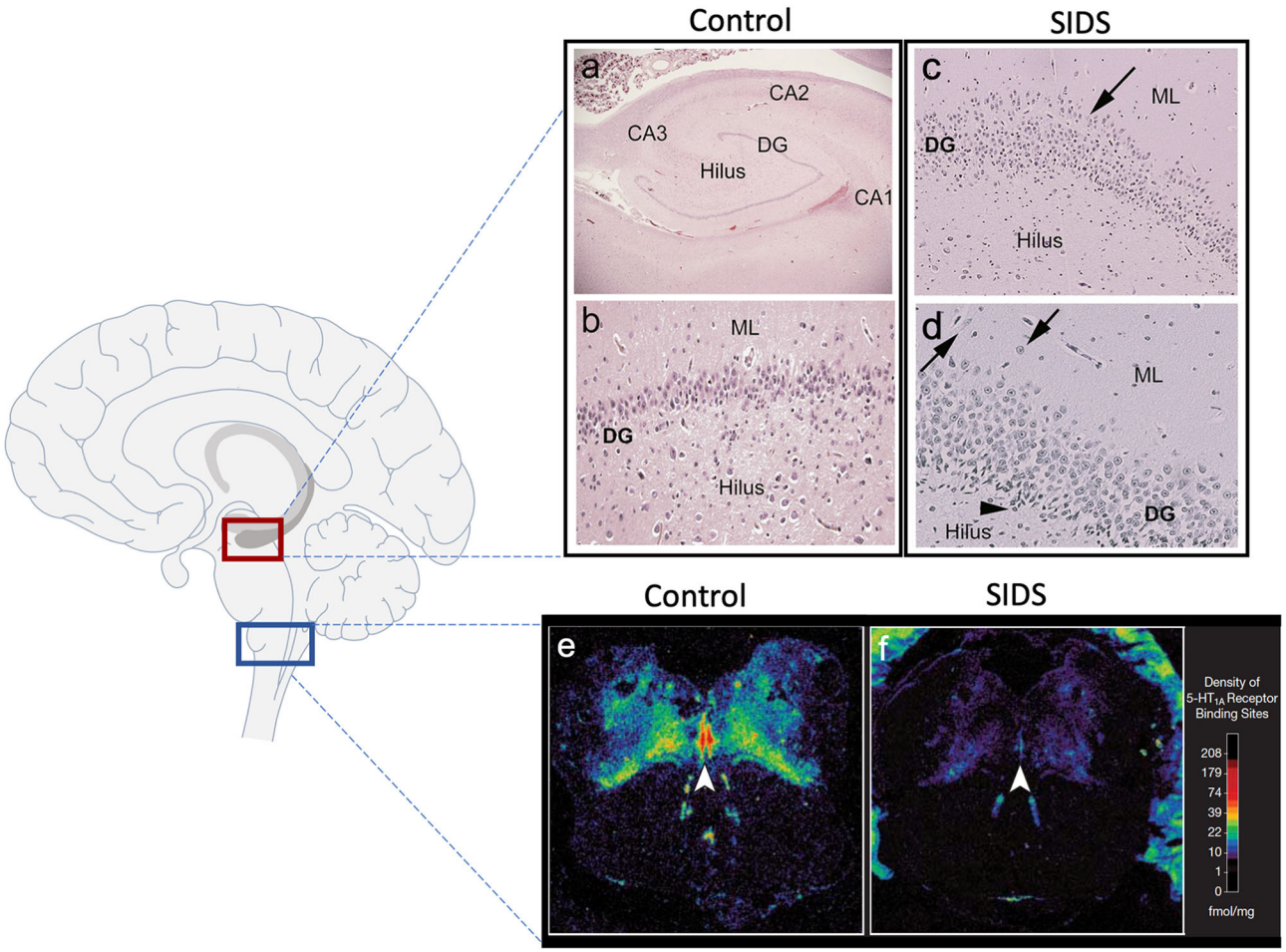

FIGURE 1 | Hippocampal and medullary pathology identified in SIDS infants. The diagram on the left shows general brain structure with the hippocampus and medulla highlighted with red and blue boxes, respectively. Images **(a–d)** show hematoxylin and eosin staining of the hippocampus. Hippocampal anatomy is shown at 4x in a control infant for reference **(a)**. The dentate gyrus (DG) in a control infant is shown at 10x with a densely packed, single layer of granule cells **(b)**. The hippocampus of a SIDS infant displays **(c)** bilamination of the DG (arrow), **(d)** single, ectopic granule cells in the molecular layer (arrow), and **(d)** progenitor cells in the subgranular layer (arrowhead). Hippocampal images were modified from Kinney et al. (8). Examples of medullary 5-HT_{1A} autoradiography are shown in **(e,f)**. The density of 5-HT_{1A} receptor binding, including in the raphe obscurus (arrowhead), is visually lower in a SIDS case **(f)** compared with a control **(e)**. The receptor binding surrounding the control medulla **(e)** represents binding in cerebellum tissue. A colored density scale is included for reference. Brainstem images were modified with permission from Paterson et al. (4). DG, dentate gyrus; CA, cornu ammonis; ML, molecular layer.

hypothesized relationship between the hippocampal findings and brainstem 5-HT_{1A} abnormalities, this research investigated three specific questions: (1) do SIDS cases with identified hippocampal abnormalities have lower medullary 5-HT_{1A} binding compared with SIDS cases without abnormalities?; (2) are SIDS cases with the lowest medullary 5-HT_{1A} binding in the SIDS cohort at higher risk for hippocampal abnormalities compared with SIDS cases with normal or elevated binding?; and (3) are there clinical and/or risk factors specifically associated with the concurrent presence of both abnormalities? To address these questions, we used an analytic cohort with both a histological assessment of fixed hippocampus (8) and neurochemical analysis of frozen medulla (4, 5). In our analysis of the 5-HT_{1A}-hippocampal relationship, we focused specifically on hippocampal features shown to have a higher prevalence in SIDS infants compared with controls, namely, focal granule cell bilamination of the DG, clusters of immature cells in the subgranular layer of the DG, and single ectopic granule cells in the molecular layer of the DG (8). We focused on eight brainstem nuclei reported to be abnormal in SIDS (as determined by 5-HT_{1A} receptor binding), including nuclei containing 5-HT cells and considered by our group as part of the core medullary serotonergic lesion in SIDS (28).

MATERIALS AND METHODS

Tissue

Tissue samples were obtained from infant autopsies between 1998 and 2013. Tissue came from the San Diego Medical Examiner's office (SDME) and were available for research under the auspice of the California Code, Section 27491.41. Deaths

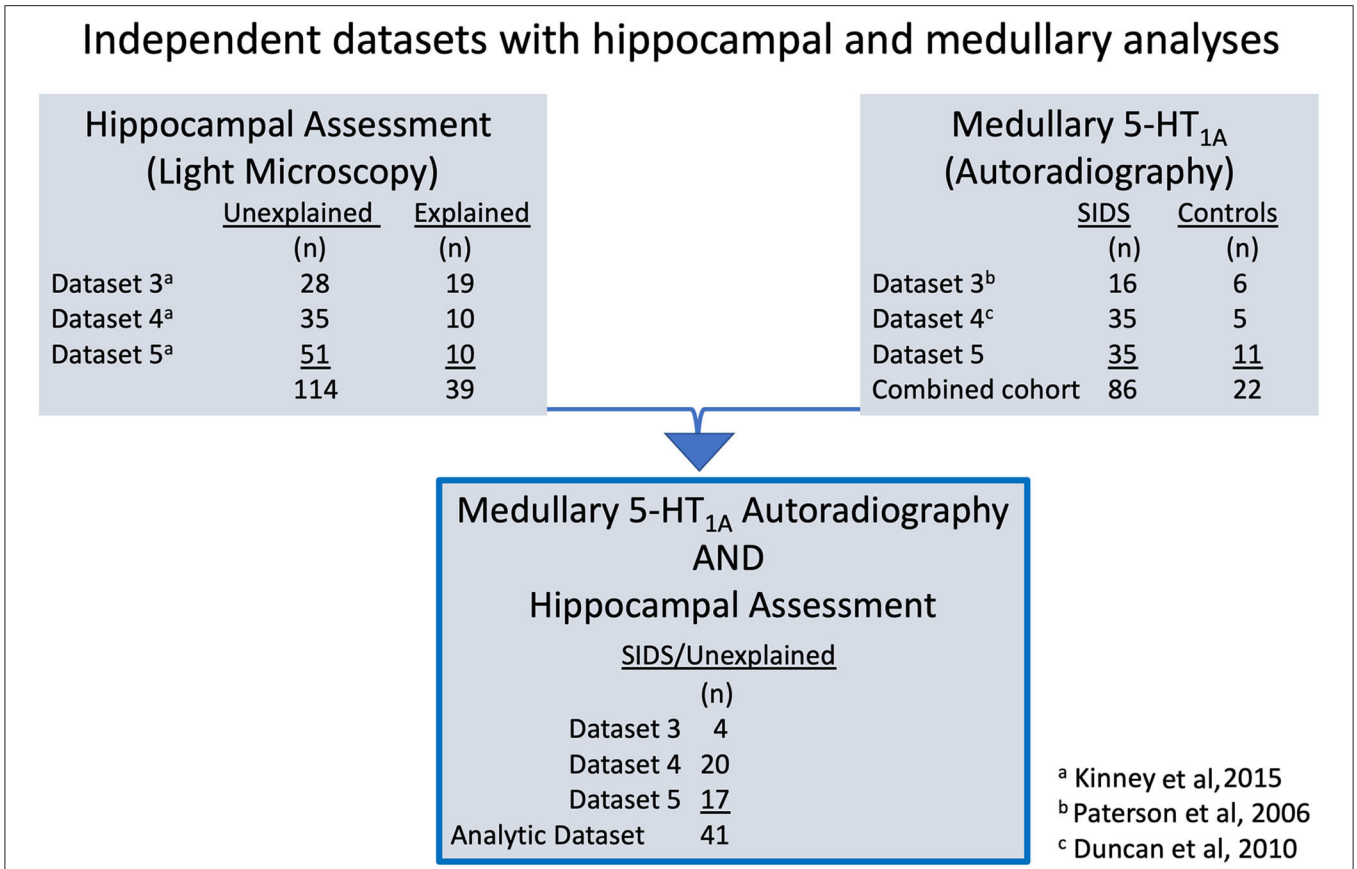

FIGURE 2 | The diagram illustrates the different laboratory datasets from which the analytic cohort ($n = 41$) originates. Datasets 3–5 are independent datasets with no overlap in SIDS or control cases. Fixed hippocampus tissue was available for morphological assessment on a total of 153 cases. Hippocampal results were reported in Kinney et al. (8) using adjudications of unexplained ($n = 114$) and explained ($n = 39$). Frozen medulla tissue was available for 5-HT_{1A} receptor autoradiography on 108 total cases. Results from analysis of medullary 5-HT_{1A} binding data from Datasets 3 and 4 have been previously published in Paterson et al. (4) and Duncan et al. (5), respectively. Additional 5-HT_{1A} binding data from a third independent dataset, Dataset 5, have been collected and added to published Datasets 3 and 4 for the combined cohort of 108, including 86 SIDS cases and 22 controls in this report (See **Figure 3**). Individual SIDS cases that had available hippocampal assessment data and medullary 5-HT_{1A} receptor binding data comprise the analytic cohort ($n = 41$ SIDS). Of note, all 41 SIDS cases were adjudicated as unexplained in Kinney et al. (8).

adjudicated as SIDS were those in which a complete autopsy, death scene investigation, and review of the clinical history and circumstances of death, failed to reveal a known cause of death (COD) (4, 5). All cases were internally adjudicated using standard protocols, autopsy, and death scene investigations. Adjudications were done blinded to findings in the medulla and the hippocampus.

Combined Cohort of SIDS and Controls for Analysis of Medullary 5-HT_{1A} Binding

Data on 5-HT_{1A} binding levels were obtained from a combined cohort of SIDS ($n = 86$) and control ($n = 22$) cases that originated from multiple, independent datasets collected over different periods of time. The individual datasets comprising the cohort were designated in our laboratory as Dataset 3 [$n = 22$; 6 controls,16 SIDS], including cases collected from 1998 to 2004 (4), Dataset 4 [$n = 40$; 5 controls, 35 SIDS], including cases collected from 2004 to 2008 (5), and Dataset 5 [$n = 46$; 11 controls, 35 SIDS], including cases collected from 2008 to 2013 [unpublished]. Medullary 5-HT_{1A} binding was performed on medulla taken at autopsy then fresh-frozen. Controls in our combined cohort for 5-HT_{1A} analysis were infants that died from a definitive COD. The CODs are as follows: congenital heart disease ($n = 7$); respiratory infection ($n = 4$); asphyxial accident (e.g., wedging of head) ($n = 4$); drowning ($n = 1$); gastroesophageal reflux disease ($n = 1$); complication of prematurity ($n = 1$); fatty acid oxidation disorder ($n = 1$); hemolytic anemia associated with febrile illness ($n = 1$); meconium aspiration ($n = 1$); complications of traumatic placental abruption ($n = 1$). The combined cohort represents all SIDS and control cases to date that originated from the SDME and were analyzed in our laboratory for medullary 5-HT_{1A} binding. Of the 86 SIDS cases in this combined cohort, 41 had hippocampal data available for analysis, as described below in "*SIDS subset with both medullary 5-HT_{1A} binding and hippocampal analyses*" and depicted in **Figure 2**.

Original Dataset of SIDS and Controls for Hippocampal Features

Hippocampal features were originally examined in 153 cases. These cases included 114 cases adjudicated as unexplained deaths and 39 cases adjudicated as explained deaths (8). Histological assessment was performed on formalin-fixed tissue taken at autopsy. The definition of unexplained, as published by Kinney et. al. (8), is equivalent to the definition of SIDS as reported in previous 5-HT_{1A} binding studies (4, 5). In our current study, we use the term SIDS, rather than unexplained, to be consistent with previous published brainstem neurochemistry studies (4, 5). Of the 114 SIDS cases with hippocampal assessment, 41 had medullary 5-HT_{1A} binding measurements available for analysis, as described below in "*SIDS subset with both medullary 5-HT_{1A} binding and hippocampal analyses*" and depicted in **Figure 2**.

SIDS Analytic Cohort With Both Medullary 5-HT_{1A} Binding and Hippocampal Analyses

Forty one SIDS cases had both hippocampal assessment and medullary 5-HT_{1A} binding data and comprise the analytic cohort (**Figure 2**). This combined SIDS cohort with data from frozen medulla and fixed hippocampus includes the following: Dataset 3 SIDS ($n = 4$) (4), Dataset 4 SIDS ($n = 20$) (5), and Dataset 5 SIDS [unpublished] ($n = 17$).

Hippocampal Study Review

Hippocampi analyses and data were previously published (8). Briefly, coronal hippocampal sections (6μm) were independently analyzed by pediatric neuropathologists (Kinney, Armstrong). The presence or absence of 44 developmental and acquired features in the DG, Ammon's horn, subiculum, entorhinal cortex, temporal cortex and white matter was assessed for each case (8).

Brainstem Receptor Autoradiography

Receptor autoradiography for medullary 5-HT_{1A} binding was previously performed on frozen medulla of Datasets 3 and 4 using ^{3}H 8-hydroxy-2-[di-N-propylamino]-tetralin (^{3}H-DPAT) as described (4, 5). Frozen medulla from Dataset 5 were analyzed using these same protocols. For this report, we focused our analysis on eight nuclei that contain 5-HT-producing neurons (raphe obscurus [RO], gigantocellularis [GC], paragigantocellularis lateralis [PGCL], intermediate reticular formation [IRZ], and arcuate nucleus [ARC]) and nuclei that contain 5-HT projections (nucleus of the solitary tract [NTS], hypoglossal nucleus [HG], and dorsal motor nucleus of the vagus [DMX]).

Statistical Analyses

Medullary Abnormalities in 5-HT_{1A} Across the Combined Cohort of Cases With 5-HT_{1A} Binding

Analysis of covariance was performed to examine differences in mean 5-HT_{1A} binding in SIDS vs. Controls, adjusted for postconceptional age and dataset, as these two variables are potential confounders due to their association with both 5HT_{1A} binding and diagnosis (SIDS vs. Control).

A test of interaction between diagnosis (SIDS vs. Control) and postconceptional age was also performed. Least-squares (adjusted) means with standard error for SIDS vs. Controls were reported for the models involving nuclei that had no age by diagnosis interaction. Slope estimates of 5-HT_{1A} binding as a function of age were reported for the models from nuclei that displayed a significant age by diagnosis interaction.

Comparison of Mean 5-HT_{1A} Binding With the Presence or Absence of Specific Hippocampal Abnormalities

To look for an association between low 5-HT_{1A} binding and hippocampal abnormalities, we chose to focus on hippocampal features that were significantly more common in SIDS cases compared with controls (8). These features, thought to be developmental in nature as opposed to acquired (e.g, due to hypoxia), include focal granule cell bilamination, clusters of immature cells in the subgranular layer, and single ectopic granule cells in the molecular layer of the DG. The primary outcomes were 5-HT_{1A} binding values in fmol/mg (continuous outcome) in each nucleus. Multivariable linear regression was used to compare mean 5-HT_{1A} binding in SIDS cases with and without the hippocampal feature, adjusted for dataset and postconceptional age (PCA) [gestational age + postnatal age] (**Table 5**).

Association Between the Presence of a Hippocampal Abnormality and Low 5-HT_{1A} Binding

For each nucleus, multivariable logistic regression was used to estimate the association between the binary, 5-HT_{1A} (lowest quartile [Q1] vs. above first quartile) outcome variable and the presence vs. absence of a hippocampal feature, adjusted for PCA. Classification into the lowest quartile was based on the distribution of binding specific to each dataset. Classification of 5-HT_{1A} binding within individual datasets was necessary because of small, but significant, differences in binding data across datasets collected over the 14 year period of case collection and analysis. For **Table 6**, the presence vs. absence of a hippocampal abnormality was instead modeled as the outcome, and for each model the PCA-adjusted predicted probability of having a hippocampal abnormality was reported.

Analyses of SIDS Subsets as Defined by the Presence or Absence of Low Medullary 5-HT_{1A} Binding and Hippocampal Features

SIDS cases were grouped into four subsets according to the presence vs. absence of low medullary 5-HT_{1A} binding and presence vs. absence of a specific hippocampal feature. A SIDS case was defined as having low medullary 5-HT_{1A} binding if 5-HT_{1A} binding was in the lowest quartile (Q1) for two or more of the eight medullary nuclei. A test of association between clinical features and SIDS subsets (four groups: presence vs. absence of hippocampal abnormality X binding in Q1 vs. binding above Q1) was performed using a Fisher exact test for categorical features, and a Wilcoxon rank sum test for continuous features.

In all analyses, a $p < 0.05$ was considered statistically significant. Comparisons were not adjusted for multiplicity associated with examination of differences in multiple brain nuclei.

Analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.0.3.

RESULTS

Medullary Abnormalities in 5-HT$_{1A}$ Across the Combined Cohort of SIDS and Control Cases With 5-HT$_{1A}$ Receptor Binding Data

Before analyzing the analytic cohort of SIDS cases with both hippocampal assessment and medullary 5-HT$_{1A}$ binding data, we examined the full combined 5-HT$_{1A}$ cohort of SIDS cases ($n = 86$) for abnormalities in 5-HT$_{1A}$ binding compared to control cases ($n = 22$). The demographics of SIDS and control cases are noted in **Table 1**. The two groups differed with respect to median PCA; therefore, SIDS vs. control comparisons were adjusted for PCA. Mean postmortem interval (PMI) was higher ($p = 0.025$) in the SIDS cases. As previously published (4, 5), however, there was no effect of PMI on 5-HT$_{1A}$ binding. In two nuclei, the GC and NTS, there was lower PCA-adjusted mean binding in SIDS infants compared to controls ($p = 0.006$ and 0.02, respectively) (**Table 2**). Statistical analyses of this combined cohort showed a significant age vs. diagnosis interaction in the following nuclei: RO ($p = 0.005$), PGCL ($p = 0.006$), IRZ ($p = 0.046$), HG ($p = 0.02$) (**Table 2**; **Figure 3**). Within these nuclei the age vs. diagnosis interaction shows that 5-HT$_{1A}$ binding decreases with PCA in SIDS cases, but binding does not vary with age in control cases. In the remaining two nuclei, the ARC and DMX, there was no interaction and no difference in mean binding between SIDS infants and controls (**Table 2**).

TABLE 1 | Demographics of the SIDS and control cases comprising the full combined cohort for 5-HT$_{1A}$ binding analysis.

	Controls	SIDS	*p*-value
	Mean ± SD or *n* (%)		
N	22	86	
Gestational age (wk)	38.8 ± 1.9	38.3 ± 3.2	0.46
Postnatal age (wk)	9.1 ± 12.8	15.7 ± 8.9	0.006
Postconceptional age (wk)	47.9 ± 13.3	54.0 ± 8.8	0.01
Median (IQR) Postconceptional age (wk)	41.9 (40.3, 53.3)	52.6 (48.0, 58.2)	0.001
Prematurity (GA<37 weeks)	3 (14%)	17 (20%)	0.76
Postmortem interval (hr)	15.5 ± 6.7	19.2 ± 7.0	0.03
Male sex	8 (36%)	14 (64%)	0.15
Race/ethnicity			0.04
White	6 (30%)	36 (44%)	
Black	5 (25%)	9 (11%)	
Hispanic	9 (45%)	23 (28%)	
Other	0 (0%)	13 (16%)	
Unknown	7	5	

SIDS, sudden infant death syndrome; 5-HT, serotonin; SD, standard deviation; wk, week; PCA, postconceptional age; GA, gestational age; hr, hours. SD, Standard Deviation; IQR, interquartile range.

Hippocampal Features

We focused on three hippocampal features that were significantly more common in SIDS cases compared with controls (8); focal granule cell bilamination, clusters of immature cells in the subgranular layer, and single ectopic granule cells in the molecular layer of the DG. **Figure 1** shows an example of these features while **Table 3** shows the prevalence of these abnormalities in the original report (8) and in the SIDS analytic cohort from this report that have medullary 5-HT$_{1A}$ data. Of note, the prevalence of clusters of immature cells in the subgranular layer was higher (73.2% vs. 53.5%, $p = 0.04$) in the current SIDS cases compared to the prevalence in the published cases (**Table 3**). This may be due to sampling variation. The prevalences of the other hippocampal features were similar for the Kinney et al. (8) and present study.

TABLE 2 | 5-HT$_{1A}$ receptor binding in the medullary serotonin system in a combined cohort of SIDS and controls.

		Age- and dataset-adjusted mean ± SE fmol/mg tissue				Estimated slope ± SE, fmol/mg tissue	
Nucleus	**N SIDS/ Controls**	**SIDS**	**Controls**	***p*-value**	**Age x Diagnosis Interaction *p*-value[a]**	**SIDS Change in binding per week**	**Controls Change in binding per week**
RO	78/22	–	–	–	0.005	−0.61 ± 0.26[b]	+0.57 ± 0.33
GC	78/22	16.30 ± 1.01	22.36 ± 1.87	0.006	n.s.		
PGCL	78/22	–	–	–	0.006	−0.21 ± 0.09 [b]	+0.18 ± 0.11
IRZ	77/22	–	–	–	0.05	−0.18 ± 0.07 [b]	+0.03 ± 0.08
ARC	56/16	5.32 ± 0.40	6.54 ± 0.71	0.14	n.s.		
HG	68/17	–	–	–	0.02	−0.09 ± 0.04 [b]	+0.08 ± 0.05
DMX	53/11	8.26 ± 0.52	9.55 ± 1.16	0.32	n.s.		
NTS	68/17	10.26 ± 0.54	13.08 ± 1.06	0.02	n.s.		

All estimates are adjusted for postconceptional age and dataset. Abbreviations. SIDS, sudden infant death syndrome; 5-HT, serotonin; RO, raphe obscurus; GC, gigantocellularis; PGCL, paragigantocellularis lateralis; IRZ, intermediate reticular zone; ARC, arcuate nucleus; HG, hypoglossal nucleus; DMX, dorsal motor nucleus of the vagus; NTS, nucleus of the solitary tract; SE, standard error; n.s., not significant. The numbers (N) of SIDS and controls are given in the second column. The total N varies due to the fact that not every case had binding data available for every nucleus.

[a] *With a significant postconceptional age X diagnosis interaction, estimated slopes are provided because the difference in means between SIDS cases and controls varies by age.*

[b] *Slope differs from zero, $p < 0.05$.*

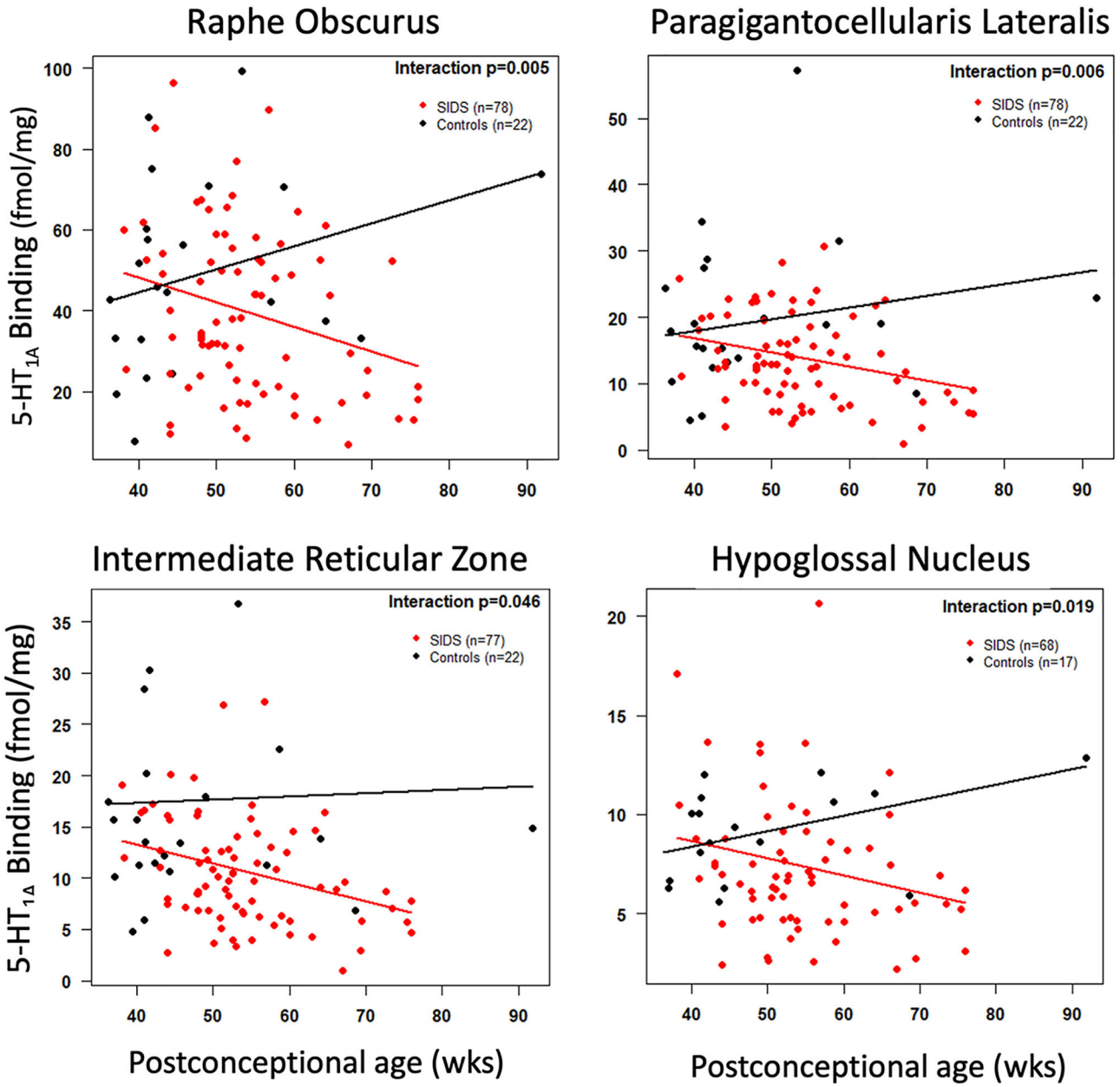

FIGURE 3 | Cross-sectional association of postconceptional age and medullary 5-HT_{1A} binding in selected nuclei. The red and black lines represent the estimated dataset-adjusted mean of 5-HT_{1A} binding according to postconceptional age for SIDS and controls from combined datasets, respectively. The *p*-value reflects a postconceptional age × Diagnosis interaction.

Demographic Data of SIDS Analytic Cohort With Both Hippocampal Analysis and Medullary 5-HT_{1A} Binding

Demographic data for all SIDS cases in the analytic cohort are shown in **Table 4**. There were no significant differences in the demographics of the cases from the three datasets (Datasets 3, 4, and 5) (data not shown).

Comparison of Mean 5-HT_{1A} Binding With the Presence or Absence of Specific Hippocampal Abnormalities

In the SIDS analytic cohort with both hippocampal analysis and 5-HT_{1A} binding data ($n = 41$), we addressed the hypothesis that the SIDS cases with a hippocampal abnormality will have lower medullary 5-HT_{1A} binding compared to SIDS cases

TABLE 3 | Prevalence of hippocampal features of interest in Kinney et al. (8) and their prevalence in the analytic cohort of SIDS with available medullary 5-HT_{1A} binding data.

Hippocampal feature	Published prevalence in controls (8)	Published prevalence in SIDS (8)*	Prevalence in the analytic cohort of SIDS cases with medullary 5-HT_{1A} data
Focal granule cell bilamination	7.7%; 95% CI 1.6–20.9% (3/39)	41.2%; 95% CI 32.1–50.8% (47/114)	56.1%; 95% CI 39.8–71.5% (23/41)
Clusters of immature cells in subgranular layer	10.3%; 95% CI 2.9–24.2% (4/39)	53.5%; 95% CI 43.9–62.9% (61/114)	73.2%; 95% CI 57.1–85.8% (30/41)
Single ectopic granule cells in molecular layer of dentate gyrus	33.3%; 95% CI 19.1–50.2% (13/39)	57.9%; 95% CI 48.3–67.1% (66/114)	63.4%; 95% CI 46.9–77.9% (26/41)

**The prevalence of each hippocampal feature is significantly greater in SIDS than controls ($p \leq 0.01$) (8). SIDS, sudden infant death syndrome; 5-HT, serotonin; CI, confidence interval.*

TABLE 4 | Demographics of the SIDS analytic cohort with hippocampal assessment and 5-HT_{1A} binding.

	Analytic cohort of SIDS cases with medullary 5-HT_{1A} analysis and hippocampal assessment Mean ± SD or *n* (%)
N	41
Gestational age (wk)	38.7 ± 2.9
Postnatal age (wk)	16.3 ± 8.5
Postconceptional age (wk)	54.9 ± 8.1
Median (IQR) postconceptional age (wk)	53.0 (49.0, 59.0)
Prematurity (GA<37 weeks)	6 (15%)
Postmortem interval (hr)	19.7 ± 6.2
Male sex	25 (61%)
Race/ethnicity	
White	18 (46%)
Black	2 (5%)
Hispanic	12 (31%)
Other	7 (18%)
Unknown	2

SIDS, sudden infant death syndrome; 5-HT, serotonin; wk, week; GA, gestational age; hr, hour; SD, Standard Deviation; %, percent; IQR, interquartile range.

without a hippocampal feature (**Table 5**). We found no difference in medullary 5-HT_{1A} binding levels in SIDS cases with or without granule cell bilamination (**Table 5**). There was no difference in medullary 5-HT_{1A} binding in 7 of 8 nuclei with or without clusters of immature cells in the subgranular layer. One exception, the raphe obscurus (RO), showed higher mean binding in SIDS cases with the hippocampal abnormality ($p = 0.04$) (**Table 5**). There was no difference in medullary 5-HT_{1A} binding in 6 of 8 nuclei with or without single ectopic granule cells in the molecular layer of the DG. In the HG and DMX, mean medullary 5-HT_{1A} binding was lower ($p = 0.033$ and 0.01, respectively) in SIDS cases with the hippocampal feature compared to SIDS cases without the hippocampal feature (**Table 5**).

TABLE 5 | Medullary 5-HT_{1A} binding in SIDS cases with and without specific hippocampal abnormalities.

Medullary Nucleus	N Absent/ Present	Adjusted Mean 5-HT_{1A} binding in fmol/mg ± SE: Hippocampal abnormality-ABSENT	Adjusted Mean 5-HT_{1A} binding in fmol/mg ± SE: Hippocampal abnormality-PRESENT	Age- and dataset-adjusted *p*-value
FOCAL GRANULE CELL BILAMINATION				
RO	16/23	38.67 ± 6.36	33.57 ± 5.06	0.49
GC	16/23	15.73 ± 2.27	14.58 ± 1.80	0.66
PGCL	16/23	12.80 ± 1.76	11.79 ± 1.40	0.62
IRZ	16/22	10.03 ± 1.44	8.75 ± 1.16	0.45
ARC	10/15	3.88 ± 1.27	4.80 ± 0.95	0.51
HG	15/16	7.47 ± 1.17	7.21 ± 1.05	0.86
DMX	14/13	8.08 ± 1.05	7.64 ± 1.13	0.78
NTS	15/16	9.13 ± 1.09	9.05 ± 0.98	0.95
CLUSTERS OF IMMATURE CELLS IN SUBGRANULAR LAYER				
RO	9/30	21.82 ± 7.67	39.34 ± 4.49	**0.04**
GC	9/30	11.97 ± 2.83	15.87 ± 1.65	0.21
PGCL	9/30	9.70 ± 2.19	12.87 ± 1.29	0.20
IRZ	9/29	7.80 ± 1.82	9.65 ± 1.08	0.36
ARC	5/20	4.65 ± 1.62	4.49 ± 0.90	0.92
HG	8/23	6.52 ± 1.60	7.57 ± 0.92	0.57
DMX	7/20	7.65 ± 1.64	7.94 ± 0.89	0.88
NTS	8/23	7.76 ± 1.48	9.48 ± 0.85	0.30
SINGLE ECTOPIC GRANULE CELLS IN MOLECULAR LAYER OF DG				
RO	14/25	41.24 ± 6.32	31.80 ± 5.14	0.22
GC	14/25	15.13 ± 2.29	14.92 ± 1.86	0.94
PGCL	14/25	12.56 ± 1.78	11.91 ± 1.45	0.76
IRZ	14/24	10.49 ± 1.43	8.41 ± 1.18	0.24
ARC	10/15	4.08 ± 1.13	4.86 ± 1.05	0.57
HG	13/18	9.08 ± 1.08	5.98 ± 0.96	**0.03**
DMX	5/11	10.17 ± 1.06	6.27 ± 0.89	**0.01**
NTS	13/18	10.55 ± 1.04	7.97 ± 0.92	0.06

SIDS, sudden infant death syndrome; 5-HT, serotonin; RO, raphe obscurus; GC, gigantocellularis; PGCL, paragigantocellularis lateralis; IRZ, intermediate reticular zone; ARC, arcuate nucleus; HG, hypoglossal nucleus; DMX, dorsal motor nucleus of the vagus; NTS, nucleus of the solitary tract; SE, standard error. The numbers (N) of SIDS cases with the presence or absence of the hippocampal feature are given in the second column. The total N varies due to the fact that not every SIDS case had binding in every nucleus. Significant p-values ($p < 0.05$) are bolded.

TABLE 6 | Estimated age-adjusted prevalence of hippocampal abnormality in SIDS cases with low (first quartile) vs. higher 5-HT_{1A} binding (quartiles 2–4).

Medullary nucleus	N Q1/ Q2–Q4	% with hippocampal feature ± SE		Age-adjusted *p*-value
		Q1	Q2–Q4	
FOCAL GRANULE CELL BILAMINATION				
Composite*	16/25	66 ± 12	50 ± 10	0.35
RO	10/29	61 ± 16	59 ± 9	0.90
GC	10/29	43 ± 16	65 ± 9	0.25
PGCL	11/28	58 ± 16	60 ± 9	094
IRZ	10/28	50 ± 16	61 ± 9	0.54
ARC	7/18	44 ± 19	66 ± 11	0.31
HG	9/22	55 ± 17	50 ± 11	0.81
DMX	8/19	67 ± 17	40 ± 12	0.25
NTS	9/22	45 ± 17	54 ± 11	0.62
CLUSTERS OF IMMATURE CELLS IN SUBGRANULAR LAYER				
Composite*	16/25	74 ± 12	76 ± 9	0.90
RO	10/29	73 ± 15	81 ± 8	0.59
GC	10/29	68 ± 16	83 ± 7	0.34
PGCL	11/28	71 ± 15	82 ± 7	0.45
IRZ	10/28	60 ± 17	85 ± 7	0.14
ARC	7/18	89 ± 11	79 ± 10	0.56
HG	9/22	67 ± 17	81 ± 9	0.42
DMX	8/19	84 ± 13	72 ± 11	0.52
NTS	9/22	69 ± 16	80 ± 9	0.53
SINGLE ECTOPIC GRANULE CELLS IN MOLECULAR LAYER OF THE DENTATE GYRUS				
Composite*	16/25	68 ± 13	62 ± 10	0.71
RO	10/29	73 ± 15	62 ± 10	0.57
GC	10/29	57 ± 17	68 ± 10	0.56
PGCL	11/28	72 ± 15	63 ± 10	0.62
IRZ	10/28	60 ± 16	65 ± 9	0.78
ARC	7/18	46 ± 19	66 ± 12	0.36
HG	9/22	79 ± 14	50 ± 11	0.17
DMX	8/19	89 ± 11	43 ± 14	0.08
NTS	9/22	81 ± 14	49 ± 12	0.14

Estimates are adjusted for post-conceptional age and classification of low binding is performed within dataset. SIDS, sudden infant death syndrome; 5-HT, serotonin; RO, raphe obscurus; GC, gigantocellularis; PGCL, paragigantocellularis lateralis; IRZ, intermediate reticular zone; ARC, arcuate nucleus; HG, hypoglossal nucleus; DMX, dorsal motor nucleus of the vagus; NTS, nucleus of the solitary tract; SE, standard error. The numbers (N) of SIDS cases in Q1 and Q2–Q4 are given in the second column. The total N varies due to the fact that not every SIDS case had binding in every nucleus.

**Composite measure is an indicator for a case having low 5-HT_{1A} binding (Q1) in at least 2 nuclei.*

Association Between the Presence of a Hippocampal Abnormality and Low 5-HT_{1A} Binding

We addressed the hypothesis that SIDS cases with the lowest medullary 5-HT_{1A} binding have a higher prevalence of hippocampal abnormalities compared to SIDS cases with higher binding. We rationalized that if there is an association between a hippocampal feature and low medullary 5-HT_{1A} binding, there would be a higher prevalence of the feature in the SIDS cases with the lowest binding. We saw no difference in the prevalence of hippocampal abnormalities in SIDS cases with the lowest binding (Q1) compared to SIDS cases defined as having higher binding (Q2-Q4). This was true for all hippocampal abnormalities and all medullary nuclei including a composite measure representing low binding in at least two nuclei (**Table 6**).

Analyses of SIDS Subsets as Defined by the Presence or Absence of Low Medullary 5-HT_{1A} Binding and Hippocampal Features

Although we did not find significant associations between low medullary 5-HT_{1A} binding (defined as binding in the lowest quartile) and hippocampal abnormalities (**Table 6**), there are cases within the cohort that exhibit both lesions [Subset 4] (**Figure 4**). **Table 7** shows clinical and risk factor data associated with SIDS subsets based on the presence or absence of medullary 5-HT_{1A} binding in the lowest quartile of binding (Q1) with and without the presence of focal granule cell bilamination. There were 10 SIDS cases (10/41, 24%) that showed both low medullary 5-HT_{1A} binding and DG bilamination [Subset 4]. There was no significant difference in PCA, gestational age (GA), male sex, illness 24–48 h prior to death, body position (prone), face position (face down or face covered), prevalence of bedsharing, or sleep site across the different groups. There was a significant difference ($p = 0.007$) in the prevalence of premature birth (birth <37 gestational weeks), with the highest prevalence of premature birth in the SIDS subset with low 5-HT_{1A} binding only (50%) (**Table 7**) [Subset 2]. There were no premature infants in the SIDS subset with focal granule cell bilamination, with or without low medullary 5-HT_{1A} binding [Subset 3 and 4, respectively]. There was no difference in reported prenatal alcohol exposure. There was a higher prevalence of prenatal smoking (60%) in the subset with medullary 5-HT_{1A} abnormalities only [Subset 2] compared with the other three subsets (0–33% prenatal smoking), but this comparison was not statistically significant ($p = 0.10$). In addition to the clinical and risk factors listed, we also examined the prevalence of the following factors: history of illness 1 week prior to death, position to sleep, position found, prenatal exposure to selective serotonin reuptake inhibitors (SSRIs), complications of pregnancy, complications of labor, complications of delivery, complications of the postnatal period, and minor congenital abnormalities. There were no statistical differences found with these clinical features among the SIDS subsets (data not shown).

We performed similar analyses on SIDS subsets with and without hippocampal clusters of immature cells in the subgranular layer of the hippocampus (**Table 8**). Mean PCA was higher in the SIDS subset without either lesion (Subset 1) ($p = 0.04$) (**Table 8**). This reflects a higher postnatal age in this subset, given that gestational age is not different. Cases from this same group were also more likely to have been sleeping somewhere besides the crib ($p = 0.03$). There were no significant differences among the subsets in prenatal exposures to SSRIs, alcohol, and smoking.

In the analysis of SIDS subsets with and without single ectopic granule cells in the molecular layer of the DG (**Table 9**), there was a borderline significant difference in PCA ($p = 0.05$) and the face position (face down or face covered) ($p = 0.09$). There

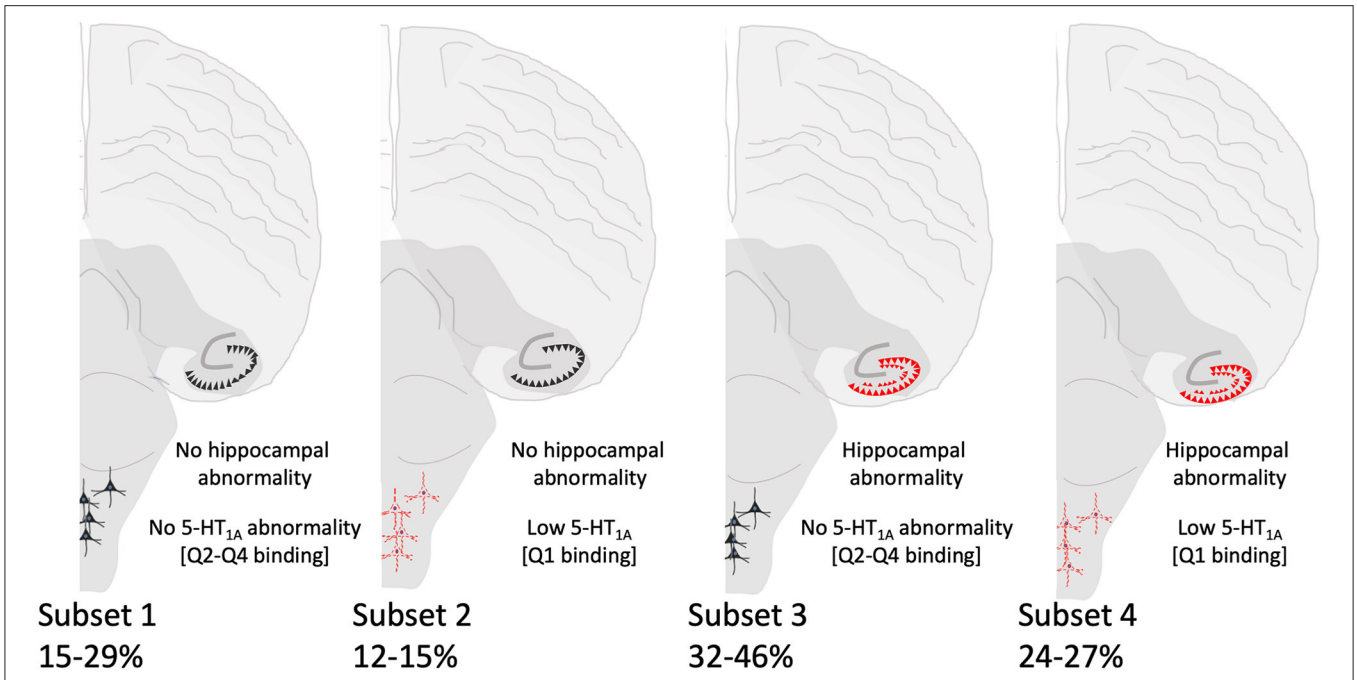

FIGURE 4 | Summary of SIDS subsets based on hippocampal and brainstem (5-HT_{1A}) abnormalities. Hippocampal morphological and brainstem 5-HT_{1A} abnormalities are depicted in red. The percentages of SIDS cases falling within each subset are shown and vary depending on the hippocampal feature.

TABLE 7 | Clinical and risk factor profile by medullary 5-HT_{1A} binding and hippocampal feature (focal granule cell bilamination) status.

Clinical feature/ risk factor	5-HT_{1A} binding within Q2–Q4 without hippocampal feature [Subset 1]	Low (Q1) 5-HT_{1A} binding only [Subset 2]	Hippocampal feature Only [Subset 3]	Low (Q1) 5-HT_{1A} binding with hippocampal feature [Subset 4]	*p*-value
N	12 (29%)	6 (15%)	13 (32%)	10 (24%)	
Postconceptional age (wk)	54.7 ± 6.8	61.0 ± 11.2	53.0 ± 8.3	54.2 ± 6.4	0.24
Gestational age (wk)	37.8 ± 4.4	37.5 ± 3.6	39.3 ± 1.1	39.7 ± 0.9	0.10
Prematurity	3 (25%)	3 (50%)	0 (0%)	0 (0%)	**0.007**
Male sex	7 (58%)	4 (67%)	9 (69%)	5 (50%)	0.82
Illness 24–48 h prior to death (*N* = 12; 6; 13; 9)	2 (17%)	2 (33%)	4 (31%)	4 (44%)	0.59
Found prone (*N* = 12; 4; 12; 8)	5 (42%)	2 (50%)	6 (50%)	7 (88%)	0.19
Face down or Face covered (*N* = 9; 3; 9; 7)	4 (36%)	2 (18%)	1 (9%)	4 (36%)	0.18
Bed Sharing	3 (25%)	1 (17%)	4 (31%)	2 (20%)	0.96
Smoking (*N* = 6; 5; 12; 6)	0	3 (60%)	2 (17%)	2 (33%)	0.10
Alcohol (*N* = 6; 4; 9; 7)	0	0	0	1 (14%)	0.65
Sleep site (*N* = 12; 6; 11; 10)					0.18
Crib	7 (58%)	4 (67%)	2 (18%)	5 (50%)	
Adult bed	4 (33%)	1 (17%)	8 (73%)	4 (40%)	
Sofa	0	0	0	0	
Car seat	0	0	1 (9%)	0	
Other	1 (8%)	1 (17%)	0 (0%)	1 (10%)	

5-HT, serotonin; Q, quartile; N, number; wk, week. Information on some risk factors was not available for every case. The N's shown under the risk factor in the first column indicate the number of cases in each subset with information available when missing data were present. Significant p-values (p < 0.05) are bolded.

TABLE 8 | Clinical and risk factor profile by medullary 5-HT_{1A} binding and hippocampal feature (clusters of immature cells in the subgranular layer).

Clinical feature/ risk Factor	5-HT_{1A} binding within Q2–Q4 without hippocampal feature [Subset 1]	Low (Q1) 5-HT_{1A} binding only [Subset 2]	Hippocampal feature only [Subset 3]	Low (Q1) 5-HT_{1A} binding with hippocampal feature [Subset 4]	*p*-value
N	6 (15%)	5 (12%)	19 (46%)	11 (27%)	
Postconceptional age (wk)	61.3 ± 9.3	57.1 ± 13.6	51.4 ± 5.1	56.5 ± 6.6	**0.04**
Gestational age (wk)	38.8 ± 2.4	37.7 ± 3.5	38.5 ± 3.4	39.4 ± 1.9	0.77
Prematurity	1 (17%)	2 (40%)	2 (11%)	1 (10%)	0.33
Male sex	4 (67%)	4 (80%)	12 (63%)	5 (45%)	0.60
Found prone (*N* = 6; 3; 18;9)	2 (33%)	2 (67%)	9 (50%)	7 (78%)	0.35
Face down or Face covered (*N* = 5; 3; 13;7)	0 (0%)	2 (18%)	5 (45%)	4 (36%)	0.18
Bed Sharing	1 (17%)	0 (0%)	6 (32%)	3 (27%)	0.67
Illness 24–48 h prior to death (*N* = 6; 4; 19; 11)	1 (17%)	1 (25%)	5 (26%)	5 (45%)	0.65
Smoking (*N* = 4; 3; 14; 8)	0	2 (67%)	2 (14%)	3 (38%)	0.14
Alcohol (*N* = 4; 2; 11; 9)	0	0	0	1 (11%)	0.58
Sleep site (*N* = 6; 5; 17; 11)					**0.03**
Crib	1 (17%)	3 (60%)	8 (47%)	6 (55%)	
Adult bed	3 (50%)	0 (0%)	9 (53%)	5 (45%)	
Sofa	0	0	0	0	
Car seat	1 (17%)	0	0	0	
Other	1 (17%)	2 (40%)	0	0	

5-HT, serotonin; Q, quartile; N, number; wk, week. Information on some risk factors was not available for every case. The N's given under the risk factor in the first column indicate the number of cases in each subset with information available when missing data were present. Significant p-values (p < 0.05) are bolded.

was a difference in prenatal smoking ($p = 0.02$) with the highest prevalence of smoking (71%) in the cases with both hippocampal and brainstem 5-HT_{1A} abnormalities [Subset 4]. There were no significant differences amongst the groups in any other clinical or risk factors analyzed (data not shown).

DISCUSSION

We used a combined analytic cohort of SIDS cases from our laboratory to statistically address the hypothesis that hippocampal abnormalities and medullary 5-HT_{1A} abnormalities are associated, with one dependent on the presence of the other. We hypothesized that evidence supporting a dependent relationship between the two lesions would be demonstrated in either (1) decreased medullary binding in the presence of one or more hippocampal lesions, (2) an increased prevalence of hippocampal abnormalities in the cases with the lowest medullary binding, and/or (3) a uneven distribution of cases across the 4 designated subsets with an increased number of SIDS cases with both abnormalities present compared to SIDS cases with only one abnormality. While our resulting data largely support the important observation that our overarching hypothesis is not true, they also highlight the complexity of SIDS etiology. Below we discuss our findings, the limitations of the methods, and contribution of the data to our understanding of SIDS pathology.

Hippocampal-Brainstem Relationship

Our analyses focused on three hippocampal features reported by Kinney et al., to be significantly present in SIDS infants compared to controls (8). The prevalence of these features, particularly granule cell bilamination, among different SIDS cohorts has varied (14, 15) as has the reported specificity of the finding to pathology in pediatric cohorts including SIDS and sudden unexplained death in childhood (9, 10, 12, 14, 29–32). Differences in the statistical significance of these hippocampal features likely reflect cohort size, availability and definitions of controls, differences in and availability of consistent hippocampal levels, and differences among neuropathological assessments. Despite differences among studies, our combined analytic cohort presented a unique opportunity to examine potential relationships between the observations in our laboratory of hippocampal abnormalities and medullary 5-HT_{1A} deficiencies. Using statistical methods, we were largely unable to detect the hypothesized relationships.

TABLE 9 | Clinical and risk factor profile by medullary 5-HT_{1A} binding and hippocampal feature (single ectopic granule cells in the molecular layer of the dentate gyrus) status.

Clinical feature/ risk factor	5-HT_{1A} binding within Q2-Q4 without hippocampal feature [Subset 1]	Low (Q1) 5-HT_{1A} binding only [Subset 2]	Hippocampal feature only [Subset 3]	Low (Q1) 5-HT_{1A} binding with hippocampal feature [Subset 4]	*p*-value
N	9 (22%)	6 (15%)	16 (39%)	10 (24%)	
Postconceptional age (wk)	56.5 ± 9.4	62.3 ± 8.9	52.3 ± 5.9	53.4 ± 7.3	0.05
Gestational age (wk)	39.5 ± 2.1	39.0 ± 2.5	38.1 ± 3.6	38.8 ± 2.6	0.67
Prematurity	1 (11%)	1 (17%)	2 (13%)	2 (20%)	0.93
Male sex	3 (33%)	2 (33%)	6 (38%)	5 (50%)	0.89
Illness 24–48 h prior to death (*N* = 9; 6; 16; 9)	3 (33%)	1 (17%)	3 (19%)	5 (56%)	0.26
Found prone (*N* = 8; 4; 16; 8)	2 (25%)	4 (100%)	9 (57%)	5 (63%)	0.12
Face down or Face covered (*N* = 5; 3; 13; 7)	0	1 (9%)	5 (45%)	5 (45%)	0.09
Bed Sharing	2 (22%)	1 (17%)	5 (31%)	2 (20%)	0.92
Smoking (*N* = 7; 4; 11; 7)	1 (14%)	0	1 (9%)	5 (71%)	**0.02**
Alcohol (*N* = 5; 4; 10; 7)	0	0	0	1 (14%)	0.62
Sleep site (*N* = 7;6;16;10)					0.32
Crib	2 (29%)	4 (67%)	7 (44%)	5 (50%)	
Adult bed	3 (43%)	2 (33%)	9 (56%)	3 (30%)	
Sofa	0	0	0	0	
Car seat	1 (14%)	0	0	0	
Other	1 (14%)	0	0	2 (20%)	

5-HT, serotonin; Q, quartile; N, number; wk, week. Information on some risk factors was not available for every case. The N's given under the risk factor in the first column indicate the number of cases in each subset with information available when missing data were present. Significant p-values ($p < 0.05$) are bolded.

Nonetheless, we did see significant differences in medullary 5-HT_{1A} values when comparing cases with and without clusters of immature cells in the subgranular layer (increased binding in the RO of cases with the hippocampal abnormality) and when comparing cases with and without single ectopic granular cells in the molecular layer of the DG (decreased binding in the HG and DMX of cases with the hippocampal abnormality). The biological significance of these findings is unknown however, particularly given the lack of statistical significance when we examined the prevalence of the hippocampal lesions in cases with low 5-HT_{1A} binding at these medullary sites.

Our original hypothesis that medullary and hippocampal findings in SIDS infants coexist was based partially on the known trophic role of 5-HT during development in neuronal migration and neurogenesis, including in the dentate gyrus of the hippocampus (22–25). While 5-HT present in the hippocampus during hippocampal development is thought to mainly derive from rostral 5-HT groups in the midbrain and pons (33, 34), connectivity between medullary 5-HT nuclei and limbic structures including hippocampus have been shown in the human (27), suggesting a potential additional role for caudal 5-HT groups in hippocampal development. We speculated that abnormalities in the hippocampus in SIDS reflect proliferation and/or migration defects and are due to defective or deficient brainstem 5-HT innervation of the hippocampus, including innervation of the hippocampal Cajal Retzius cells that produce the reelin during development and regulate neuronal migration (24). In addition to potential trophic implications of an abnormal serotonergic system on hippocampal formation, we also considered a potential implication of an abnormal hippocampus on the medullary 5-HT system. Our findings in the hippocampus represent a putative morphological marker of an impaired central homeostatic network involving the limbic system (including hippocampus), brainstem and forebrain (35). An instability in limbic regions, potentially resulting in abnormal seizure-like electrical discharges, could propagate to the medullary regions involved in breathing and/or autonomic function decreasing activity of the 5-HT neurons. The effect of seizure on 5-HT neuronal activity in the medulla during and after seizure activity has been shown in rat models (26) and patients with temporal lobe epilepsy exhibit decreased binding to 5-HT_{1A} receptors within the midbrain raphe (36, 37). Given this, we also postulated a scenario where an abnormal hippocampus and hippocampal electrical discharge, either acutely at the time of death or intermittently during the postnatal period, could lead to abnormal medullary 5-HT neuronal activity in SIDS infants.

In our analysis of SIDS subsets (summarized in **Figure 4**), our assessment of available clinical and risk factor data shows no distinct profile associated with SIDS cases presenting with both hippocampal and medullary abnormalities, SIDS cases with neither hippocampal nor medullary abnormalities, nor SIDS cases presenting at autopsy with abnormalities at only one site (hippocampus or medulla). Interestingly, in our analysis of SIDS subsets with and without low medullary 5-HT_{1A} binding and single ectopic granule cells in the molecular layer of the DG (**Table 9**), we showed a significantly higher rate of prenatal exposure to smoking in the subset of cases with both the brainstem and the hippocampal abnormality. Prenatal smoking is a known risk factor for SIDS and has been related to lower 5-HT_{1A} receptor expression in medullary nuclei of postmortem infants (SIDS and controls) compared with cases with no prenatal smoking history (7). Rodent and primate models of prenatal nicotine exposure also show an effect of prenatal nicotine exposure on the 5-HT_{1A} receptor, albeit with increased 5-HT_{1A} receptor expression (38) and binding (39), respectively. Relative to hippocampal development, prenatal nicotine exposure has effects on hippocampal neuronal signaling and function (40) as well as morphological indices [reviewed in (41)]. Our findings related to this subset of SIDS cases suggest a developmental relationship or connectivity between the medullary and hippocampal entities that is affected more so by prenatal exposure than is either entity alone. The number of cases with exposure information is relatively small and therefore this result should be considered as hypothesis-generating (see Limitations below). In our analysis of SIDS subsets with and without low medullary 5-HT_{1A} binding and focal granule cell bilamination, there was a higher rate of prematurity in the SIDS subset with low medullary 5-HT_{1A} binding only (**Table 7**). Prematurity is a known risk factor for SIDS (42) and vulnerability within this group related to deficits in the medullary 5-HT system is of interest and warrants further study. In this same analysis of SIDS subsets with and without low medullary 5-HT_{1A} and clusters of immature cells in the subgranular layer (**Table 8**), we showed a significant difference in sleep site with a higher proportion of cases with neither hippocampal or medullary abnormalities sleeping in sites other than the crib (e.g., adult bed). Given the low numbers included in this analysis, the significance is unknown. It may, however, reflect a need for an increased burden of SIDS risks factors (sleeping in an adult bed) to precipitate death in cases without these abnormalities.

In our analysis of SIDS subsets, the number of cases (∼25%) with both hippocampal and 5-HT_{1A} abnormalities is of interest. We postulate that in these cases, the hippocampal and brainstem abnormalities may be related, either via mechanisms suggested above or in ways related to an unknown common cause lying upstream of both. In cases displaying only one abnormality, we cannot rule out the possibility that the other abnormality would present itself had the infant lived long enough. Finally, in cases with neither abnormality, the question remains as to the underlying pathogenesis. Death in these cases may be related to other intrinsic (e.g., genetic) or extrinsic (e.g. environmental) risk factors alone or in combination postulated to play a role in SIDS [reviewed in (43)].

In our analyses, we focus on brainstem abnormalities as determined by binding deficiencies in the 5-HT_{1A} receptor in the medulla only. We cannot rule out the possibility that hippocampal abnormalities co-exist with potential 5-HT abnormalities in rostral brainstem structures (pontine or midbrain). Of note, in addition to medullary 5-HT_{1A} abnormalities, we have also observed abnormalities in other 5-HT indices in the medulla including a defect in binding to ^{3}H- lysergic acid diethylamide (LSD), a much broader 5-HT receptor ligand (1, 3), a deficiency in 5-HT levels as determined by high performance liquid chromatography (HPLC) (5), and an increased number of neurons expressing tryptophan hydroxylase 2 (TPH2) [rate determining enzyme in 5-HT production] as determined by immunocytochemistry (4). Thus, we cannot rule out the possibility that hippocampal abnormalities co-exist with other 5-HT abnormalities in rostral or caudal brainstem structures. Overlap between cases to date with hippocampal data and medullary measures of 5-HT level and TPH2 cell number is insufficient to look for associations as we have done here.

Medullary 5-HT_{1A} Abnormalities in the Combined Cohort

In addition to new data discussed above on the relationship between hippocampus and medullary abnormalities, it is important also to emphasize the medullary 5-HT_{1A} data in the full combined cohort [published and unpublished] of SIDS and controls (**Table 2**, **Figure 3**). In this combined cohort, we have confirmed published deficiencies in 5-HT_{1A} binding in multiple nuclei of the rostral and caudal medulla, including nuclei containing 5-HT neurons (RO, GC, PGCL, and IRZ) and nuclei containing 5-HT projections (HG and NTS). These data support the robustness of the published 5-HT_{1A} binding abnormalities in SIDS. Abnormalities in binding include overall decreased binding in SIDS compared to controls (GC and NTS) and significant age vs. diagnosis interactions (RO, PGCL, IRZ, and HG). The latter finding, first reported in Duncan et. al. (5), shows a decreased binding with age in the SIDS cases only. This decrease in binding potentially reflects a dynamic change with age due to instability in binding or compensation over time in response to some other factor or developmental abnormality. Alternatively, it may reflect the possibility that the most vulnerable infants (lowest 5-HT_{1A} binding) are still susceptible at an older age or that infants with a greater deficiency live longer, potentially avoiding for a longer period of time the external stressors that we hypothesize trigger sudden death.

Limitations of Methods

To address the relationship between hippocampal and brainstem 5-HT_{1A} abnormalities, we have utilized a analytic cohort of SIDS cases only. Overlapping hippocampal and brainstem data exist for only 5–9 control cases thus limiting our ability to utilize controls for comparison. Within the SIDS analytic cohort, we have defined low 5-HT_{1A} binding as cases in the lowest quartile (lowest 25%) of binding compared to SIDS cases with binding in all other quartiles (26–100%). We cannot exclude the possibility that hippocampal abnormalities statistically associate with more subtle 5-HT_{1A} deficiencies—that is, SIDS cases falling within

the second quartile of binding (25–50%). Mostly non-significant differences in medullary 5-HT_{1A} binding with or without hippocampal dysmorphology suggests however, that this is not the case (**Table 5**). We also cannot rule out that hippocampal abnormalities associate with medullary 5-HT_{1A} abnormalities defined as low based on controls, an analysis that we could not do due to reasons discussed. Within our SIDS analytic cohort, medullary 5-HT_{1A} data were not available for all medullary nuclei. Thus, in our analysis of SIDS subsets (**Tables 7–9**), our designations of subsets based on low 5-HT_{1A} binding in two or more medullary nuclei have been given without knowledge in some cases of binding in all nuclei. Our receptor binding analyses over 14 years covered three independent datasets. In the binding experiments, we utilize radioactive standards, which normalize the data across experiments. However, over the three different datasets, there were small but significant differences, specifically with Dataset 5 compared with Datasets 3 and 4. This difference was statistically adjusted for in our final analysis but is included in the limitations given the unavoidable nature of experimental variation over such a long period of time. Finally in our analysis of clinical and risk factor data, we report only on what is available in the autopsy and investigative reports. While we analyzed the data for differences in prenatal exposures, we consider these data with caution. The information that is not available is likely missing at random and thus not incurring bias into the comparisons performed. However, the number of cases where exposure information is provided is relatively low and the exposure data that we do have on the cases is general (yes/no) with little information about quantity of exposure or when the exposure occurred (e.g, first, second, or third trimester).

Implications of Independent Hippocampal and Medullary 5-HT_{1A} Brainstem Lesions

Our data support that the presence of the three hippocampal features identified previously as increased in SIDS infants (8) is not strictly dependent on the presence of abnormalities in medullary 5-HT_{1A} binding. Whether these lesions reflect two independent diseases or one disease with minor differences in pathological phenotypes remains unknown. The former supports a heterogenous etiology of SIDS while the latter suggests a common disease process with mechanisms affecting different nodes within the integrated central homeostatic network. Given the number of SIDS cases with and without one or both of the lesions, our data support the heterogenous nature of SIDS with different vulnerabilities in different infants. Hypotheses regarding biological or mechanistic relationship(s) between different vulnerabilities in SIDS and the means by which risk factors intersect these vulnerabilities to increase susceptibility to sudden death remain critical.

DATA AVAILABILITY STATEMENT

Requests to access these datasets should be directed to robin.haynes@childrens.harvard.edu.

AUTHOR CONTRIBUTIONS

RH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RH, HK, and LS: concept and design and drafting of the manuscript. RH, HK, EH, JD, MR, FT, DA, SA, JC, HK, MH, RG, and LS: critical revision of the manuscript for important intellectual content. LS: statistical analysis. RH, HK, and RG: obtained funding. EH, JD, MR, FT, RG, SA, DA, JC, HK, and MH: administrative, technical, or material support. RH and HK: supervision. All authors contributed to the article and approved the submitted version.

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Interventions to Improve Safer Sleep Practices in Families With Children Considered to Be at Increased Risk for Sudden Unexpected Death in Infancy: A Systematic Review

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Background: Advice to families to follow infant care practices known to reduce the risks of Sudden Unexpected Death in Infancy (SUDI) has led to a reduction in deaths across the world. This reduction has slowed in the last decade with most deaths now occurring in families experiencing social and economic deprivation. A systematic review of the literature was commissioned by the National Child Safeguarding Practice Review Panel in England. The review covered three areas: interventions to improve engagement with support services, parental decision-making for the infant sleep environment, and interventions to improve safer sleep practices in families with infants considered to be at risk of SUDI.

Aim: To describe the safer sleep interventions tested with families with infants at risk of SUDI and investigate what this literature can tell us about what works to reduce risk and embed safer sleep practices in this group.

Methods: Eight online databases were systematically searched in December 2019. Intervention studies that targeted families with infants (0–1 year) at increased risk of SUDI were included. Studies were limited to those from Western Europe, North America or Australasia, published in the last 15 years. The Quality Assessment Tool for Studies with Diverse Designs was applied to assess quality. Data from included studies were extracted for narrative synthesis, including mode of delivery using Michie et al.'s Mode of Delivery Taxonomy.

Results: The wider review returned 3,367 papers, with 23 intervention papers. Five types of intervention were identified: (1) infant sleep space and safer sleep education programs, (2) intensive or targeted home visiting services, (3) peer educators/ambassadors, (4) health education/raising awareness interventions, (5) targeted health education messages using digital media.

Conclusion: Influencing behavior in families with infants at risk of SUDI has traditionally focused on "getting messages across," with interventions predominantly using education and awareness raising mechanisms. This review found evidence of interventions moving

from "information giving" to "information exchange" models using personalized, longer term relationship-building models. This shift may represent an improvement in how safer sleep advice is implemented in families with infants at risk, but more robust evidence of effectiveness is required.

Systematic Review Registration: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/901091/DfE_Death_in_infancy_review.pdf, identifier: CRD42020165302.

Keywords: sudden unexpected death in infants, sudden infant death syndrome, interventions, infant safe sleep, systematic review

INTRODUCTION

A baby dying suddenly is devastating for any family. The ramifications spread to wider friends and family, and to health care professionals who supported them during the first months of the baby's life (1). Sudden unexpected death of an infant (SUDI) is the term used at the point of presentation and includes deaths for which a cause will be identified, such as infection, and those that cannot be fully explained and are categorized as sudden infant death syndrome (SIDS) (2) or unascertained, accounting for ∼200 infant deaths annually in England and Wales (3). The demographic profile of these deaths now reveals an inequity gradient, with younger parents living in socio-economic deprivation experiencing the highest rate of infant deaths at 1.18 per 1,000 live births, more than four times the rate in the general population (3). Several characteristics have been associated with higher rates of SUDI which include vulnerable infants (low birthweight, pre-term, multiple births, and admission to NICU), young maternal age, smoking exposure during and after pregnancy, bottle feeding, male preponderance, and lower socio-economic status (3–5). The peak age of death is not the first few weeks of life when infants are at their most vulnerable but at 2–3 months of age. Observational evidence over the last 30 years has identified risk factors pertaining to the infant sleep environment that, when modified, have been shown to reduce the risk of some infant deaths (6). These risks include placing infants to sleep on their side or front, using too many and/ or loose bedclothes, solitary sleep room in the first 6 months, and specific hazardous circumstances for bed-sharing and co-sleeping, such as infants sleeping next to carers who smoke, have consumed alcohol or drugs, or share inappropriate surfaces, for example, sofas; or bedsharing or co-sleeping with a baby born with a low birthweight or pre-term (4, 6, 7).

Some of the background characteristics and recognized risks for SUDI overlap with, but are not predicted by, those of child maltreatment, and families with children who may be at risk of abuse or neglect often face multiple vulnerabilities, including risks of SUDI (8). A recent thematic analysis of 27 SUDI cases leading to Serious Case Reviews in England (9), found families had complex social backgrounds, with long-term neglect, alcohol or drug misuse and non-engagement with services as a prominent feature. The review also identified that safer sleep advice was only documented in half of these families. One of the key challenges in working with high-risk families is not limited to just sharing safer sleep advice, but ensuring the evidence underpinning these messages is better communicated to, and understood by parents, and implemented into both usual and out of routine parenting practices. Out of routine situations which change the infant sleep environment can unintentionally increase risk for infants where make-shift sleeping arrangements or co-sleeping may be the only option and particularly where the priority is to achieve sleep for both infant and parent rather than consider the safety of the sleep environment (10–15). Understanding how best to reach and engage vulnerable families to adopt safer infant care practices has been highlighted in previous research (14–16), however, identifying the most effective interventions or methods to achieve this, or identifying the effective components of interventions that are successful are lacking (17). The second National Child Safeguarding Practice Review (NCSPR) (18) focused on the occurrence of SUDI in families where children were considered to be at risk of abuse or neglect, aiming to identify the most effective methods for professionals to provide effective support to ensure that safer sleep advice can be clearly understood and embedded. As part of their work, the NCSPR Panel commissioned a systematic review in three key areas (19): (1) interventions to improve engagement with support services (20), (2) improving our understanding of parental decision-making processes related to the infant sleep environment (21), and (3) the evidence on interventions for improving the uptake of safer sleep advice, which is the subject of this paper.

This systematic review focuses on the third key area addressing the research question: what safer sleep interventions have been tested for families with infants at risk of SUDI, and what can these tell us about what works to reduce the risk and embed safer sleep practices for infants at higher risk?

METHODS

The review protocol was registered with the International prospective register of systematic reviews, PROSPERO number: CRD42020165302. We focused our review on families with children considered to be at high risk for SUDI, which may significantly overlap with the wider group of families with children considered to be at high risk of significant harm through abuse or neglect. The population of interest included families with infants under the age of 1 year and considered to be at high risk of SUDI, however defined by individual studies. Inclusion criteria for what constituted "high risk" populations

were wide due to the variability of definitions within individual studies. We included all studies that took a targeted approach to intervention and included interventions aimed at improving infant safer sleep practices and included those which sought to influence the infant sleep environment, rather than those aimed at reducing risks such as stopping smoking or increasing breastfeeding. We therefore included interventions with an aim to have any impact on infant sleep position, co-sleeping, bed-sharing, dummy/pacifier use, swaddling, room sharing, infant bedding, exposure to tobacco smoke in the home, or room temperature. Where studies tested an intervention, the comparator was expected to be either standard care or a less intensive version of the intervention.

Our search strategy included terms relating to our population, outcome of interest and intervention terms. Our sample search terms are shown in **Appendix 1**. Our inclusion criteria at screening limited studies of interventions to those reported in the last 15 years and those form Western Europe, North America or Australasia. Given that infant care practices change over time, a scope of 15 years was felt to be reasonable to capture the current practices of parents and carers. One of the main aims of the review was to describe the literature on interventions relevant to the UK population, which meant that consideration for the context in which interventions took place was a relevant factor. While we did not wish to ignore effective interventions from other parts of the world, we did want to focus on those which had been developed and evaluated within broadly similar cultural contexts and infant care practices.

Unpublished reports were included where they met the inclusion criteria and included data on the results or outcomes of the study. Other exclusion criteria included papers relating to explained non-sleep causes of death, for example infections or metabolic disorders found at post-mortem (non-relevant outcome); studies describing interventions for the general population with no high-risk targeting (non-relevant population) and studies describing interventions not related to safer sleep or the sleep environment (non-relevant intervention).

The review was conducted in December 2019 and eight online databases were searched (see **Appendix 1**). Additional searches for gray literature and relevant interventions were conducted in January 2020, by emailing all English Child Death Overview Panels, Designated Doctors for Child Death and Safeguarding, UK safeguarding children's partnerships, and the membership of The International Society for the Study and Prevention of Perinatal and Infant Death, a global non-profit organization of researchers, health professionals and parents. Further snowball searches of included and relevant papers' reference lists were also conducted.

Four authors (AP, JG, CE, DW) scoped the initial search terms and refined a final list of terms for inclusion in each search by assessing the first 30 titles and abstracts in Medline for relevance and other terms. Titles and abstracts were deduplicated in Endnote and imported into Rayyan, online screening software (https://rayyan.qcri.org/). All returned titles and abstracts were screened by four authors (AP, JG, CE, DW), applying the inclusion and exclusion criteria, and conflicts were resolved by examination of the full text and discussion. All included texts were sourced, and the quality of papers assessed using the Quality Assessment Tool for Studies with Diverse Designs (QATSDD) (22). This approach was developed specifically for review questions where the evidence addressing a research question uses a variety of different study designs. The tool is used across both quantitative and qualitative research designs, to facilitate assessment of the quality of studies comparatively across all included studies. Four team members (AP, JG, CE, DW) scored each paper from 0 to 3 on either 14 or 16 items (depending on study design) and converted each score into a percentage. Included papers of review author's own work were independently rated by another team member. Given the expected paucity of data in this field studies were not excluded based on quality assessment but limitations to the findings are discussed where necessary.

Data extraction templates were piloted and refined for use with nine of the included papers of different study designs. The final data extraction form included fields for author's names, year of publication, study design, country, sample size, target population, type of outcome, comparator, outcomes measured and effectiveness. Specific fields for qualitative studies included method of analysis and broad topic categories. For the intervention papers, the mode of delivery was extracted using variables influenced by Michie et al.'s Mode of Delivery Taxonomy (23) and collected data on whether interventions were face to face, on printed material, digital, used equipment, delivered individually, in groups, involved one-way or two-way interaction, and whether they were tailored, meaning that the intervention was responsive to, or changed depending on circumstances of participants. Popay et al.'s (24) framework for conducting narrative reviews is used to standardize narrative approaches to systematic reviews, where the primary synthesis comes from understanding how and why an intervention worked or did not work, rather than meta-analysis which was not possible in this review given the heterogeneity of the reported results. Narrative synthesis offers a systematic approach to evaluating both outcomes and processes in intervention studies and is therefore particularly relevant in the review of these papers.

RESULTS

Following de-duplication in Endnote, a total of 3,367 records were screened. Ten percent of records (324 records) were screened by two authors with a 97% agreement rate. Twenty-four conflicts were resolved through discussion and examination of the full text. Duplicates identified at the full text screening stage were conference abstracts from studies that were included as full text papers. Sixty-seven papers were included in the systematic review, 23 of which identified interventions to reduce the risk of SUDI in high-risk families (**Figure 1**).

Twenty-three papers of interventions with populations identified as vulnerable were included for synthesis and are grouped by intervention type in **Table 1**.

From these 23 publications, over half of the studies (14/23) were conducted in the USA (26, 28, 30, 33, 35, 37, 40–47), four in New Zealand (25, 29, 32, 38), three in the UK (31, 34, 39), and two

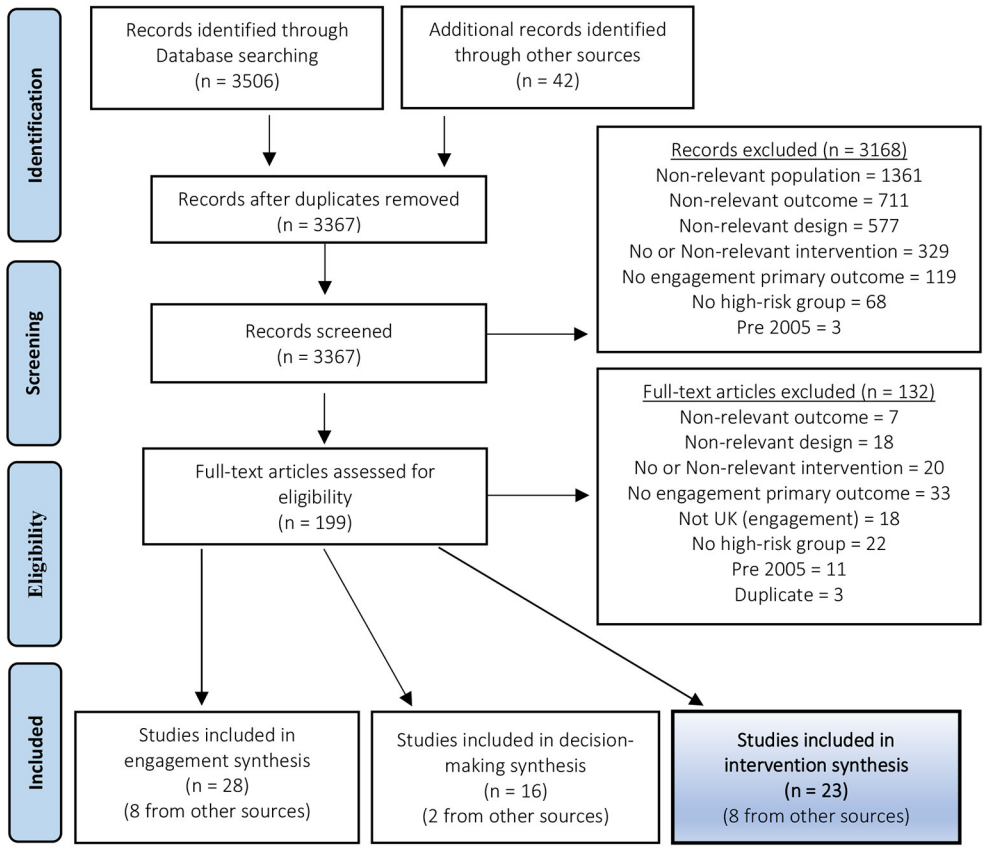

FIGURE 1 | PRISMA flow diagram of literature search and selection process.

in Australia (27, 36). The studies span 14 years from 2005 to 2019 and the overall quality scores ranged from 23 to 83%, with 20/23 papers scoring 50% and above. The paper scoring 23.8% was a short descriptive digest, a "case study" of good practice describing the intervention and key outcomes, rather than a research paper (34). The majority of these studies were quantitative; eight were randomized controlled trials (25, 32, 35–37, 45–47) and six were evaluations (26, 29, 38–41); the remainder were mixed methods or used a variety of quantitative approaches. Three papers utilized the same research data set, but presented different outcomes (45–47). The number of participants ranged from seven (38) to 6,515 (30) and participants were pregnant women, mothers or families identified to have some vulnerability, or characteristics that increased risk of SIDS to their infants. Seven studies recruited based on ethnicity alone (27, 32, 40, 43, 45–47), with ethnicity being used as a marker for deprivation or increased risk due to socioeconomic status.

From these 23 results, five types of intervention were identified which are discussed below:

1. Infant sleep space and safer sleep education programs – 9 papers (25–33)
2. Intensive or targeted home visiting services – 4 papers (34–37)
3. Peer educators/ambassadors – 2 papers (38, 39)
4. Health Education/Raising Awareness Interventions – 5 papers (40–44)
5. Targeted health education messages using digital media – 3 papers (45–47)

Infant Sleep Space and Safer Sleep Education Programs

Nine papers (25–33) reported on the provision of a safe infant sleep space (crib, Pepi-Pod®, Wahakura or plastic box baby bed) with a safer sleep educational component, aiming to improve parental safe sleep knowledge and influence behavior to reduce the risks of hazardous infant sleep environments. Studies investigated safe sleep devices for both use external to the parental bed (cribs) (26, 28, 30, 33), and devices intended as a separate safe sleep space for the infant, but for use within the parental bed (Pepi-Pod®, Wahakura or plastic box baby bed) (25, 27, 29, 31, 32).

There were a number of study designs within this theme comprising of mixed methods evaluations of cohort studies based on parental self-report behavior and/or intention data (26, 28, 30, 33) two RCT's (25, 32), two feasibility studies (27, 31) and one report of intervention implementation (29).

Four studies evaluated crib distribution and safer sleep education programs in the USA (26, 28, 30, 33). Carlins and Collins (26) found that all participants used the crib provided, commenting that 38% of participants at enrolment did not have a crib and would have bedshared. All participants reported

TABLE 1 | Characteristics of included interventions to reduce the risk of SUDI in families with children considered to be at high risk.

References Country	Study design and sample size	Target population	Intervention/ control	Study aim	Mode of delivery	Key findings/ measure of success	QATSDD score/%
Infant sleep space and education program							
Baddock et al. (25) New Zealand	RCT 98 I/V 101 Control	Maori pregnant women living in low socio-economic areas	Provision of a woven flax bassinet (Wahakura) designed to provide a consistent infant sleep environment. Control: Usual bassinette	To compare an indigenous sleep device (Wahakura) for infants at high risk for sudden unexpected death with a bassinet, for measures of infant sleep position, head covering, breastfeeding, bed- sharing, and maternal sleep and fatigue.	Face to Face Printed material Infant sleep space Individual	No significant differences in infant risk behaviors in Wahakura compared with bassinets. Increase in sustained breastfeeding in the Wahakura group.	29/42 69.0%
Carlins et al. (26) USA	Evaluation 150	Low-income families	Crib distribution and safe sleep education	Evaluate Cribs for Kids campaign; crib distribution and safe sleep education	Face to Face Printed material Infant sleep space Individual	100% reported use of the distributed crib. No SUDI deaths reported for the crib distribution families (still resident in locality).	18/42 42.9%
Young et al. (27) Australia	Test of concept trial 158	Aboriginal and Torres Strait Islanders	Pepi-Pod program	Pepi-Pod program evaluation	Face to Face Printed material Infant sleep space Individual	Pepi-Pods acceptable to and used by families; improved safe sleep recommendation adherence.	25/48 52.1%
Engel et al. (28) USA	Pre-post surveys and observation 75	Need was determined holistically by maternal infant health program (MIHP) staff, with indicators including low-income, racial minorities, and migrant worker status.	Crib distribution and safe sleep education	Identify changes in knowledge and how many parents used the cribs provided by Crib distribution program	Face to Face Printed material Infant sleep space Individual	99% using the distributed crib. Increased knowledge supine position (59% pre−89% post).	27/42 64.3%
Cowan (29) New Zealand	Evaluation of program implementation 3,616	Infants aged < 2 weeks, smoke-exposed, premature or low birth weight, with local discretion for exceptions based on safety assessments of the care-giving professional	Pepi-Pod program	To examine distribution, follow-up and user- feedback records	Face to Face Printed material Infant sleep space Individual	Maori IMR decreased. Pepi-Pods acceptable to and used by families; improved safe sleep recommendation adherence.	31/48 64.6%
Hauck et al. (30) USA	Prospective cohort study 6,515	(1) no crib in the home; (2) low income status (3) at least one risk factor for SIDS and sleep-related death (ethnicity, maternal smoking, pre- term or low birth weight, or sibling of a SIDS infant)	Crib distribution and safe sleep education	Evaluate Bedtime Basics for Babies campaign; crib distribution and safe sleep education	Face to Face Printed material Infant sleep space Individual	Knowledge of sleep position improved from 76 to 94%, bed-sharing decreased from 38 to 16%, 90% of parents used a crib.	32/42 76.2%

(Continued)

TABLE 1 | Continued

References Country	Study design and sample size	Target population	Intervention/ control	Study aim	Mode of delivery	Key findings/ measure of success	QATSDD score/%
Yuill et al. (31) UK	Feasibility study 79 I/V 70 Control	Young parents, parents who had smoked in pregnancy, and those known to be substance users.	Plastic baby box bed and safe sleep education Control: Usual care	Feasibility study for RCT to introduce UK version of Pepi-Pod program	Face to Face Printed material Infant sleep space Individual	Intervention reduced sofa co-sleeping to 6 vs. 23% of controls and decreased mean bed-sharing hours to 2.6 per night compared to 6.8 for controls.	21/48 50.0%
McIntosh et al. (32) New Zealand	RCT 101 I/V 110 Control	Maori and Pacific women	Pepi-Pod program Control: Better than usual care and infant sleep space	Assess acceptability and effectiveness at improving SUDI protective knowledge and safe sleep practice from the Pepi- Pod program compared to usual care	Face to Face Printed material Infant sleep space	Improvements seen in both I/V and control groups due to more than usual care provision for control group, as all participants were provided a cot.	25/42 59.5%
Salm Ward et al. (33) USA	Cohort study 208	High-risk parents (demonstrated financial need)	Crib distribution and safe sleep education	Compare parental knowledge and practices related to infant sleep before and after receipt of safe sleep educational programme and receipt of a crib	Face to Face Printed material Infant sleep space Group Interactive	Knowledge of recommendations on position, surface, environment, pacifier, smoking and breastfeeding increased significantly between pre and post-test and most maintained knowledge at follow-up.	24/42 57.1%
Intensive home visiting or targeted services							
Dillon (34) UK	Service Case Study 1,047	Alcohol/ substance misuse, violent criminal history, previous child not living with parent, late ante natal booking, homelessness with mental health/domestic abuse/probation, hearing impaired.	Vulnerable baby service: multi agency case planning meetings, and a public health approach.	Engage vulnerable families in the design of their support package with the aim to reduce risks of SUDI	Face to Face Interactive	Infant deaths reduced by 60% in Manchester. SUDI rate decreased from 1.8/1,000 to 0.52 in 2011.	10/42 23.8%
Hutton et al. (35) USA	RCT 160 I/V 122 control	Low SES mothers	Home visiting education with Baby Book Control: Usual brochures for safe sleep knowledge	To test the efficacy of a specially designed children's book compared to brochures for safe sleep knowledge and adherence	Face to Face Printed material Individual	Safe sleep knowledge increased cross all time points for both groups. Bed-sharing was higher and exclusive crib use lower in the brochure group. Greater dialogue and emotional engagement were reported with use of the book.	30/42 71.4%
Kemp et al. (36) Australia	RCT 111 I/V 97 Control	Vulnerable parents: one of a list of risk factors	Maternal Early Childhood Sustained Home-visiting (MECSH) Program Control: Usual care	To develop a theory of change for pre-natal home visiting by nurses in the context of sustained nurse home visiting	Face to Face Individual Interactive	Less instrumental deliveries; improved health and well-being scores; improved coping and self-efficacy in parenting in the	30/42 71.4%

(Continued)

TABLE 1 | Continued

References Country	Study design and sample size	Target population	Intervention/ control	Study aim	Mode of delivery	Key findings/ measure of success	QATSDD score/%
				programs by exploring pre- and postnatal outcomes and the characteristics of the MECSH program intervention		intervention group.	
Olds et al. (37) USA	RCT 458 I/V 680 Control	African American mothers living in highly disadvantaged urban neighborhoods	Nurse-Family Partnership Control: Usual care	All-cause maternal mortality and preventable-cause infant mortality	Face to Face Individual Interactive	Intervention group mothers less likely to die from all-causes and offspring less likely to die from preventable causes.	35/42 83.3%
Peer educators							
Cowan (38) New Zealand	Evaluation of a pilot study 7	Women and their partners who had successfully quit smoking during pregnancy	6 + 1 peer education	To achieve high levels of awareness of 6 + 1 information in communities that make low use of traditional health services, to achieve 50 "6 + 1" conversations in 1 month	Face to Face Printed materials Individual Interactive	Link workers (parents) reported 70 6 + 1 conversations; total of 90 6 + 1 conversations reported at evaluation. Hard to reach became "easy to reach" by changing the communication paradigm.	28/48 58.3%
Gilchrist (39) UK	Evaluation of web-based peer support for young parents 55	Young parents	Little Lullaby project: raise awareness and reduce risk for SIDS in young parents	Young parents adopt and feel confident in applying the Lullaby Trust's recommended "safer sleep for babies" advice	Face to Face Digital	97.5% of young parents learned about safe sleep and SIDS risk reduction; some parents changed behavior as a result.	30/48 62.5%
Health education interventions							
Ahlers-Schmidt et al. (40) USA	Evaluation surveys 180	African American women	Safe sleep community baby shower	To describe participants' knowledge and intentions regarding safe sleep following a Community Baby Shower	Face to Face Printed material Infant sleep space Group	High levels of safe sleep knowledge and stated intentions to follow safe sleep recommendations were reported by participants.	27/42 64.3%
Ahlers-Schmidt et al. (41) USA	Evaluation surveys 845	Pregnant women of low socioeconomic status or with high risk of infant mortality	Safe sleep community baby shower	To evaluate outcomes of Safe Sleep Instructor-led community baby showers, which included safe sleep promotion, breastfeeding promotion and tobacco cessation education.	Face to Face Printed material Infant sleep space Group	Significant increases were observed in Baby Shower participants' reported plans to follow the AAP Safe Sleep guidelines (all $p <$ 0.001).	26/42 61.9%
Ostfeld et al. (42) USA	Pre-post intervention surveys 810	Adolescents/ parents	High school education program	Improve SIDS risk knowledge	Face to Face Group	Awareness that supine sleep position carried less risk and infant smoke exposure increased risk of SIDS improved post intervention.	14/42 33.3%

(Continued)

TABLE 1 | Continued

References Country	Study design and sample size	Target population	Intervention/ control	Study aim	Mode of delivery	Key findings/ measure of success	QATSDD score/%
Burd et al. (43) USA	Pre-post intervention surveys 341	Native American women	Discussion covering 9 risk factors, provision of a printed baby blanket and printed materials.	To complete a community-based efficacy study of a SIDS risk reduction methodology.	Face to Face Printed material Individual	Pre-test identified significant safe sleep knowledge deficit, higher in Native American group. Intervention improved knowledge on all nine items in both groups	24/42 57.1%
Rienks et al. (44) USA	Telephone surveys following campaigns 1,458	African Americans 18–64 yrs	3 media campaigns	Evaluate campaign effectiveness in African Americans	Digital Leaflet Posters	Exposure to 3 campaigns was successful in raising awareness of IM disparity in African Americans.	32/42 76.2%
Targeted education messages *via* digital media							
Carlin et al. (45) USA	RCT 569 I/V 625 Control	African American mothers	Targeted and enhanced safe sleep messages Control: Standard messaging emphasizing AAP recommended safe sleep practices	Evaluate the impact of targeted messages about safe sleep and SIDS risk reduction on African American mothers decisions regarding the infant sleep environment: Sleep position	Digital	Supine position use decreased over time. Behavior unchanged by enhanced message intervention.	30/42 71.4%
Mathews et al. (46) USA	RCT 569 I/V 625 Control	African American mothers	Targeted and enhanced safe sleep messages Control: Standard messaging emphasizing AAP recommended safe sleep practices	Evaluate the impact of targeted messages about safe sleep and SIDS risk reduction on African American mothers decisions regarding the infant sleep environment: Soft bedding	Digital	Decrease in use of soft bedding in the intervention group: previous night 43.0 vs. 52.4% in controls and over previous week 49.2 vs. 59.6% in controls.	26/42 61.9%
Moon et al. (47) USA	RCT 569 I/V 625 Control	African American mothers	Targeted and enhanced safe sleep messages Control: Standard messaging emphasizing AAP recommended safe sleep practices	Evaluate the impact of targeted messages about safe sleep and SIDS risk reduction on African American mothers decisions regarding the infant sleep environment: Sleep location	Digital	Women receiving enhanced messages were no less likely to bedshare: no effect of intervention.	25/42 59.2%

attending all well baby checks however, only 65% of parents stated they placed their infant supine to sleep, and although all participants claimed to have read the educational information, 50% could not explain SIDS. Engel et al. (28) reported that 99% of participants used the crib, and knowledge of supine sleep position increased from 59 to 89% following education. Hauck et al. (30) found that knowledge of sleep position improved from 76 to 94%, bed-sharing decreased from 38 to 16%, and 90% of parents used a crib for infant sleep. Salm Ward et al. (33) found that self-reported parental knowledge on risk factors for sleep position, sleep surface, sleep environment, pacifier use, smoking and breastfeeding all increased significantly following intervention, and participants demonstrated that knowledge was retained at 10-week follow up.

Five studies investigated devices intended as a separate safe sleep space for the infant, but for use within the parental bed

(25, 27, 29, 31, 32). These devices included the Wahakura, a traditionally woven flax basket baby bed (25) and the Pepi-Pod®, a plastic box supplied with appropriate bedding (27, 29, 31, 32). Baddock et al. (25) investigated the use and acceptability of the Wahakura compared with usual bassinette use in the control group, concluding that the Wahakura increased the safety to the infant of bed-sharing, with the advantage of increasing breastfeeding rates. Three studies (27, 29, 32) reported on the Pepi-Pod program, originating in New Zealand, which involves the provision of a safe infant sleep space (plastic box) and a SIDS risk reduction education session delivered face to face by the provider. Parents are encouraged to pass on the Pepi-Pod and share the SIDS risk reduction messages with the new owners. Pepi-Pods in some studies also had safe sleep guidance labels stuck to them to facilitate sharing of accurate safer sleep messages. Cowan (29) reported that the program was applied consistently, Pepi-Pods were accepted, used, and liked by parents and were portable. Follow up demonstrated high uptake of safer sleep (supine position and infant placed in their own sleep space) and safe baby (immunization, breastfeeding, gentle handling, being smoke-free or receiving support to quit, and registration with health services) outcomes, and 80% of recipients reported sharing safer sleep messages across their networks. McIntosh et al. (32) investigated the impact of the educational element of the program on SUDI protective knowledge and infant care practices, and the acceptability of the Pepi-Pod as an infant sleep space. One quarter of participants did not have a suitable sleep space for their infant at enrolment to the study. McIntosh reported that knowledge of smoking and bed-sharing as risks for SUDI improved post intervention in both groups, however, 25% of participants reported regular bed-sharing at follow-up in both groups. All families, both intervention and control group parents, were supplied a Pepi-Pod and safe sleep education; the control group in effect received better than usual care, therefore it was difficult to assess efficacy of this element of the program by comparison to the control group in this study. Young et al. (27) evaluated the Pepi-Pod program in Australia, reporting improvements in quality of maternal sleep; breastfeeding; convenience and ease of use, and improved infant settling. Fifty-seven percentage of smoking families reported using the Pepi-Pod. A feasibility study of introducing a similar intervention based on the Pepi-Pod program in the UK was conducted by Yuill et al. (31). They reported mixed reviews but generally, parents liked the concept, and would recommend its use. Yuill identified less exposure to some hazardous sleep environments such as sofa sharing at 1 month (6 vs. 23% control) and co-sleeping with overly tired parents at 13 vs. 27% in controls.

Intensive or Targeted Home Visiting Services

Four studies investigated intensive or targeted multi-modal home visiting interventions (34–37); two were RCTs (35, 37); one process evaluation (36) and a short descriptive "digest" of a citywide intervention (34). These interventions shared characteristics such as incorporating evidence-based elements and frameworks for service delivery shown to reduce the impact of biological, social, and environmental factors predisposing infants and children to ill health and reducing their life potential. Due to their intensive and longitudinal nature, these interventions are based on building a relationship between professional and service recipient, and as such facilitate constructive conversations and education/ advice giving based on the needs of the family. Hutton et al. (35) tested the efficacy of a specially designed children's book compared to usual brochures (advice leaflets) for safer sleep knowledge and adherence to safer sleep practices. Home visitors provided safer sleep teaching and assessments during 3 visits. Results showed that safer sleep knowledge improved across all time points in both groups, however, exclusive crib use and reduced bed-sharing was greater in the intervention group which was attributed to the enhanced dialogue and emotional engagement with the book content, suggesting that the relationship between professional and parent was a key factor. Benefits of the book were identified as the interactive delivery, and 81% of the intervention group were reading the book with their infant at 2 months. The researchers posit that emotional engagement with the book content might support the translation of knowledge into behavior and identified the benefits of access to the home provided an ecological view of how safer sleep knowledge may be assimilated and translated into adherence. Three interventions were delivered by midwives and specialist nurses, beginning in the antenatal period, and continuing well into the postnatal period or up to 2 years (34, 36, 37). Olds et al. (37) reported on 20-year follow up data on the Nurse Family Partnership (USA). The Nurse Family partnership was launched in 1990 aiming to improve life chances and outcomes for families in the poorest communities in the USA and improve the associated mortality rates influenced by racial and economic disparity. The intervention aimed to tackle through education, issues of maternal smoking and substance use, encouraged healthy spacing of pregnancies, supported parenting capability, and facilitated young mothers into further education. Mortality rates were used as an outcome measure to assess the efficacy of the program due to higher rates of mortality being related to SIDS, unintentional injuries and homicide in children of the target population. Using maternal all-cause mortality and child preventable-cause mortality outcome measures, women in the intervention group were less likely to have died and their children were much less likely to die of preventable causes such as SIDS, unintentional injuries, and homicide however, this was a small sample from which to make inferences about mortality. The Vulnerable Baby Service (34) delivered in Manchester, a large English city, aimed to engage vulnerable families in the design of their support package with the objective to reduce risks of SUDI. Since the start of this multi-agency service in 2003, the infant death rate in Manchester, UK has declined by 60% and no SUDI have been reported in the intervention group, however, no causal association is identified in the paper. Parental attendance at appointments improved, disclosure of domestic abuse increased, and 86% of fathers continue to be involved in families. Organizational benefits of increased staff engagement to reduce SUDI, attendance at SUDI training and a consistent workforce approach to delivering safer sleep advice were also

observed. Kemp et al. (36) conducted a process evaluation on a program theory for pre-natal home visiting by nurses in the context of a sustained nurse home visiting program. Kemp explored pre and postnatal outcomes and characteristics of the intervention that may have contributed to the outcomes. She found that mothers in the intervention group reported significantly better general health and well-being at 4–6 weeks post-partum, and a significantly higher proportion could identify two or more measures to reduce the risk of SIDS compared to controls. In identifying intervention characteristics, Kemp noted that comprehensive support in the context of an enabling client-nurse relationship and continuity of carer, achieved both clinical and improved service engagement benefits for women and their infants.

Peer Educators/Ambassadors

Two papers evaluated interventions with peer educators (38, 39). An infant health promotion activity in New Zealand (38) aimed to support link workers (parents) from the community to have focused discussions, supported by a baby book resource, with family and friends on key health topics to raise awareness in communities that make low use of traditional health services. The "pay-it-forward" principle of this project aimed to create a "ripple effect" of knowledge transfer to penetrate deeper into communities by using members of that community to share health education messages; this principle was observed to create leverage in sharing health education within the community. Link worker experiences were positive, the baby book was designed as an easy read, compact and colorful prompt for conversations based on the "Facts for Life" publication by UNICEF/WHO and UNESCO (48), and covered topics including a smoke-free pregnancy and environment, back sleeping in a safe sleep space, breastfeeding and the benefits of reading to your infant. The book supported and structured conversations and was valued, and information was received well by friends and family. This intervention provides an easily scalable reach for safer sleep messages into traditionally "hard to reach" communities, however, one of the concerns with this method of intervention was the loss of control and fidelity of information being shared by link workers, and difficulties in recruiting men as link workers (38). Gilchrist (39) evaluated an intervention provided by Little Lullaby, a subsidiary of The Lullaby Trust, a UK SIDS prevention charity. Little Lullaby trains young parents as Ambassadors to deliver safer sleep advice and work with young people and professionals to raise awareness and reduce risks of SIDS. The service is delivered *via* a website and face to face talks and workshops. Evaluation of the intervention indicates that safer sleep messages are being understood and applied by young parents, with 97.5% reporting they had learnt something new about safer sleep and SIDS, and 36.7% of young parents would change their parenting practice because of the session. Benefits of the intervention include providing an effective model for engaging and empowering young parents, however, at the time of the evaluation, the Ambassador program was based in London and a survey of relevant health professionals found that awareness of this scheme and the work of Little Lullaby was reported to be relatively low.

Health Education/Raising Awareness Interventions

All five studies in this section were conducted in the USA (40–44); two were evaluations (40, 41), two were pre and post-test designs (42, 43) and one tele-survey (44). The focus of these studies was on health education or raising awareness, and although Ahlers-Schmidt et al. (40) provided a cot to participants, this was not the focus of their study. While specific educational elements are presented here, it is acknowledged that there is some potential for overlap between these studies and those reported in theme 1. Ahlers-Schmidt et al. (40) evaluated safer sleep community "baby showers" designed to increase knowledge and practice of safer sleep advice and promote social cohesion; participants were also given portable cots. While knowledge of safe sleep and intentions for safe infant care were high, no baseline measure or use of controls means that changes in knowledge or intentions due to the intervention could not be assessed. In a later study of knowledge, confidence, and intentions to follow safer sleep recommendations, Ahlers-Schmidt et al. (41) found significant increases in participants' reported plans to follow the American Academy of Pediatrics Safer sleep guidelines however, these were again parental self-reported intentions, not a reflection of actual infant-care practice. However, 86.4% of mothers reported their infant would have slept in an alternative potentially hazardous sleep space, had they not received the cribs. Burd et al. (43) evaluated an educational intervention delivered by hospital nurses or home visiting staff, where nine SIDS risk factors were discussed. Many participants had young children, therefore there was expectation that parents already had some knowledge regarding recommended safer sleep practices, however at base-line testing, substantial knowledge deficits were identified in both groups. Following intervention, participants from both groups demonstrated equivalent rates of learning across each of the risk concepts. An evaluation by Ostfeld et al. (42), of an interactive high school program to address health risks associated with smoke exposure and non-supine infant sleep, found that students were able to recognize specific risks for SUDI, retained that knowledge over time, and demonstrated better knowledge of SUDI risk factors than a convenience sample of first-time parents. Reinks and Oliva (44) evaluated three multi-media campaigns to raise awareness of infant mortality disparity in black infants. Reinks concluded that social marketing is an effective tool to increase disparity awareness, especially among groups disproportionately affected by the disparity, however, no overall significant increase in knowledge about sleep position was identified.

Targeted Health Education Messages Using Digital Media

Three papers (45–47) reported on different aspects of the results from a RCT which evaluated the impact of targeted safe sleep messages in the USA (45). Controls were sent standard text messages emphasizing recommended sleep practices while the intervention group received enhanced messages to include suffocation prevention. Results identified a decrease in use of supine sleep position (45) and a gradual increase in bed-sharing

(47) over time and in both groups, despite families being in trial conditions advising the opposite, and despite reported good parental knowledge of the recommended sleep position. Commonly cited reasons for using sleep positions other than the recommended supine position were fear of suffocation, choking and infant preference. Some influence was noted on maternal selection of supine sleep position if nurses had discussed sleep position with the mothers, however, where mothers discussed this with the father of their infant, these mothers were more likely to select prone position and over time, the opinion of maternal friends became more significant on influencing choice of sleep position. Matthews et al. (46) found a decrease in the use of soft bedding where mothers "believed" that soft bedding increased the risk of suffocation or SIDS, while mothers who were more likely to use soft bedding, including mothers who bed-shared, cited "vigilance" as protective.

The main findings presented here suggest that the most convincing evidence for interventions that work have a number of identifiable characteristics which are: personalized, culturally sensitive, enabling, empowering, relationship building, interactive, accepting of parental perspective, non-judgmental and are delivered over time (**Table 2**).

DISCUSSION

There is good evidence that multi-modal interventions that provide a safe infant sleep space for use both in and out of the parental bed, along with comprehensive face to face safer sleep education programs are effective, delivering improvement across several key outcome measures for safer sleep and safe baby practices in vulnerable families. Safe sleep space (equipment) provision was assessed in combination with other elements, however, most studies reported high percentage of parental use of the safe sleep space provided, even where knowledge scores varied. Therefore, consideration of equipment provision

TABLE 2 | Intervention characteristics matrix.

	Sleep device	Education	SS knowledge improvement	Behavior change element	Home visits	Inter active	Parent perspective	Empowering	Digital	Peer educator	Group	Intervention reported successful
Gilchrist (39)		•	•	•		•	•	•	•	•	•	•
Cowan (38)		•	•	•		•	•	•		•		•
Young (27)	•	•	•	•	•	•	•					•
Cowan (29)	•	•	•	•	•	•	•					•
McIntosh et al. (32)	•	•	•	•	•	•	•					•
Salm Ward et al. (33)	•	•			•	•	•				•	•
Kemp et al. (36)		•		•	•	•	•	•				•
Ahlers-Schmidt et al. (41)	•	•	•	•		•					•	•
Ahlers-Schmidt et al. (40)	•	•		•		•					•	•
Hutton et al. (35)		•		•	•	•	•					•
Hauck et al. (30)	•	•	•	•	•							•
Dillon (34)		•			•	•	•	•				•
Burd et al. (43)		•	•		•	•	•					•
Olds et al. (37)		•			•	•		•				•
Ostfeld et al. (42)		•	•			•					•	•
Mathews et al. (46)		•		•					•			•
Baddock et al. (25)	•			•								•
Engel et al. (28)	•	•	•	•								•
Rienks and Oliva (44)		•	•									•
Carlins et al. (26)	•											•
Yuill et al. (31)	•	•	•	•	•							
Moon et al. (47)		•							•			
Carlin et al. (45)		•							•			

alongside current health and social care provision in the UK may be a useful approach to consider as basic provision when resources are stretched. This has been seen in the proliferation of cardboard baby box schemes in the England since 2016 (49). However, the adoption of these programs is not without criticism and a number of concerns, including infant safety, have been identified. While there is no evidence to support that using a cardboard box for infant sleep reduces the risk for SIDS, some of these schemes are being marketed on this basis. Of more concern is that some of these schemes are being provided through commercial partnerships with health and social care services, which parents are likely to view as an endorsement to the safety of these products. The cardboard baby box schemes were not included in the systematic review as they were widely distributed and outcome data specific to high-risk groups was not available. However, 86% of parents reported that they intended to use the cardboard box for infant sleep, which supports the notion that parents are receptive to accepting an infant sleep space provided to them, data supported by Yuill's (31) feasibility study to introduce the Pepi-Pod program into the UK, which offers an evidence-based and safer alternative to the cardboard box. Several interventions engage peer educators or a mechanism of "paying-it-forward," using intervention participants to spread infant safety messages further into communities and those traditionally viewed "hard to reach" and vulnerable populations. Such interventions offer a scalable and achievable method to share safer sleep messages which need not be resource heavy. However, some concerns identified with these approaches are the potential for loss of control of fidelity of the messages being communicated by link or peer educators, and the potential that relevant and culturally appropriate peer supporters can be challenging to engage and/or retain. Targeted and long-term evidence-based interventions with continuity of service provider, delivered in the context of enabling parent-provider relationships has benefits for infants and families. The initial contact can be built upon to provide support for parents and opportunities for professionals to identify changes in both the sleep environment and infant care practices, which might decrease the risk of SUDI and SIDS as the infant grows and develops, and family circumstances change. Interventions that have been subsumed into "usual service provision" have delivered sustainable improvements in reducing risks for SUDI and SIDS for infants, and resultant decreases in infant mortality rates. One digital intervention was available for review (45) and was not identified as effective in reporting knowledge improvement and behavior change, except for reducing the use of soft bedding. However, digital interventions are potentially scalable and low cost, and are becoming more popular, particularly with the current SARS-COV-2 pandemic driving the need to find alternative delivery options. It might also be argued that this generation, and future generations of parents are more tech savvy than previous generations, providing an opportunity to capitalize on digital intervention options, and future research should consider approaches to improve the effectiveness and relevance of digital health interventions for families with children considered to be at increased risk of SUDI. One media campaign was reviewed (44), and while no improvements in knowledge were observed, it was identified that targeted campaigns may be successful in raising awareness in the population of interest. This was demonstrated in the national "Back to Sleep" campaign of the early 1990's, which had significant impact on the infant mortality rate at the time. Since then, there have been small localized safe sleep campaigns, but perhaps consideration of another national safer sleep campaign might be useful in raising awareness to a new generation of parents and coupled with targeted interventions that are considered relevant by the population of interest, could offer a cohesive approach to SUDI risk reduction.

While much of the data reported on in these intervention papers were parental self-report, and reported parental behavioral intention, several studies identify decreases in infant mortality and SIDS rates, which, while not shown to be a clear consequence of the interventions, raise the possibility that increased knowledge and adherence to safer sleep recommendations is a valid outcome of these interventions. In considering the evidence to support the development of new interventions, research would be required to understand the relevance and appropriateness for delivery to the UK target population. Seven of the 23 intervention papers used ethnicity as a marker of risk for SUDI, these studies are relevant where characteristics or behavior that increases risk for SUDI in the UK population are described. While parental motivations for certain behaviors may be culturally different, the principal of exhibiting that behavior increasing risk for SUDI should be explored when considering potential application to the UK setting. Interventions also need to have a sound theoretical foundation, for example the Health Belief model (50, 51) or the behavior change wheel (COM-B model) (52). Behavioral models support the assumptions about the links between the intervention and behavior change outcomes and should be clearly stated. To support this, interventions should have clear explanations, considering the needs for parents/carers to be provided with credible advice that incorporates mechanisms of protection which are understandable, and account for the changing needs of a sleeping infant. Intervention design should be collaborative between parents and professionals and consider incorporating robust evaluation and methods of measuring actual practice rather than parental knowledge and intention.

The strengths of this systematic review were that searches of the gray literature and a snowballing approach of relevant citations within the references of the selected records produced a further 42 papers in addition to the 3,506 records identified by the initial database searches; this suggests that our search terms were comprehensive. The agreement rate between authors on selection of included papers was high, and enough papers were identified for meaningful discussion. There are several limitations to this work. The quality of the intervention papers reviewed is variable and synthesis is difficult given the disparate ways in which studies have been reported. While eight were RCT's using large samples and reporting robust results, the remainder of papers reported evaluations or mixed methods approaches potentially impacting on the quality and robustness of reported evidence. The lack of controlled observations in some studies or comparing intentions of infant care practice to actual practice is often very different and leads to a weak design and questionable conclusions. To include papers on interventions specific to high-risk populations, we relied on individual studies' definitions of "high-risk," meaning

that included studies relate to a variety of populations which was necessary as "high-risk" populations vary across cultures and countries. While this means that our conclusions are drawn from a wider pool of literature, it does mean that care must be taken to consider the specific circumstances of, and relevance to, UK high-risk families. We restricted included studies to those which were targeted to higher risk groups, and while the justification for this is clear, it does also mean that we did not include interventions for the general population (e.g., Cardboard baby box schemes) as we would not be able to review their impact in high-risk families separately.

CONCLUSION

This paper reports the findings from one arm of a wider systematic review to identify current evidence about how best to increase uptake of safer sleep advice in families with infants considered to be at risk of harm through abuse or neglect. Overall, we found evidence suggestive of how future interventions might be designed to achieve a large scale, targeted approach to risk reduction in families where the infants are considered to be most at risk of SUDI. Interventions should, ideally, be delivered face to face, and from the evidence, innovations that consider how to capitalize on leverage from peer-to-peer models may be of use in this context. Parents and carers require evidence-based advice so they can make decisions on how to keep their infants safe and health professionals should be provided with consistent advice that can be delivered using plain language to families, with plausible explanations as to why this advice will keep their infant safe. Advice should consider parents' own experience and tailor the content of safer sleep conversations to individual families' needs, while also taking account of how to include partners, peers, and wider family members, to extend knowledge and understanding of safer sleep and safe infant care practices to all those who may be caring for a young baby. Further research into how to translate successful interventions for appropriate and relevant application to the UK target population is required. Intervention design should be collaborative between parents and professionals and must include robust evaluation and methods of measuring infant care practice rather than parental knowledge and behavior intention.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: NCBI with the accession number PRJNA778186 (https://www.ncbi.nlm.nih.gov/sra?linkname=bioproject_sra_all&from_uid=778186).

AUTHOR CONTRIBUTIONS

AP, PB, PF, CE, JG, and DW led the review, designed the scope of the work, and wrote the protocol. AP conducted the searches with support on terms from PF, PB, CE, JG, and DW. CE, JG, AP, and DW screened the titles, abstracts and full texts, and discussed final papers for inclusion. Themes were discussed between all authors *via* input into drafts of the final report. All authors contributed to the writing of the manuscript drafts providing comments and changes until a final manuscript for submission was agreed.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.778186/full#supplementary-material

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Cerebrospinal Fluid Histamine Levels in Healthy Children and Potential Implication for SIDS: Observational Study in a French Tertiary Care Hospital

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Objective: A defect of the waking systems could constitute a factor of vulnerability for sudden infant death syndrome (SIDS). A decrease in orexin levels, which promotes wakefulness and activates histaminergic neurons (another hypothalamic wake-promoting system) has already been demonstrated between 2 and 6 months. This work aims to study the levels of histamine (HA), tele-methylhistamine (t-MeHA), its direct metabolite, and t-MeHA/HA ratio in the cerebrospinal fluid (CSF) of healthy children, to evaluate the maturation of the histaminergic system and its possible involvement in SIDS.

Methods: Seventy Eight French children between 0 and 20 years (48.7% boys) were included, all of whom had a clinical indication for lumbar puncture, but subsequently found to be normal. Measurements of HA and t-MeHA in CSF were performed by reverse phase liquid chromatography coupled to mass spectrometry detection. Statistical analyses were performed using Spearman correlations and Non-parametric pairwise ranking tests.

Results: A negative correlation was found between age and CSF HA ($r = -0.44$, $p < 10^{-4}$) and t-MeHA ($r = -0.70$, $p < 10^{-4}$) levels. In pairwise comparisons, no difference in CSF HA and t-MeHA levels was observed between youngest age groups (i.e., 0–2 mo vs. 3–6 mo), but CSF HA and t-MeHA levels were significantly lower in older children (i.e., >6 mo vs. 0–6 mo). The CSF HA decrease with age was only observed in boys, who also presented global lower CSF HA levels than girls.

Conclusion: CSF HA and t-MeHA levels decrease with age in boys, and global levels are lower in boys than in girls. These results reveal changes in histaminergic transmission and metabolism during maturation. Whether lower CSF histamine values in boys compared to girls could contribute to their higher risk of SIDS warrants further research.

Keywords: histamine, maturation, sleep, children, infant, SIDS

INTRODUCTION

Sudden Infant Death Syndrome (SIDS) consists in the sudden and unexpected death of a child under 1 year old and usually beyond the perinatal period, which remains unexplained after an extensive investigation, including a complete autopsy and analysis of death circumstances and anterior clinical history (1). SIDS remains the main cause of post-neonatal mortality, with a rate of 38 deaths per 100,000 live births in 2016 in the United States, accounting for 42% of Sudden Unexpected Infant Deaths (SUID) (2). SIDS is a multifactorial entity (3). Main known risk factors are prenatal (born premature, maternal smoking, male) and postnatal (sleep position, infections, sleep deprivation . . .) during the critical period of development defined between 2 and 6 months (4, 5).

Despite intensive and long-lasting research, the underlying mechanisms involved in SIDS remain unclear. Arousability from sleep could provide a protective mechanism for survival and the temporal association between SIDS and sleep periods suggests that when confronted with a life-threatening challenge during sleep, this vital response may be impaired in infants who succumb to SIDS. Infants who subsequently died of SIDS moved less during sleep and aroused less frequently; furthermore, these observations occurred predominantly during the last part of the night, when most deaths from SIDS occur (6, 7). It has been shown that infants who subsequently became victims of SIDS not only aroused less from sleep than control infants, but had different arousal characteristics (8). Compared to a group of age-matched control infants, these SIDS victims had significantly more subcortical activations during the first part of the night between 9:00 p.m. and midnight, and fewer cortical arousals during the latter part of the night, suggesting an incomplete arousal process (8). On the other hand, all known major risk factors for SIDS such as prone sleep position, *in utero* tobacco exposure, preterm births,... have been consistently associated with decrease in both spontaneous and induced arousals from sleep (9–11).

Arousal requires a convergent action of assorted systems, such as brainstem cholinergic, aminergic neurons and some neuropeptides. Patho-anatomical studies in SIDS infants demonstrated diffuse lesions (gliosis, hypoplasia or apoptosis) within different brain structures, essentially the brainstem (12). To date, the most robust evidence has been associated with the medullary 5-hydroxytryptamine system (5-HT), with abnormalities found in ∼50 to 75% of SIDS victims including decreased 5-HT1A receptor bindings and serotonin levels (13). The medullary 5-HT system is considered critical for the modulation and integration of diverse homeostatic functions such as respiratory, cardiovascular and arousal controls.

Orexin/hypocretin and histamine (HA) neurons, located proximately in the posterior hypothalamus, constitute two hypothalamic wake-promoting systems (14). Under physiological conditions, they must cease their activity to allow the initiation and maintenance of sleep, probably thanks to multiple GABA inhibitory inputs (15). With reference to SIDS, an impairment of either system could lead to a defect of arousal. The neuropeptides orexins contribute to behavioral aspects of wakefulness, including maintenance of muscle tone and posture, locomotion, food intake and emotional responses (14, 16). Orexins therefore promotes wakefulness through locomotion and behavioral activation. We recently found that the period of major incidence of SIDS (2–6 months) matches with a decrease in CSF orexin levels (17) which could trigger a more important vulnerability facing SIDS with difficulties to awaken.

Orexin neurons project directly to the tuberomammillary nucleus and depolarize HA neurons, another hypothalamic widespread projecting and wake-promoting system whose deficiency is associated with sleepiness in animal and human models of sleep disorders such as narcolepsy (18–20). Concerning SIDS, a decrease in orexin excitatory inputs could entail a parallel decline in HA levels between 2 and 6 months.

In the mammalian brain system, HA is exclusively synthesized by histidine decarboxylase before being inactivated after release by histamine N-methyltransferase into its sole direct metabolite: tele-methylhistamine (t-MeHA). The latter is stable during several hours in the CSF, hence HA, t-MeHA and the ratio between t-MeHA/HA constitute a mirror of the brain HA turnover and transmission (21, 22). Although HA levels in adult sleep disorders such as narcolepsy remains controversial (22–26), we recently showed in childhood narcolepsy at the early stage of the decease has shown an impaired HA turnover and neurotransmission. These results together with those in animal studies indicate that HA could be involved in various sleep disorders with impaired vigilance.

The objective of the present study was therefore to better understand the maturation of the cerebral histaminergic system during childhood, *via* measurement of HA, t-MeHA levels and t-MeHA/HA ratio in patients between 0 and 20 years old with focus on potential links between an impairment in maturation and SIDS. Indeed, a decline in orexin between 2 and 6 months may have an effect on HA levels at the same period by decreasing excitatory inputs.

MATERIALS AND METHODS

Patients

The CSF samples of 91 children were collected at the Hôpital Femme Mère Enfant in Lyon, France. At the hospital admission, parents were informed that biological samples from their children could be used for research purposes and they signed a consent form.

Children born premature were excluded to avoid potential biases due to a lack of maturation of the nervous system and consequently of HA production ($N = 6$) as well as those with a documented meningitis ($N = 7$) resulting in a sample of 78 children aged 0 to 20 years old.

For children ≤1 year old ($n = 42$), indications for lumbar puncture were available for $N = 30$ and were fever ($N = 24$), febrile seizures ($N = 2$), acute gastroenteritis with dehydration ($N = 2$), respiratory distress by meconium. For older children ($N = 36$), medical records were available for 32 of them and indications for lumber punction were headache ($N = 6$), visual disorders (diplopia, scotoma...) ($N = 6$), epilepsy ($N = 3$), sensory-motor

TABLE 1 | Population characteristics and CSF measures by age group.

Age group	*N*	Age (weeks)	Boys	CSF-HA (pM)	CSF-t-MeHA (pM)	CSF-t-MeHA/HA
		Median (min-max)	(%)	Median (min-max)	Median (min-max)	Median (min-max)
≤2 months	20	4.5 (1.0–8.0)	50	706.33 (207.30–2,166.88)	5,870.15 (2,576.77–13,376.75)	7.59 (2.02–20.52)
[2–6] months	15	12.0 (9.0–26.0)	47	642.58 (183.14–3,208.27)	5,386.82 (1,293.42–10,179.70)	7.37 (0.68–35.11)
[6–12] months	7	40.0 (32.0–52.0)	71	565.17 (342.82–809.75)	3,965.26 (2,612.06–8,509.37)	7.80 (4.10–14.86)
[1–10] years	13	426.0 (246.0–483.0)	38	442.21 (27.32–1,192.80)	2,379.59 (566.55–9,648.69)	6.78 (0.78–133.06)
>10 years	23	734.0 (552.0–1,034.0)	48	297.97 (10.92–1,596.74)	1,192.31 (498.23–7,413.11)	3.81 (0.42–123.10)

CSF, cerebrospinal fluid; HA, histamine; t-MeHA, t-methylhistamine.

deficit of the lower limbs ($N = 3$), gait disturbances ($N = 2$), fever ($N = 1$), epileptic encephalopathy ($N = 1$), moya-moya disease ($N = 1$), 6-month check-up after encephalitis ($N = 1$), peripheral facial palsy ($N = 1$), arthritis ($N = 1$), acute bronchitis ($N = 1$), intrathecal infusion pump filling ($N = 1$), cranial trauma ($N = 1$), cystitis ($N = 1$), paresthesia ($N = 1$) and transitory isolated behavioral disorder ($N = 1$). All biological results were subsequently found to be normal.

Histamine Assay

The CSF samples were immediately preserved at −80°C after sampling. Blood contamination was checked visually and specimens of CSF with abnormal color were excluded from the study. The HA and t-MeHA assays were carried out simultaneously, on CSF samples without abnormal color at visual checking, at Bioprojet-Biotech in Saint Gregoire (France) using the analytical method internally developed by Croyal et al. (25). These measurements rely on derivatization of primary amines using 4-bromobenzenesulfonyl chloride and subsequent analysis by reverse liquid chromatography (UPLC: ultra-performance liquid chromatography) with mass spectrometry detection. The combination of these two methods makes it possible to solve the problem inherent in the sensitive analysis of two amines with close physicochemical properties (26). All measurements were performed blindly. The ratio of t-MeHA/HA was calculated.

Statistical Analysis

Children age was considered in the statistical analyses both as a continuous and a categorical variable. Age categories were then 0–2 months ($n = 20$), 2–6 months ($n = 15$), 6–12 months ($n = 7$), 1–10 years ($n = 13$), and 10–20 years ($n = 23$). The 2–6 months age group was the one of specific interest to study potential implication in SIDS.

Correlations between age and CSF measures were assessed by Spearman correlation test. Comparisons between CSF measures (HA, t-MeHA and t-MeHA/HA) according to age groups were performed using Non-parametric Kruskal-Wallis tests globally and based on pairwise rankings corrected for multiple comparisons when considering pairwise two-sided analysis.

All statistical analyses were performed using SAS 9.4. The significance level was set at $p < 0.05$.

RESULTS

Children were aged 1 week to 20 years and boys represented 48.7% of the population. There was no sex difference according to age groups ($p_{\text{chisq-exact}} = 0.77$). The characteristics according to age categories are presented in **Table 1**.

Global CSF HA, CSF t-MeHA levels and their ratio according to age groups are presented in **Figure 1**. Significant negative correlation was observed between age and CSF HA (rho = −0.44, $p < 10^{-4}$) and t-MeHA levels (rho = −0.70, $p < 10^{-4}$). No correlation was observed between age and t-MeHA/HA ratio (**Supplementary Figure**). Significant global differences for HA and t-MeHA levels were observed according to age groups ($p = 0.001$ and $p < 10^{-4}$, respectively). The 2x2 group comparisons showed no significant difference for HA and t-MeHA levels between 0–2 and 2–6 months ($p = 0.98$ and $p = 0.84$, respectively) but significant decrease in both HA and t-MeHA levels between groups aged up to 6 months and the older ones (**Figure 1**).

CSF HA levels were globally lower in boys than in girls (median [25–75%] 432.57 [258.85–643.48] vs. 680.99 [383.89–1016.19], $p = 0.03$). No other difference according to sex was observed. In stratified analysis by sex, the same global relations for CSF HA levels and age groups were observed in boys ($p = 0.005$) but not in girls ($p = 0.13$) (**Figure 2**).

Sensitivity analyses excluding outliers ($n = 6$) provided similar results plus a significant correlation between age and t-MeHA/HA ratio when considered as continuous variables (rho = −0.31, $p = 0.006$).

DISCUSSION

Main Findings

The present study provides measures of the assay of HA and its metabolite, t-MeHA and t-MeHA/HA ratio in CSF in healthy patients. The purpose is, on the one hand, to obtain normative data in order to better understand the maturation of the histaminergic system during childhood under physiological conditions, and on the other hand, to attempt to relate these results to SIDS.

We have highlighted high levels of CSF HA and t-MeHA at age before 6 months, then a progressive decrease toward the adult levels around 10 years old ($p < 10^{-4}$). The difference in HA

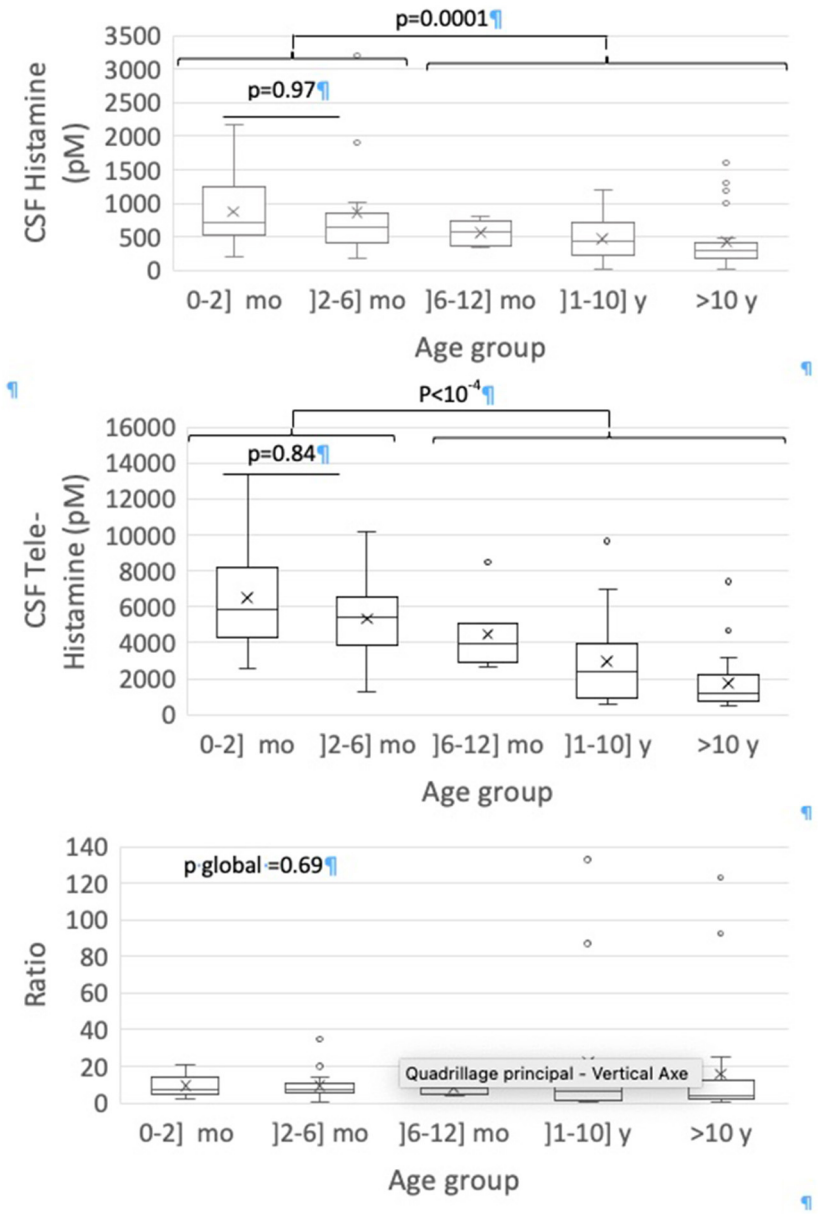

FIGURE 1 | Box-and-whisker plots for CSF measures according to age groups. The minimum value, 25th percentile, median, 75th percentile, and the maximum value are represented. The cross is the mean value.

levels is more pronounced on either side of an artificial limit of 6 months old, since we do not find any statistically significant difference by comparing two-by-two lower age groups or upper age groups. Nevertheless, this decrease in HA levels after the age of 6 months should be interpreted within a general downward trend between 0 and 20 years, with the negative correlation found between age and HA levels. These results match with a previous study by Dauvilliers et al. (26), showing that patients with high HA levels are significantly younger than patients with low HA levels ($p = 0.03$) with a negative correlation between age and HA levels ($r = -0.22$, $p < 0.005$), as we found. However, that study included a wider population of patients from 4 to 86 years old. Another rare study also finds higher t-MeHA levels at 3 months old and then a subsequent progressive decrease during 15 y (27). Thus, the negative correlation that we found concerning healthy children from 0 to 20 years old seems to be maintained in adulthood. In our study, the CSF HA decrease with age is mostly driven by the CFS-HA decrease in boys, not observed in girls (**Figure 2**). This sex difference was not studied in the two above cited studies (26). We also detected a negative correlation between CSF t-MeHA levels and age ($p < 10^{-4}$), consonant with previous findings (22). The decrease of CSF

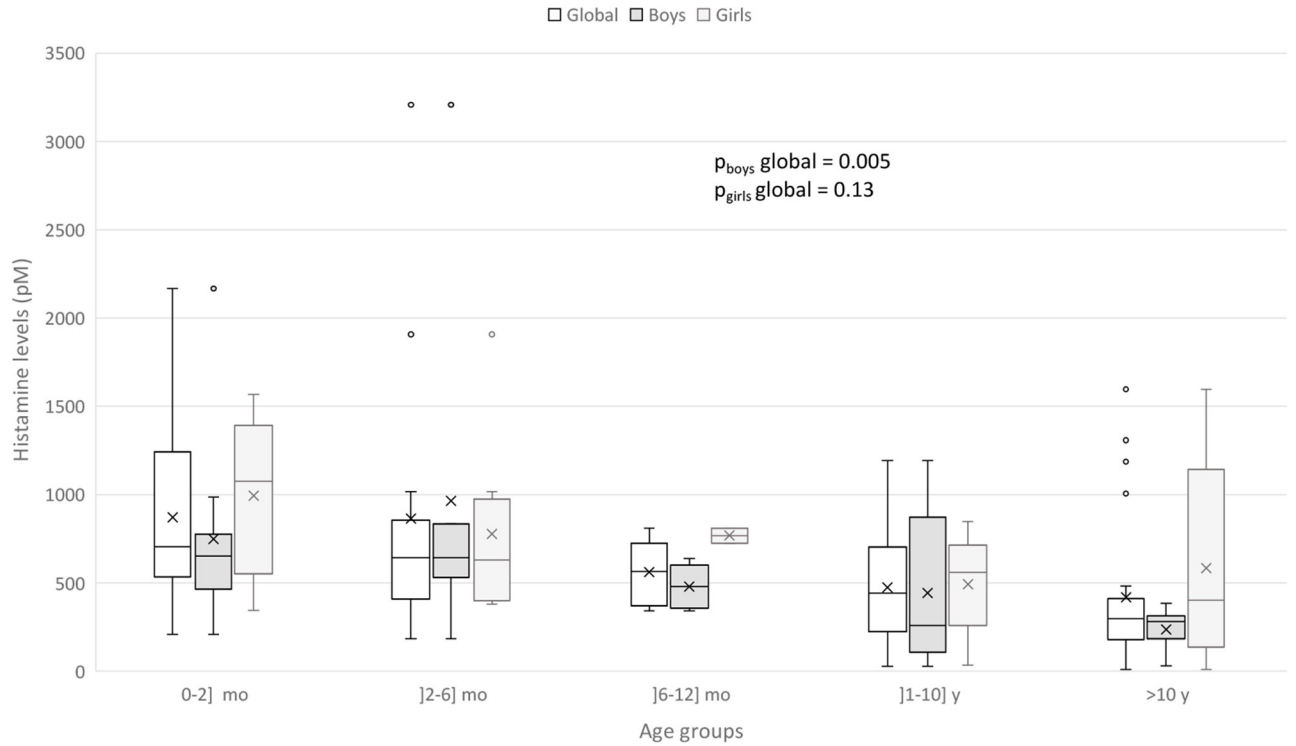

FIGURE 2 | Box-and-whisker plot for CSF HA according to sex and age groups. The minimum value, 25th percentile, median, 75th percentile, and the maximum value are represented. The cross is the mean value.

HA and t-MeHA levels and t-MeHA/HA ratio suggest possible changes in the histaminergic transmission and metabolism over the child's brain development.

Interpretation

Several assumptions can be made about the origin of the decline of HA and t-MeHA levels. Synaptic space between neurons is known to be wider in children. HA production could therefore be more important in children to ensure an effective transmission to post-synaptic neurons. Furthermore, histamine is also produced by mast cells. An increase of the number of mast cells in children could result in a rise of the production of histamine during childhood. Changes in the choroid plexus characteristics during postnatal life could be implicated in the cerebrospinal fluid clearance (28) with a potential increased rate of entry of substances from the systemic circulation into CSF at this age (29). Such assumptions require next in-depth investigations.

Pitolisant is a potent, selective histamine 3 (H3)-receptor antagonist/inverse agonist that increases histamine synthesis, release, and transmission in the brain (30–32). Recently, we showed in a pharmacokinetic study that after a simple dose, the maximum serum concentration (Cmax) and area under the serum concentration-time curve from time zero to time of last sample collection (AUC0–10 h) were markedly higher in the younger pediatric subgroup (aged 6–<12 years) relative to older pediatric participants (aged 12–<18 years) and young adults (aged 18–45 years) suggesting in the same way a maturation in the histaminergic metabolism (33).

Regarding SIDS, the group of interest between 2 and 6 months did not have an HA level significantly different from the lower age groups (0–2 months). There is no decrease in HA during the critical time period of the peak incidence of SIDS, like we found for orexin (17), to amplify the vulnerability to SIDS between 2 and 6 months with a failure in the two arousal systems. Even so the absence of decline of HA levels in the 2–6 months group may seem unexpected at the sight of results from previous studies. Indeed, the consensus is that orexin directly excites histaminergic neurons and it has been shown that orexin levels are significantly lower at this period of child's development (17). The lack of excitatory inputs on histaminergic neurons should result in an impairment in histaminergic transmission. However, our results tally with the findings of a normal histaminergic transmission in orexin knock-out mice, similar to that of wild-type mice; as evidenced by measurement of cortical HA and t-MeHA levels (34). Thus, a decrease of orexin would not necessarily affect the histamine levels and its transmission, thanks to the likely existence of compensatory mechanisms of the brain arousal systems organized in redundant neuronal networks. We found that infants <6 months of age had higher CSF HA and t-MeHA levels than infants older than 6 months. These high levels could reflect a higher activity of the histaminergic system at this age

and could constitute a factor of protection for SIDS, an idea that is supported by animal studies. Indeed, HA neurons are sensitive to high serum CO2 (hypercapnia), low pH medium and hypoxia and enhance their activity facing such situations (35, 36) that may be associated with SIDS (12). However as there were few patients between 6 and 12 months, necessary cautions should be made. As the decrease of orexin levels and the increase of HA did not take place in the exactly same period likely 2–6 months, we could suggest at this point that there is no relation between the decreased level of orexin and the increase in histamine. We unfortunately do not have joint measurements of both CSF HA and orexin in the very same patients to actually study whether the infants having a decrease in orexin levels do not have a decrease or an increase in HA levels, as we suggest here. A study of this kind would allow more affirmative interpretations. The difficulty in linking SIDS up to HA also lies on the postmortem measurements of CSF HA and t-MeHA in victim infants of SIDS. Indeed, their levels cannot be interpreted since they systematically rise significantly after death, probably due to a postmortem release from mast cells. A solution could then be the study of the number of histaminergic neurons in SIDS infants as it has already been done by Hunt et al. for orexin (37).

We found that boys presented global lower CSF HA levels than girls and that HA decrease with age was only observed in boys. From epidemiological studies, male infants have a 50% increased risk of dying of SIDS than female infants (38). This gender risk is not well understood. Dysfunction in the 5-hydroxytryptamine system, critical for the modulation and integration of diverse homeostatic functions such as respiratory, cardiovascular and arousal controls, has been implicated in the vulnerability of these future SIDS infants (13). Intrinsic factors such as prematurity, male sex, *in utero* tobacco exposure could decrease 5-hydroxytryptamine1A receptor binding density affecting the underlying vulnerability in these infants. The higher risk for males could also be explained by genetic factors (39). A modeling, using a single X-linked gene locus with a dominant allele ($p = 1/3$) for protective of cerebral anoxia, predicted the observed male excess SIDS susceptibility in US (39). On the other hand, the tachykinin neurokinin-1 receptor (NK1R) which plays a relevant role in the mediation of the chemoreceptor reflex in response to hypoxia in the medulla seem to be altered in males (40). Boys seem also to have more immature sleep than girls (41). The lower levels of HA and t-MeHA could also reflect an impairment of histamine system in male infants.

Limitations

One of the study limitations concerns the selection of the population. Indeed, getting CSF samples of healthy patients is not an easy task whatsoever since parents as children are rather reluctant to do a lumbar puncture, this procedure being an invasive act used only to rule out or diagnose a pathology. This is why the choice was made to use CSF samples from patients admitted to the emergency department, for whom a lumbar puncture had to be performed during the care. However, to limit potential bias, only the CSF samples whose results came back normal were kept for analysis in the present study (22). In addition, the population recruitment pattern is similar to that of other studies using human CSF (17, 22). It should also be kept in mind that HA is not produced solely by the tuberous-mamillary neurons but also by the basophilic and the mast cells. Consequently, we only chose samples without the least trace of blood so as to avoid any blood contamination that could lead to erroneous data. Furthermore, we managed to exclude the role of the time of lumbar puncture as a potential confounding factor in the assay of HA and t-MeHA levels and no association was found between the time of lumbar puncture (day vs. night) and HA or t-MeHA levels. Indeed, children were awake when the CSF sample was taken. Another study limitation is the number of included children that did not allow stratified statistical analysis by sex and age-groups. However, this study sample in children is one of the largest published. Finally, in this retrospective study, we did not collect serum histamine in the population involved. However, in view of the very high serum levels of serotonin in SIDS (42) and the association of HA with hypercapnia, it would be of particular interest to accomplish a study to assess whether there are any interactions between brain and peripheral HA and serotonin.

CONCLUSION

We report in the present study the CSF HA and t-MeHA levels in healthy children from 0 to 20 years old. We therefore obtained normative data in order to better understand the maturation of the histaminergic system. CSF HA levels seem to be high in infant and then to decrease during childhood with age, as t-MeHA levels do. These results suggest changes in the histaminergic transmission and metabolism over the child's brain development, that we should further investigate. These normative data can be put into perspective with measurements under pathological conditions so as to better appreciate the role and adaptations of the histaminergic system in various pathologies. Regarding SIDS, this study did not show any decrease of HA levels concurrently with that of orexin levels during the physiological period at risk for SIDS between 2 and 6 months. There is therefore no defect of the histaminergic system at this period that could have been accountable for a greater vulnerability toward SIDS. Contrary, we found that the histaminergic system seems to be highly activated during the first 6 months of age and could be a protector factor of SIDS during this high-risk period of SIDS. As the decrease of orexin levels and the increase of HA did not take place in the same period likely 2–6 months, this increase probably do not correspond to compensatory mechanisms of histaminergic neurons facing lack of orexin. Further studies with measurements of orexin and histamine levels in the CSF of the same healthy children or on evaluation of orexin and histamine neurons in the hypothalamus on SIDS victims could help to understand the physiology of these awakening systems and their potential role in the pathophysiology of SIDS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethic review and approval was not required for this study on human participant as samples and information on children were collected in clinical situation and for diagnosis purpose in accordance with the local legislation and institutional requirements. At the hospital admission, parents were informed that biological samples from their children could be used for research purposes and they signed a consent form.

AUTHOR CONTRIBUTIONS

PF and JSL contribute to the conception and design of the study and interpret the results. AG, COI, and MZ collected and managed the data. SP performed the statistical analyses and interpret the results. PG wrote the first draft of the manuscript. PR interpret the results. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.819496/full#supplementary-material

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REVIEW
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Hyperthermia and Heat Stress as Risk Factors for Sudden Infant Death Syndrome: A Narrative Review

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Background and Objectives: Heat stress and hyperthermia are common findings in sudden infant death syndrome (SIDS) victims. It has been suggested that thermal stress can increase the risk of SIDS directly *via* lethal hyperthermia or indirectly by altering autonomic functions. Major changes in sleep, thermoregulation, cardiovascular function, and the emergence of circadian functions occur at the age at which the risk of SIDS peaks—explaining the greater vulnerability at this stage of development. Here, we review the literature data on (i) heat stress and hyperthermia as direct risk factors for SIDS, and (ii) the indirect effects of thermal loads on vital physiological functions.

Results: Various situations leading to thermal stress (i.e., outdoors temperatures, thermal insulation from clothing and bedding, the prone position, bed-sharing, and head covering) have been analyzed. Hyperthermia mainly results from excessive clothing and bedding insulation with regard to the ambient thermal conditions. The appropriate amount of clothing and bedding thermal insulation for homeothermia requires further research. The prone position and bed-sharing do not have major thermal impacts; the elevated risk of SIDS in these situations cannot be explained solely by thermal factors. Special attention should be given to brain overheating because of the head's major role in body heat losses, heat production, and autonomic functions. Thermal stress can alter cardiovascular and respiratory functions, which in turn can lead to life-threatening events (e.g., bradycardia, apnea with blood desaturation, and glottal closure). Unfortunately, thermal load impairs the responses to these challenges by reducing chemosensitivity, arousability, and autoresuscitation. As a result, thermal load (even when not lethal directly) can interact detrimentally with vital physiological functions.

Conclusions: With the exception of excessive thermal insulation (which can lead to lethal hyperthermia), the major risk factors for SIDS appears to be associated with impairments of vital physiological functions when the infant is exposed to thermal stress.

Keywords: SIDS, thermoregulation, sleep, respiration, infant, hyperthermia, thermal stress

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INTRODUCTION

Sudden infant death syndrome (SIDS) has been defined as "the sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (1). A great number of factors (including the laryngeal closure reflex, sleep state disturbances, depressed

arousal, apnea cerebral ischemia, and hyperthermia) have been suggested as causal in SIDS. In particular, heat stress and hyperthermia are common findings in SIDS victims. In 1984, Stanton reported that of the 34 SIDS victims studied, "19 babies were unusually hot or sweating when found dead; 14 died in an unusually warm environment; 17 had evidence of a terminal infective illness; and 24 were excessively clothed or overwrapped. In 6 of 15 babies (40%) whose rectal temperature was recorded after death, the temperature was above 37°C, the highest being 42°C" (2). Profuse sweating has been found on the scene of SIDS (3, 4), and some SIDS twins were found covered with abundant sweat (5)—a possible marker of the risk of SIDS during sleep (6). There is evidence to suggest that the risk of SIDS increases in overly hot environments, and so this aspect is an integral part of the Safe to Sleep® campaign in the USA and the "Reduce the Risk"/"Back to Sleep" campaigns in other countries (7). In a multivariable regression analysis of the relationship between the overnight rectal body temperature and other variables (including putative risk factors), Tuffnell et al. (8) demonstrated that protective factors (supine position, birth weight, age, etc.) decreased the rectal temperature while risk factors (room temperature, bottle feeding, and parents who smoked) increased it. However, there is no consensus on the mechanisms that underlie the "overheating" hypothesis in SIDS.

The incidence of SIDS peaks before 4 months in preterm and term infants, respectively (9, 10). The infant is vulnerable during this period because its temperature regulation mechanisms are still developing and the rhythms of various physiological functions change after birth (11–14). Term neonates are characterized by a high body surface/body volume ratio (∼0.8 cm^{-1}); body heat losses to the environment are therefore greater than in older children weighing 20 kg (ratio = ∼0.2 cm^{-1}), for example (15). When combined with a thicker layer subcutaneous fat and an 46% increase in heat production during the first week of life (16), all the afore-mentioned anatomical and physiological characteristics augment the likelihood of excess body heat storage; the infant becomes more vulnerable to heat stress and harmful hyperthermia. Moreover, dehydration, fever, and abnormal central control of the thermoregulatory system can shorten the time to lethal hyperthermia and might thus lead to SIDS.

Infants exchange heat with the environment by radiation (between the body and the surrounding surfaces), convection (through the movement of air around the body and over the mucous membranes of the respiratory tract), conduction (*via* materials in direct contact with the skin surface) and evaporation (through transcutaneous water loss, sweating, and respiratory water losses). Body heat losses depend on the room, the radiant temperatures, the air humidity, the air flow velocity, and the clothing insulation. In France, **heat stress** has been defined as a rectal body temperature over 37.5°C, with a warning threshold of 38°C (17). When the heat load becomes too great and overcomes the effectors' thermoregulatory responses, **hyperthermia** sets in. Heat stress and hyperthermia are produced by an alteration in the body's heat balance, i.e., when body heat production and gains exceed body heat losses. This can occur following a reduction in heat dissipation from the body to the environment (mainly *via* the skin) and/or an increase in metabolic heat production. In addition to the effect of the Q_{10} temperature coefficient (a measure of a chemical reaction's temperature sensitivity, as described by van't Hoff's equation) during heat stress and hyperthermia, heat production is increased by circulating catecholamines and by the activity of the respiratory and cardiac systems. The rise in body temperature can thus be described as an accelerating system. The core body temperature increases, leading to heat stroke (over 41°C) and death (43°C has been defined as the lethal threshold) (18).

Besides the direct effects of hyperthermia, interactions between thermal stress with protective homeostatic responses might lead to potentially life-threatening events and thus SIDS during sleep. In a retrospective epidemiological study performed in the United States, Scheers-Master et al. (19) showed that heat stress was not directly and significantly related to the pathogenesis of SIDS. This finding reinforced the hypothesis whereby an elevated body temperature only acts as an additional stressor that interferes with protective homeostatic processes. Thus, it appears that heat stress alone does not cause SIDS but triggers other potentiating factors. In view of these observations, Filiano and Kinney (20) and the Task Force on Sudden Infant Death (21) suggested a triple-risk hypothesis, in which SIDS occurs in vulnerable infants exposed to environmental stressors during a critical developmental period. However, this hypothesis is subject to debate and has not been demonstrated (22).

Here, we review the literature on whether (i) thermal stress increases the risk of SIDS directly by lethal hyperthermia or indirectly *via* heat stress which induces alterations in autonomic functions, and (ii) conventional risk factors for SIDS can be interpreted in terms of the thermal load.

IS HYPERTHERMIA A DIRECT RISK FACTOR FOR SIDS?

During hyperthermia, the body core temperature is high and may lead to severe heat stress and, ultimately, death. Experiments on heated piglets showed that the hematologic, metabolic, cardiorespiratory and histological changes observed in hyperthermia were the same as those encountered in SIDS (23–25). A rapid increase in brain temperature can be associated with hemorrhagic shock and encephalopathy (26, 27). In rats, mild hyperthermia (a brain temperature of 39°C for 20 min) can produce severe ischemia in various brain structures and can induce severe neuronal necrosis (28). Hence, the hyperthermia hypothesis for SIDS is based (at least in part) on the similarities between postmortem necropsy findings and SIDS.

Hyperthermia results from the interaction of several factors, such as a high air temperature, heavy wrapping, head covering, and (sometimes) fever.

Abbreviations: PACAP, pituitary adenylate cyclase-activating polypeptide; REM, rapid eye movement sleep; SIDS, sudden infant death syndrome.

Elevated Outdoors Temperatures and Clothing or Bedding Insulation

In a retrospective study of four US states (Georgia, Arkansas, Kansas, and Missouri) that experienced heat waves in 1980, Scheers-Masters et al. (19) reported that the daily outdoors temperature was not related to the incidence of SIDS and concluded that the association between climate and SIDS was far from consistent. However, studies in various other countries found that SIDS occurs frequently in the winter months, when the temperature outside is low (29–33). In a case-crossover analysis performed in Montreal from 1981 to 2016, Auger et al. (3) showed that after 2 months of life, SIDS was associated with an elevated outdoors temperature on the day before death and on the day of death. The discrepancies between these studies might be due to differences in infant care practices from one country to another (33). The most plausible explanation for these discrepancies relates to the fact that infants are often overwrapped and/or the parents have set an excessively high room temperature (11, 33–35), although this is also subject to debate. For air temperatures of between 15 and 25°C, Wigfield et al. (36) compared the level of clothing insulation need to maintain thermoneutrality (calculated using a mathematical model based on body heat balance equations) with the level of clothing insulation chosen by parents. The two levels were similar, and the researchers concluded that parents provided appropriate levels of thermal clothing insulation for sleep in thermal comfort, whatever the air temperature. Wailoo et al. (11) came to a similar conclusion, after reporting that in a cold British winter, the clothing insulation chosen by parents for the infants sleeping in cots was appropriate; under these conditions, the infants were able to thermoregulate and to maintain their rectal temperature within the normal range.

Values for clothing thermal insulation are found in the literature on adults (37) but are scarce in the literature on infants; the latter topic requires further research.

Hyperthermia and the Prone Position

Prone sleeping and side sleeping positions are reportedly associated with hyperthermia (38) and SIDS (39, 40). In a study performed in New Zealand, Williams et al. (41) showed that a combination of excessive thermal insulation (>2 tog, >1.29 clo) and the prone position triggered SIDS. Similarly, Ponsonby et al. (42) reported that the risk of SIDS in prone sleepers was increased by swaddling, the use of a natural fiber mattress, recent illness, and a warm environment.

Several studies have sought to determine the thermal impact of prone sleeping on the risk of SIDS. Petersen et al. (43) compared the changes in **rectal temperature** in infants sleeping in the supine, lateral or prone position. For the prone infant, the rectal temperature did not differ significantly but tended to rise more quickly at the end of the night than for the other positions. The researchers concluded that the prone position could increase vulnerability to SIDS (43). However, the difference with the other positions was very small and would easily be compensated for by active thermoregulation. This can be explained by Tuffnell et al.'s (44) modeling of exponential body cooling; at bed-time, the **heat loss coefficient** for a prone infant was ∼60% lower than those of supine and side sleepers. This is because heat loss from the head and exposed limbs is lower in the prone position than in a non-prone position. The calculated mean body temperature was the same for all the body positions. However, the non-prone sleepers reached their body temperature faster—indicating that they lost heat more rapidly than prone sleepers.

The results of many physiological studies have suggested that the prone position is associated with peripheral cutaneous vasodilation, which could increase body heat losses to the environment. Thus, Yiallourou et al. (45) have suggested that the elevated **skin temperature** found in the prone position reflects a lower level of vasomotor tone, which decreases the blood pressure and increases the heart rate. This is consistent with the lower autonomic vasoconstriction in response to a tilting test when sleeping prone (46). Longitudinal studies of infants between the ages of 2–3 weeks and 5–6 months (47) showed that **abdominal temperature** was 0.3–0.7°C higher in the prone position than in the supine position. However, the **rectal temperature** did not differ significantly when comparing the two positions. Chong et al. (48) reported that in the prone position, the **chin skin temperature** (but not the abdominal skin temperature) was higher. Skadberg and Markestad (49) observed that a distal skin temperature (measured on the left foot) during rapid-eye-movement (REM) and non-REM sleep was significantly higher in the prone position. In low-birth-weight infants (postconceptional age: 33–38 weeks), and despite the fact that the **metabolic rate** was lower in the prone position, Ammari et al. (50) observed that sleeping prone was associated with significantly higher **proximal** temperatures (+0.2°C for the forehead and flank) and **distal** temperatures (+0.4 to +0.5°C for forearm and leg) and narrowed the difference between central and peripheral temperatures (0.4°C less for forehead-to-forearm and 0.2°C less for forehead-to-environment) during both REM and non-REM sleep.

Elabbassi et al. (51) used a multisegment anthropomorphic thermal manikin (simulating a newborn with a birthweight of 1,400 g) on a plastic foam mattress to show that dry heat losses were similar in the prone and supine positions and regardless of whether the mannequin was clothed (with a diaper, a pajama, cotton swaddling, and a lightly padded sleeping bag with sleeves) or not. This is consistent with Tuffnell et al.'s (44) calculation of the same steady-state body temperature in both sleeping positions.

One can conclude that the thermal impact of the prone sleeping position is limited to higher skin temperatures and that prone sleeping does not have marked effects on internal body temperatures. Hence, it is not possible to conclude that the prone position induces hyperthermia and heatstroke.

It should be emphasized that the relationship between the prone position and thermal stress is not limited to (slight) heat stress resulting from elevated whole-body heat storage. One cannot dismiss the results of observational studies in

which the prone position led to sleep modifications [more non-REM sleep, a longer sleep cycle, and higher arousal thresholds (47)], cardiorespiratory effects (higher heart and respiratory rates, lower heart and respiratory rate variability, rebreathing mechanical obstruction of the airways, and asphyxia). Although it is difficult to know whether these modifications result from the position *per se* or from the higher body temperatures in prone position, some appears to be specifically related to the body position and are independent of thermal effects (47).

Hyperthermia and Bed-Sharing

In the review by Baddock et al. (52), bed-sharing (i.e., an infant sleeping in the same bed or on the same surface as his/her mother and sometimes his/her father) is a common practice. It is associated with positive and negative infant outcomes, which depend on the characteristics of the infant and the parents and the sleeping environment. Observations of more frequent arousals (53–55) and infant-mother interactions suggested that bed-sharing might reduce the risk of SIDS. In contrast, other studies have described bed-sharing as an unsafe sleeping environment that increases the risks of not only accidental death (e.g., suffocation) but also SIDS (56–59)—especially when the infant is sleeping with people other than the parents (59).

Several researchers have suggested that the hyperthermia induced by bed-sharing is associated with SIDS. The level of bedding thermal insulation is higher in bed-sharing and is not counterbalanced by a lower level of clothing insulation (60, 61) or by a lower room temperature. Hence, bed-sharing infants had higher levels of excessive thermal insulation than those sleeping alone (62), even after the effect of closeness to the mother's body had been taken into account. Peripheral vasodilation occurs to maintain homeothermia, with a 0.8°C increase in skin temperature [a temperature that continues to increase during the night (60) or an elevated axillary temperature during non-REM sleep (61)]. As a result, the impact on the internal body temperature is usually considered to be small [a 0.1°C increase in the rectal temperature (63)] or null (60, 64). This is in line with Young's observation [1999, cited by (53)] whereby all infants were able to regulate their body temperature. Richard (61) suggested that differences in the axillary temperature between bed-sharers and solitary sleepers during non-REM sleep only were due to homeostatic factors and not passive heating by the mother. Given that (i) the thermal impact of bed-sharing is rather small, and (ii) the interaction between bed-sharing and the thermal resistance of the infant's clothing and bedding does not significantly increase the risk of death, it appears that overdressing and hyperthermia when bed-sharing do not increase the risk of SIDS.

Interpretation of the risks associated with bed-sharing is complicated by possible additional risk factors, including the infant's age (65), cultural factors (62, 66), and maternal smoking. Many studies [but not all (59)] have concluded that the risk of SIDS is increased by bed-sharing only when the mother smokes (57, 58). According to Scragg et al. (57), 20% of all cases of SIDS in New Zealand could be explained by the combined effect of bed-sharing and maternal smoking. Similarly, Blair et al. (65) and Ruys et al. (67), respectively, reported that the risk is higher for bed-sharing infants below the age of 14 or 16 weeks.

Hyperthermia and Head Coverings

A significant number of infants who die suddenly are found with bed covers over the head (58, 68, 69). Bacon et al. (70) pointed out that covering the infant's head with bedding increased the risk of developing hemorrhagic shock encephalopathy syndrome, which has similar pathological features to heat stroke. In a case-control study carried out in 20 European regions, Carpenter et al. (71) reported that the head was covered in 23% of deaths when sleeping. This situation was observed more frequently in prone-sleeping infants. When sleeping prone, the head remains covered because the infant cannot easily turn his/her head and/or remove the covers with his/her upper limbs and thus increase body heat losses. Moreover, an infant in the prone position can easily slip under bedding, which reduces heat losses. Sleeping bags can thus be used to prevent this risk (if appropriately used, i.e., with the right room temperature and clothing) (72).

The failure of behavioral thermoregulatory processes might be amplified by neurologic abnormalities. Korobkin and Guilleminauld (73) reported that "near-miss SIDS" infants aged under 3 months had hypotonia of the limbs and shoulder muscles, which could limit their body motility. These abnormalities disappeared with age. Blair et al. (68) systematically reviewed reports on the prevalence of head covering among SIDS victims and reported that the lack of a head covering reduced the risk of SIDS by 27.4%. The estimated risk with a head covering was five times higher than the risk in the prone position. The head is not only a major heat loss site (accounting for over 25% of the body's surface area) but is also a site of heat production (accounting for 40% of the total oxygen consumption in the brain) (74, 75). Therefore, covering the head drastically reduces heat losses by convection and radiation (which depend on vasodilation on the face) and also by evaporative skin cooling (by increasing the temperature and the humidity of the air trapped between the skin surface and the clothing). Using a mathematical model of the body heat balance that had been tested on weanling piglets covered (head and body) with infant blankets (thickness: 3 cm), Jardine and Haschke (76) showed that the time needed to raise the mean body temperature from 41°C to a lethal temperature of 43.9°C was 96 min, while removal of the blankets decreased the rectal temperature from 42 to 38°C in 82 min. After completing this experiment with a single weanling piglet, the researchers concluded that the risk of hyperthermia was zero if the entire head and a portion of the trunk's skin surface were uncovered and could lose enough heat. Similarly, Jardine (18) concluded that covered febrile infants can lose enough heat to avoid hyperthermia if a sufficient portion of the head remains uncovered. For example, the risk of hyperthermia was zero even when <30% of the head's skin surface area was exposed—as long as the blanket was not thicker than 3 cm. This finding was supported by Nelson et al.'s (38) report that in a heavily clothed infant, heat loss was particularly impaired by placing the head face down or by covering the head with bedding. Anderson et al. (77) showed that heavily covered sleeping infants can maintain

normal patterns of rectal temperature as long as the head and hands are not covered.

By monitoring the rectal temperature of sleeping infants, Tuffnell et al. (8) identified low birth weight and the prone and lateral positions as major factors in SIDS, since they were associated with a higher rectal temperature. The researchers suggested that radiative heat loss from the head and the face was lower in the prone and lateral positions because contact with the insulating mattress was greater. However, it should be noted that the prone sleeping position is also associated with lower convective and evaporative heat losses. We examined this hypothesis by using a thermal manikin (nude or heavily clothed) in the prone position (face to the side) *vs.* the supine position (face straight up or face to the side) (78). When the head was not covered by a bonnet, local heat losses were similar in all positions. However, when the head was covered by a 100% acrylic bonnet (covering 85% of the head's surface area), radiative, convective and conductive heat losses from the head were greater in the face-straight-up position than in the face-to-the-side positions in which part of the head was insulated by the mattress. We calculated that the change in head position would increase the mean body temperature by 0.29°C/h for a newborn weighing 1,400 g (51). It should be noted that this increase might be much smaller for older, heavier infants (e.g., those aged 2–3 months), since the change in mean body temperature was inversely proportional to the infant's body mass. Our observation was in line with Kleemann et al.'s (4) report in which the position of the face did not play a role in SIDS: most of the infants without preterminal hyperthermia were found face down.

The results of the above-cited studies show that the association between body hyperthermia and SIDS is subject to debate. However, one cannot rule out an involvement of the brain temperature. Indeed, the brain's temperature can increase rapidly even when the core body temperature is stable (79, 80). As shown in experiments on newborn piglets (81), covering the head can also induce a lethal rise in the brain temperature. The latter temperature depends on the balance between cerebral heat production and convective heat loss *via* cooled blood flow from the vena angularis oculi. During hyperthermia, venous blood flow from the face to the sinus cavernus surrounding the posterior hypothalamus increases. This selective brain cooling mechanism (82–85) might be involved in the incidence of SIDS. When the head is entirely covered, the skin temperature of the face increases as a result of the reduced convective, radiative and evaporative heat losses. This increase might be accentuated when the infant sleeps with its face to the side because the insulating mattress impairs conductive heat loss. When the face and head skin temperatures are above the body temperature, the brain's structures (particularly the hypothalamus, which controls several vital functions) are less well cooled. Russell and Vink (86) assumed that thermoregulatory stress is a critical situation that increases the likelihood of apneic respiratory events. According to this hypothesis, REM sleep might be a critical period because animal studies have shown that the brain temperature increases during this sleep stage (87, 88). Roussel et al. (88) assumed that this rise was due to vasoconstriction. In human infants, the metabolic rate is greater during REM sleep than during non-REM sleep (89–91). All these differences might account for the higher incidence of apnea during REM sleep (92, 93).

Selective cooling of the brain *via* the vena angularis oculi might account for the data reported by Coleman-Phox et al. (94). The researchers found that in infants sleeping in the prone or lateral position at a room temperature around 21°C, the use of a fan reduced the risk of SIDS by 72%. Coleman-Phox et al. suggested that the fan reduced the build-up of carbon dioxide. However, another explanation might involve selective brain cooling; when the air temperature is below the face's skin temperature, forced ventilation around the head would increase convective and evaporative heat losses and would cool the face.

Fever

Infection (95) and fever are frequently mentioned pathological factors in SIDS. In contrast to hyperthermia, fever increases the set-point temperature (i.e., the threshold temperature over which thermal responses are elicited); although the body's core temperature is higher than normal, it is still regulated. Many studies have reported that a mild viral infection alone is not a major risk factor for SIDS (1, 96, 97) but has a causative role when combined with heavy wrapping (clothing and bedding). In prone infants, excessive thermal insulation is associated with illness (0.93 tog, 0.60 clo). This is particularly true for SIDS victims (2.7 tog, 1.74 clo) (31). Gilbert et al. (98) reported that in heavily wrapped infants [with more than 10 tog (6.45 clo) of thermal insulation through bedding and clothing], viral infections greatly increased the risk of SIDS. Thermal stress is also magnified by the fact that the parents' response to illness (especially among less educated mothers) is often to keep their infants warm by raising the degree of thermal insulation and/or increasing the room temperature (99).

Using a mathematical model of body heat exchanges in a low-birthweight newborn wearing a bonnet and wrapped in a plastic bag, we showed that the mean body temperature increased from 40 to 43°C in 102 min (100). Metabolic heat production increased, while the mean skin temperature was kept constant (100). We also simulated acute fever during which a rise in metabolic heat production and greater peripheral vasoconstriction reduced body heat losses. The time required to reach a lethal temperature fell to 67 min. Although these results must be interpreted with a degree of caution (they relate to premature newborns, which lose heat more markedly and more quickly than older babies), they nevertheless show that lethal hyperthermia can occur rapidly in a feverish, heavily dressed infant.

Fever can thus be seen as a precipitating factor for SIDS (101). Thus, feverish infants should not be heavily clothed because thermal insulation is a key determinant of the risk of SIDS.

THERMAL LOAD HAS INDIRECT EFFECTS ON VITAL PHYSIOLOGICAL FUNCTIONS

Along with the direct thermal effects on SIDS, prenatal and/or postnatal heat exposure can impair the autonomic nervous

system. Thermal stress might thus disrupt cardiorespiratory drive and/or dampen arousal processes when a vital system is compromised.

Prenatal heat exposure can result in neural damage which can compromise later compensatory breathing or cardiovascular responses. Edwards et al.'s comprehensive review (102) of research on various animal species found that hyperthermia during organogenesis can have teratogenic effects. In the pregnant baboon, hyperthermia (a maternal body temperature above 41–42°C, in the absence of fever) increases fetal hypoxia, hypercapnia, acidosis, blood pressure, and heart rate (103). Maternal hyperthermia during the first trimester is associated with a greater risk of neural tube malformations and impaired brain development (104, 105). Even though data on pregnant women are rare, the few available studies also show that fetal hyperthermia (after heat exposure in a sauna or hot tub) is teratogenic (106). In feverish pregnant women, Chambers et al. (107) reported that teratogenic effects were only found for exposure with oral temperatures of 38.9°C or more and a duration >24 h in the first month of pregnancy. Although severe embryonic damage tends to lead to abortion, shorter and/or less intense heat exposures might delay the brain's development and impair its function. SIDS might thus result from *in utero* heat exposures (or other non-thermal harmful factors) *via* developmental defects in the brainstem and/or the autonomic nervous system's control of certain vital functions. Further research should seek to determine whether even subtle abnormalities can impair compensatory responses to a thermal challenge.

Heat Stress and Cardiovascular Failure

It has been suggested that impaired cardiovascular control (i.e., failure to counter hypotension) is involved in SIDS. A number of studies have assessed the heart rate, heart rate variability (HRV), blood pressure, and blood pressure variability. Marked changes in heart rate and blood pressure control (e.g., after a head-up tilting test) can be observed when sleeping prone—especially at the age of 2–3 months, when the risk of SIDS is the greatest (45). This is consistent with the lower autonomic vasoconstriction observed in the head-up tilting test when prone (46).

Spontaneous **bradycardia** depends on thermal load in an age-dependent manner: hyperthermia enhanced the magnitude of bradycardia in 12-day-old mouse pups but not when they were younger (108).

HRV is often studied as a marker of the sympathetic-vagal balance; a high frequency is related to parasympathetic vagal activity, whereas a low frequency is controlled by both parasympathetic and sympathetic tones of the autonomous nervous system. Future SIDS victims are characterized by (i) lower overall HRV during REM sleep and when awake (109, 110), (ii) a greater level of sympathetic-vagal heart rate control, with a lower high-frequency power, and (iii) greater low frequency/high frequency HRV ratios (111). These features are suggestive of impaired autonomic control and might result from repeated episodes of hypoxia (111).

In a study of sleeping preterm neonates, we observed that small thermal loads (2°C below thermoneutrality) are associated with lower overall HRV (as a result of decreases in both short- and long-term variability), higher sympathetic activity, and lower parasympathetic activity—indicating that non-thermoneutral temperatures induced significant changes in autonomic nervous system control during both REM and non-REM sleep (112). Similar results have been obtained by in other studies (50, 92) and during the thermogenic phase of fever (113).

The baroreflex to **blood pressure** changes (elicited by vasoactive drugs in newborn piglets) is less sensitive during the thermogenic phase of fever (113).

Heat Stress and Respiratory Failure

Impaired respiratory control might be involved in SIDS. Respiration is highly dependent on thermoregulation, and so thermal stress can have marked effects on the characteristics of respiratory control. Some effects are sleep-state- and age-dependent.

The **breathing rate** increases with the higher body temperature caused by fever (114), a greater environmental heat load (115) or the thermal load associated with skin-to-skin care (116). This increase in the breathing rate results from decreased respiratory drive from the thermoreceptors and thermoregulatory integrating centers in the hypothalamus. Some (but not all) studies have reported that this increase occurs during REM sleep only (117). Siren (118) has suggested that the resulting increase in the workload of the diaphragm muscles can (together with a lack of magnesium) contribute to (but not cause) the occurrence of SIDS.

An unstable breathing pattern is even observed for mild thermal stress (i.e., within the physiological temperature range). Berterottiere et al. (117) observed more frequent and longer episodes of **periodic breathing** during REM sleep only, although this pattern did not have an impact on oxygen saturation (measured using transcutaneous oximetry). It has been suggested that hyperthermia causes hyperventilation, which in turn leads to a fall in arterial CO_2 partial pressure and then periodic breathing. Periodic breathing can be associated with clinically significant falls in cerebral oxygenation (119).

When the rectal temperature of term neonates reached 37–37.1°C, the breathing pattern was more irregular, with respiratory pauses lasting between 5 and 10 s (115). Daily et al. (120) observed that apnea was more frequent with higher skin temperatures and was only observed in conjunction with periodic breathing.

Originally, Steinschneider (121) suggested that prolonged **apnea** was part of the final pathway resulting in sudden death. The apnea theory has not, however, been proven (122). Consistently with the apnea theory, the impacts of thermal stress on apnea have been extensively studied. These studies were justified because episodes of sleep apnea are (i) longer in all sleep states in future SIDS victims, and (ii) obstructive sleep apnea is more frequent in boys (for whom the risk of SIDS is higher than

for girls). Moreover, infants with obstructive apnea were more likely to sweat profusely than controls (111).

Since episodes of apnea longer than 20 s are quite rare, most of the studies concerned physiological apnea (i.e., with a shorter duration, usually from 3 s upwards). Perlstein et al. (123) observed that apnea occurred more frequently during the rising air temperature phase and assumed that this event was triggered when a thermal threshold was exceeded. In a study of healthy infants aged at least 3 weeks, we found that episodes of apnea were more frequent and longer (in REM sleep only) in a warm condition (i.e., an air temperature 2°C above the thermoneutral value) than in a cool condition (an air temperature 2°C below the thermoneutral value) (124). Bader et al.'s (125) results varied with the sleep state and the infant's age: the thermal load was associated with a greater frequency of (i) central apnea during non-REM sleep only in preterm infants and (ii) both central and obstructive apnea during REM sleep only in term infants. Similarly, in 12-week-old term neonates exposed to an air temperature of 20–30°C, Franco et al. (92) observed more frequent episodes of central apnea during REM sleep. These episodes were more often associated with blood desaturation, even though the increase in the rectal temperature was not significant. In contrast, there were no differences during non-REM sleep or for obstructive apnea.

Apnea is usually considered to be hazardous when it is accompanied by **blood bradycardia** and/or **desaturation**. Heart rate deceleration with central apnea (but not obstructive apnea) was enhanced by a higher body temperature in REM sleep only (92). As mentioned above, the thermal load increases the frequency of episodes of apnea in general and episodes with blood desaturation in particular (93). During REM sleep, warm conditions are associated with a greater frequency of episodes of apnea (especially those with blood desaturation) and more severe desaturation, relative to thermoneutral or cool conditions (92). Baddock et al. (126) reported that desaturation events were more frequent in bed-sharing infants than in those sleeping alone. Seventy percent of the desaturation events were preceded by central apnea (lasting between 5 and 10 s). In their study, the bed-sharer infants were characterized by warmer microenvironment (defined as a smaller difference between the rectal temperatures and the chin skin temperatures); the researchers calculated that a 1°C decrease in the chin-to-rectal temperature difference (i.e., a warmer environment) increased the frequency of blood oxygen desaturation by 60%. Exposure to thermal load therefore exposes the infant to repeated episodes of (mild) hypoxia, which raises the question of how the infants respond to this challenge and how these events affect the infant.

However, it is important to note that some studies failed to evidence a significant effect of thermal load on apnea or the breathing pattern, even when the skin and/or rectal temperature was higher (116, 117, 127). These apparent discrepancies might also be related to the variable chosen to quantify the thermal load. For example, Franco et al. (92) observed more statistically significant effects when considering the air temperature than when considering the rectal temperature. One of our studies might also explain these discrepancies (93). In preterm infants reaching term, we observed that episodes of apnea were more frequent in a warm condition (but only during REM sleep) and were less frequent in a cool condition (whatever the sleep state). The frequency of episodes of apnea with blood desaturation (but not that of episodes of apnea in general) was greater in the warm condition. We did not observe any significant effect on the average duration of the episodes of apnea, although the maximum duration was shorter in the cool condition. Interestingly, these comparisons of the three thermal conditions within the closed incubator differed according to whether or not apnea was considered as a function of the body's heat losses (calculated from skin, ambient and mattress temperatures, air humidity, mean radiant temperature and clothing insulation, using indirect partitional calorimetry). Our results clearly demonstrated that the frequency of episodes of apnea and the episodes' mean and maximum durations were significantly and positively correlated with body heat storage, rather than with the body temperature *per se*. This relationship was not sleep-state-dependent. These observations were consistent with Fleming et al.'s suggestion (128) that thermal effects on respiratory patterns might be linked to the detection of heat flux through the skin, since the respiratory effects usually precede skin temperature changes. Fleming et al. also suggested that the internal body temperature is not an essential component of the mechanism through which the thermal load has harmful effects on respiratory patterns. The researchers hypothesized that as a major site for heat production, heat loss, and respiratory control, the infant's head has a major role. Hence, disturbance of the thermal balance of the head alone (without a significant effect on the thermal balance of the body as a whole) might be enough to elicit impairments of breathing patterns and breathing control. Indeed, local warming of the preoptic-anterior hypothalamic area in kittens induces panting (i.e., faster breathing interspersed with periods of slower breathing) (129).

The postmortem examination of some SIDS victims evidenced chronic tissue hypoxia, which might have resulted from repeated obstruction of the airways (130). In piglets, prolonged apnea events with pathologic features similar to those observed in SIDS were elicited by the **laryngeal chemoreflex** (131). Moreover, the glottal closing force rises with the core body temperature (132). One can reasonably assume that this chemoreflex can produce asphyxia and is therefore a potential cause of SIDS if recovery processes fail (133). With regard to the impact of thermal load on this reflex, experiments in vagotomized, decerebrated piglets have demonstrated that an elevation in body temperature of between 2 and 2.5°C resulted in a longer laryngeal chemoreflex and apnea; this might contribute to SIDS (134). Haraguchi et al. (135) found that the latency and threshold of thyroarytenoid muscle activation decreased as the body temperature was increased from 34 to 41°C in anesthetized dogs (and more so in puppies than in adults). This might result from temperature-dependent changes in axonal conduction and synaptic transmission velocities. Lindgren et al. (136) pointed out that infection (associated with a 0.5°C increase in body temperature) prolonged fatal apnea through the stimulation of laryngeal chemoreflex receptors. There is now no doubt that the prolongation of this reflex by heat stress is controlled by the temperature of brain. Indeed, Van Der Velde et al. (137) showed

that the rostral ventral medulla provides tonic facilitatory drive to ventilation (limiting the laryngeal reflex) and that the loss of this drive might contribute to SIDS if combined with stimuli that inhibit respiration. Xia et al. (138) reported that this thermal effect was mediated by the nucleus of the solitary tract (which contains both warm- and cold-sensitive neurons) and that the reflex was more prominent in younger animals.

The receptors in the larynx can be stimulated by liquids containing a low chloride concentration (139). When the head is covered by clothing, rebreathed water will saturate the air at body temperature and thus increase the absolute humidity of the inhaled air.

Respiratory responsiveness to experimental airway obstruction during both REM and non-REM sleep in piglets was delayed if the animal was recovering from of a respiratory tract infection. The threshold was also markedly affected, albeit during REM sleep only (140).

These effects on laryngeal sensitivity might result from the effects of hyperthermia on the cranial autonomic nerves [for a review, see (141)]. It has also been shown that the output of the respiratory neural network (as measured *via* electromyography of the diaphragm) was significantly less complex in young rats (but not in older ones) at higher body temperatures—probably as a result of impaired respiratory control (142). Nicotine exposure (another risk factor for SIDS, associated with hyperthermia) was also associated with a less complex output of the respiratory neural network (143).

It has been suggested that **breathing or rebreathing exhaled air** (i.e., the mother's breath or the infants own breath) can explain the increased incidence of SIDS in (i) bed-sharing infants [an infant lying face-to-face with the mother is exposed to air containing at least 2% CO_2 (126)], (ii) infants with the head covered by bedding, or (iii) prone-sleeping, face-down infants (144). Using a mechanical model, Bolton et al. (145) confirmed the higher CO_2 content near the nostrils of face-down sleeping infants. Using a geometric representation of the nostrils of an infant sleeping in the face-down position, Itzhak and Greenblatt aerodynamic study (146) demonstrated how a high-temperature environment might be a risk factor for death.

Can Thermal Stress Impair the Response to the Cardiorespiratory Challenges That Occur Before SIDS?

It has been suggested that SIDS is due to inability to recover from prolonged apnea during sleep. Several mechanisms for recovering from sleep apnea are triggered when the chemoreceptors detect hypoxia and hypercapnia. An early-stage mechanism is arousal from sleep, whereas a late-stage mechanism involves hypoxic gasping and then autoresuscitation.

The failure of peripheral **chemosensitivity** and thus breathing control in response to prolonged apnea or to asphyxia caused by rebreathing expired air (especially in the microenvironment around the infant's mouth and nose, when the head is covered) might be involved in SIDS. An analysis of cardiorespiratory data obtained from infants who subsequently died from SIDS highlighted an alteration in the breathing response to hypoxia (147) and low chemosensitivity (148).

Oscillations in the breathing pattern (commonly observed in 1- to 3-month-old infants) can be elicited or enhanced by increasing the thermal load (128). In awake adult rats, a combination of hypothermia and severe hypoxia (7 or 11% O_2) (but not each factor alone) inhibited respiration, whereas hyperthermia increased CO_2 sensitivity (149). In urethane-anesthetized adult rats, responses to hypoxia or hypercapnia are also temperature-dependent: the hypoxia-hypothermia combination leads to loss of the normal response to rising CO_2 levels during hypoventilation (150). Interestingly, when considering a warm thermal load, the response to CO_2 differs according to whether the thermal load is due to fever or to the external environment (151). When analyzing central chemoreception in adult rats during wakefulness or non-REM sleep, Nattie and Li (152) found that the response to hypoxia was greater at 30°C (within thermoneutral zone) than at 24°C (just below the thermoneutral zone), suggesting that the mechanisms of the ventilatory response to hypoxia differ according to the thermal load. In contrast, the ventilatory responses to CO_2 did not differ significantly at 24 vs. 30°C. In sleeping infants whose peripheral chemoreception had been tested *via* a hyperoxic test, the ventilatory response was enhanced (but not delayed) in warm or cool ambient conditions (2°C above and below the thermoneutral temperature, respectively) relative to thermoneutrality, during REM sleep but not during non-REM sleep (153). This enhancement might increase breathing instability and lead to periodic breathing or apnea (117).

SIDS is almost invariably sleep-related and so is very rare in awake infants (154). During sleep, an appropriate response to a respiratory, cardiovascular or thermal challenge may necessitate **arousal** or a change in the sleep state. Arousals are considered to be part of healthy sleep and constitute an important survival mechanism by ensuring the reversibility of sleep—especially when the infant is exposed to a life-threatening event. It has been suggested that impaired arousability is involved in SIDS (155). Therefore, several studies have investigated arousability in healthy infants or in infants with risk factors or who subsequently died from SIDS.

It has been observed that infants who subsequently died from SIDS had shorter periods of wakefulness and longer episodes of sleep than controls (156, 157). Some SIDS risk factors [the prone position, and maternal smoking (158)] are known to increase the threshold for arousal (i.e., decreased arousability). The same was observed in infants 10–15 days post-discharge from a pediatric ward after recovery from an infection (159); this finding is consistent with the increased risk of SIDS also observed at this time. In experiments on rat pups, Darnall et al. (160) demonstrated that repeated exposure to hypoxia (as might occur in some SIDS victims) decreased arousability (i.e., habituation occurred). The reverse was found for protective factors like pacifiers and breastfeeding.

Inhibition of the arousal response is accentuated by exposure to several external stressor exposures, including thermal exposure. Thermal stress can impact both spontaneous and provoked arousals. After assuming that neonates are imperfectly homeothermic organisms, Dvir et al. (161) demonstrated that ectothermic zebrafish experienced less frequent and shorter **spontaneous arousals** in hot conditions (31 or 34°C) than at an optimal water temperature (28°C). The researchers hypothesized that in neonates, a high ambient temperature reduces the neuronal noise generated by subthreshold voltage fluctuations in the wake-promoting groups of cells located in the rostral brainstem and the posterior hypothalamus (162), reducing arousability in response to a harmful situation.

During REM sleep, **arousability in response to an auditory stimulus** was greater in 3-month-old infants sleeping at 28°C than in those sleeping at 24°C. This was only seen during the third part of the night (3–6 a.m., when most SIDS deaths occur) and was not significant during non-REM sleep (163). When infants slept with their face covered, they concomitantly exhibited higher auditory arousal thresholds (in REM sleep only), a higher pericephalic ambient temperature (+2.2°C), and a higher rectal temperature (+0.24°C). The pericephalic ambient temperature was significantly and positively correlated with the arousal threshold (164, 165). However, Horne et al. (166) reported contrasting results. They observed that arousals provoked by air-jet stimulation to the nares of term infants sleeping prone were more frequent when the abdominal temperature was elevated (by 0.3–0.7°C) but not when the rectal temperature was elevated (47), or without any significant modifications of these temperatures in preterm infants. In contrast to other experts, Horne et al. hypothesized that decreased arousability when sleeping prone or after infection was independent of a thermal effect on the arousability threshold (167).

Slight hyperthermia of the brain can modify the activity of brain mediators and might therefore account for the longer sleep episodes observed in feverish patients (168). Thus, slight hyperthermia of the brain—whatever its origin—might depress arousal mechanisms.

Cardiorespiratory recordings from dying at-risk infants have shown that hypoxic **gasps** immediately precede death and that SIDS victims and infants who die of other causes differ with regard to the effectiveness and characteristics of hypoxic gasping (169).

This responsiveness might be impaired by the thermal load. In a study of a single hypoxic exposure in newborn rat pups, a higher core temperature was associated with a shorter time to the last gasp and a smaller total number of gasps (170). Similarly, hyperthermia exaggerated and extended the respiratory depression responses to hypoxia in pups exposed prenatally to cigarette smoke but not in a control (sham) group; eupneic breathing failed, gasping occurred, and recovery was attenuated (171, 172).

Sridhar et al. (169) suggested that SIDS is due to failure to **autoresuscitate** rather than failure to initiate gasping. The ability to autoresuscitate (i.e., to return to a normal heart rate and stop primary apnea) was lower at a higher core temperature when the subject was repeatedly exposed to hypoxia (170). In mice pups, a combination of hypoxia and hyperthermia prevented autoresuscitation during a single hypoxic event, whereas neither exposure alone produced similar results (173). One can conclude that thermal load (even when strictly nonlethal *per se*) affects the responses that normally prevent death during severe hypoxia and so can lead to death.

Heat Stress and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP): A Common Mechanism?

PACAP is widely expressed throughout the central nervous system and is involved in many vegetative functions, including sleep (174), cardiorespiratory functions, and thermoregulation [for a review, see (175)]. There is a growing body of evidence indicates that PACAP has a role in response to challenges in infants in general and in SIDS in particular (175, 176). For an example, PACAP-deficient pups die suddenly in a manner reminiscent of SIDS (177)—probably due to defective cardiorespiratory control. Huang et al. (178) observed that PACAP levels were correlated with many SIDS risk factors (smoking, bed-sharing, infections, and seasonal temperature).

It has been demonstrated that PACAP is involved in the response to hypothermic and hyperthermic environments (175)—at least if the thermal challenge is sufficient (179). Indeed, PACAP may have an important role in the cardiorespiratory response to thermal stress. When compared with wild-type controls, PACAP-null pups exposed to severe heat stress did not exhibit the typical panting response (which increases evaporative respiratory heat losses) and showed a lower increase in the heart rate and skin temperatures (reducing heat losses from the skin and thus increasing body heat storage), somewhat greater breathing instability (as indicated by longer apnea, although not observed with other markers of breathing instability), and lower HRV. All these results argue in favor of a blunted response to heat challenges in PACAP-deficient pups, relative to controls. Barrett et al. concluded that "abnormal PACAP regulation could, therefore, contribute to neonatal disorders in which the autonomic response to heat stress is impaired, such as SIDS".

CONCLUSION AND CLINICAL IMPLICATIONS

SIDS is multifactorial. Given the low incidence of SIDS, it is difficult to perform large studies of future SIDS victims—unless all infants were to undergo cardiorespiratory and hypnic recordings. In view of this difficulty, only models of SIDS can be studied. The assessment of various models might explain (at least in part) the discrepancies between some of the literature findings. Some studies looked at infants who had experienced an apparent life-threatening event, the siblings of SIDS victims, and infants with risk factors (prematurity, maternal smoking, etc.). Other studies looked at healthy infants or animals and used physical and/or mathematical models only. The cardiac, respiratory and sleep patterns recorded prior to death are not

significantly abnormal, and no reliable predictors of SIDS have yet been identified.

Although many factors appear to be involved in SIDS, **thermal factors** are particularly relevant. All the studies evidently conclude that hyperthermia must be avoided and that the parents and caregivers have to pay particular attention to factors (including appropriate clothing and bedding insulation, as a function of the room temperature) that can lead to hyperthermia or heat stress and thus perturb physiological responses. In particular, little is known about the impact of the clothing thermal insulation on the development of hyperthermia and how much clothing and bedding is required to maintain the infant's thermal comfort. Appropriate guidelines on **thermal insulation** must be developed for given air temperature ranges. Only Ponsonby et al. (31) and Wigfield et al. (36) have attempted this, using mathematical models of thermal balance based on calculations of the various heat exchanges between the body and the environment. In this context, physical models like manikins (in which body heat transfers can be directly measured) avoid many uncertainties and so appear to be highly suitable.

Special attention should be paid to the risk of **brain overheating**, since large amounts of heat are lost from the head region. Reducing heat losses from the head with a blanket (18) and/or a bonnet (180) can be dangerous when the infant is heavily dressed and/or feverish.

The association between **bed-sharing** and the likelihood of heat stress and hyperthermia appears to be weak in the absence of other risk factors (such as maternal smoking, age, and cultural factors), and SIDS prevention campaigns have tended not to mention this aspect or have been inconclusive. It is nevertheless dangerous to recommend bed-sharing (due to its positive outcomes and greater mother-baby interactions) in non-smoking mothers and/or infants older than 4 months. Baddock et al. (52) have recommended reducing bedding insulation and ensuring that the infant's face and hands remain exposed, this enables heat losses and limits the thermal challenge.

Given the possible damage to the nervous system caused by heat exposure during fetal life and which might underlie SIDS, it appears necessary to protect **pregnant women** from heat. Future research projects should seek to better understand this risk (including occupational exposure) and to define danger thresholds in term of intensity and duration.

Many literature findings suggest the presence of a harmful **interaction between thermal load (even when non-lethal directly) and vital physiological functions** through the infant's autonomic nervous system. This is particularly important because at the age where the risk of SIDS peaks, the infant is undergoing major changes in sleep, thermoregulation, cardiovascular function, and the emergence of circadian functions—increasing its vulnerability. These interactions increase both the frequency and severity of autonomous challenges potentially leading to functional failure (e.g., prolonged apnea) and reduce the infant's ability to respond effectively to these vital challenges.

It should be noted that the "thermal hypothesis" does not account for all the risk factors and so requires further investigation. Factors that are known to increase the risk of SIDS but only have small effects on the thermal load should not be neglected. These include the **prone position**, which only has a small thermal impact (producing higher skin temperatures but not significantly higher internal temperatures). However, the decreased use of this sleeping position has (along with other changes induced by the various "safe to sleep" and "reduce the risk/back to sleep" campaigns) contributed to the drastic reductions in SIDS mortality worldwide (181).

Lastly, several researchers have pointed out that heat stress can act in concert with other environmental or confounding factors, such as smoking exposure. This question requires further studies and the development of mechanistic explanations with regard to the involvement of thermal and non-thermal factors in SIDS.

AUTHOR CONTRIBUTIONS

VB and J-PL reviewed the literature and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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The Ogival Palate: A New Risk Marker of Sudden Unexpected Death in Infancy?

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Objective: Ogival palate (i.e., a narrow and high-arched palate) is usually described in obstructive breath disorder but has been found in infants unexpectedly deceased. We studied the association between ogival palate and sudden unexpected death in infancy (SUDI) on the basis of a computed tomography (CT) evaluation.

Methods: We conducted a monocentric case-control study of children under 2 years of age who died of SUDI, for which a head CT scan and an autopsy were performed between 2011 and 2018. Each case was matched by sex and age (± 30 days) to two controls selected among living children in the same center who benefited from a cranio-encephalic CT scan. Four parameters of the hard palate were measured by CT: height, width, length, and sagittal angle; the height/width ratio was calculated. The presence of an ogival palate was also subjectively evaluated by the radiologists, independently from the measurements. Standardized odds ratios (OR) were calculated using conditional logistic regression models, all expressed for +1 standard deviation (SD).

Results: Thirty-two deceased children were matched to 64 living control children. Mean ages were 5.0 and 5.3 months, respectively. Twenty-eight cases were considered to have died as a result of SIDS. The mean heights of the hard palate were significantly higher in the deceased children [4.1 (± 0.7) millimeters (mm)] than in the living children [3.2 (± 0.6) mm], with OR (+1SD) = 4.30 (95% confidence interval [CI], 2.04–9.06, $P = 0.0001$). The mean widths of the hard palate were 21.0 (± 1.9) mm and 23.2 (± 2.1) mm, respectively, with OR = 0.15 (95% CI, 0.06–0.40, $P = 0.0001$). The mean sagittal angles were significantly more acute in deceased children [134.5° (± 9.3)] than in living children [142.9° (± 8.1)], with OR = 0.28 (95% CI, 0.14–0.56, $P = 0.0003$). The mean height/width ratios were 19.8 (± 3.7) and 14.1 (± 3.3), respectively, with OR = 6.10

(95% CI, 2.50–14.9, $P = 0.0001$). The hard palate was subjectively considered as ogival in 59.4% (19/32) of the cases versus 12.5% (8/64) of the controls.

Conclusion: Radiological features of the ogival palate were strongly associated with SUDI. This observation still needs to be confirmed and the corresponding clinical features must be identified.

Keywords: SUDI (sudden unexpected death in infancy), computed tomography, ogival palate, post mortem imaging, obstructive sleep apnea

INTRODUCTION

Sudden unexpected death in infancy (SUDI) is defined as the unexpected death of a healthy infant under 1 year of age (1). French recommendations extend this definition for children up to 2 years in age (2). This definition includes deaths resulting from a characterized etiology and sudden infant death syndrome (SIDS), which are deaths that remain unexplained after complete post-mortem investigations (i.e., clinical examination, autopsy, imaging, and biological analyses) (3). SUDI is reported to be associated with multiple risk factors, such as age, sex, sleep position, environment, or intercurrent infection (4). The physiopathology of SUDI has been associated with the "triple risk" theory, namely a vulnerable infant in a critical developmental period, confronted with exogenous stress (5). Among these risk factors, the orofacial structure may be involved in the lethal mechanism of SUDI and near-miss unexpected death. A strong association between the ogival palate (i.e., a high and narrow arch palate) and SUDI was first suspected in 2012 (6). Rambaud et al. described a case series of seven children admitted for SUDI, who presented an ogival palate, clinically diagnosed by opening the mouth. An important proportion of these children presented signs of clinical obstructive sleep apnea (OSA) that affected their breathing before death. This first description suggested a strong link between these events and obstructive sleep disorders, such as obstructive sleep apnea (7–9). To date, few studies have analyzed the specific orofacial structure in deceased children (10). At the same time, the development of post-mortem imaging offers new possibilities to explore craniofacial morphology, especially the skeletal disposition of the upper airways (11, 12). The aim of our study is to determine if an ogival palate (i.e., a narrow and high-arch hard palate) is associated with SUDI in a case-control study based on CT evaluation.

MATERIALS AND METHODS

Population

Definition of the Cases

In this case-control study, we retrospectively included all children under two years of age with a post-mortem evaluation for SUDI within the Department of Pediatrics and the Department of Pathology at the University Hospital of Nantes, France, between 2011 and 2018. The criteria of inclusion for cases were as follows: children who underwent a head and/or whole-body post-mortem CT scan, with bone and soft-tissue reconstruction and a complete autopsy with histological examination. For each child, we recorded sex, term of birth, age at death, body position at discovery (i.e., prone or supine position), the use of a pacifier during sleep, treatment treated for gastroesophageal reflux, clinical and/or microbiological signs of upper airways infection, and the cause of death (if known).

Definition of the Controls

The controls were randomly selected among living children under 2 years of age who benefited from a cranio-encephalic CT scan in the same center between 2017 and 2018. The matching ratio was 1:2 and was based on sex and age (± 30 days). The criteria of exclusion for the control cases were an incomplete exploration of an osseous palate, a major orofacial malformation (i.e., cleft palate or facial dysmorphic features secondary to syndromic diseases), hospitalization for a near-miss unexpected death and/or SUDI before age 2. For each control, we recorded age, sex, the reason for performing the CT scan, and (when available) if the child used a pacifier during sleep.

Imaging

The hard palate is anatomically defined as the association of the palatine process of the maxilla with the paired palatine bones. No quantitative and/or radiological definition of the ogival palate exists. Four parameters of the orofacial structure were measured for each child using multiplanar and double-oblique multiplanar reconstructions, following the clinical definition of the ogival palate (i.e., a narrow and high-arch palate). The height, angle, and length were measured in a strict sagittal plane along the axis of the vomer. The width of the palate was measured in a coronal plane perpendicular to the hard palate. The measurements were defined as follows:

- Height of the hard palate: the distance between the highest point of the palate and a line connecting the two extremities of the palate.
- Length of the hard palate: the distance between the incisive foramen and the posterior part of the palatine process, following the curve of the palate.
- Angle of the hard palate: the posterior part of the incisive foramen, the higher point of the palate, and the posterior part of the palatine process.

Abbreviations: CT, computed tomography; OR, odds ratio; OSA, obstructive sleep apnea; SUDI, sudden unexpected death in infancy; WA, weeks of amenorrhea.

- Width of the hard palate: the distance between lateral edges of the palate, up to the fifth and the sixth dental buds.

We completed this measurement by calculating the height/width ratio (H/W) of the hard palate. We also noted if a uni- or bilateral choanal stenosis was present using an axial plane parallel to the hard palate. The modalities of the measurements are detailed in **Figure 1**. The median palatine suture, especially the posterior part between the two palatal bones, was evaluated as closed or opened in an axial plane. The presence of an ogival palate was also subjectively evaluated by the radiologist, on the basis of the incurvation of the palate in the sagittal plane and the narrowness between the dental buds in the coronal plane, independently from the measurements. On the opposite, a flat and wide palate was considered normal (**Figure 2**).

All criteria were evaluated by two independent radiologists, a junior (C.M.) with a year of experience in forensic radiology and a senior (M.D.) with six years of forensic radiology. Each radiologist was blinded to the results of the other.

Ethical Consideration

Ethical approval for this study protocol was obtained on June 8, 2020, from the Institutional Review Board of the University Hospital of Nantes. Information and written consent from the parents of the deceased children were obtained during hospital admission. Information from the parents of the living children was made through an information booklet delivered during hospital admission. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report this study (STROBE checklist).[1]

Statistical Analyses

Categorical variables are presented using frequencies (%). The quantitative variables are presented using mean ($\pm$ standard deviation, SD) if the distribution was considered as gaussian or median (25–75th percentiles) in case of a skewed distribution.

All the analyses were based only on the measurements made by the senior radiologist; similar results were obtained from the junior radiologist (data not shown). The inter-rater reliability between the junior and senior radiologist was assessed by intraclass correlation coefficients (ICC, two-way model with random effects, single unit by rater). Scatter plots and Bland-Altman plots are presented for all five parameters of interest.

To assess separately the association of the different study parameters with the group (case or control), we used univariable conditional logistic regression. A multiple conditional logistic regression was also proposed using both the palate's height and width in the model. All quantitative parameters were standardized ($f : x \rightarrow (x - mean\,(x))/sd(x)$), so the associated odds ratios (OR) were expressed for an increase of 1 SD. The associated *P*-values were calculated using a Wald test. These calculations were also completed by analyzing the area under the receiver operating characteristics (AUROC) curves, presented in the **Supplementary Material**. Considering a global alpha risk

[1]https://www.strobe-statement.org

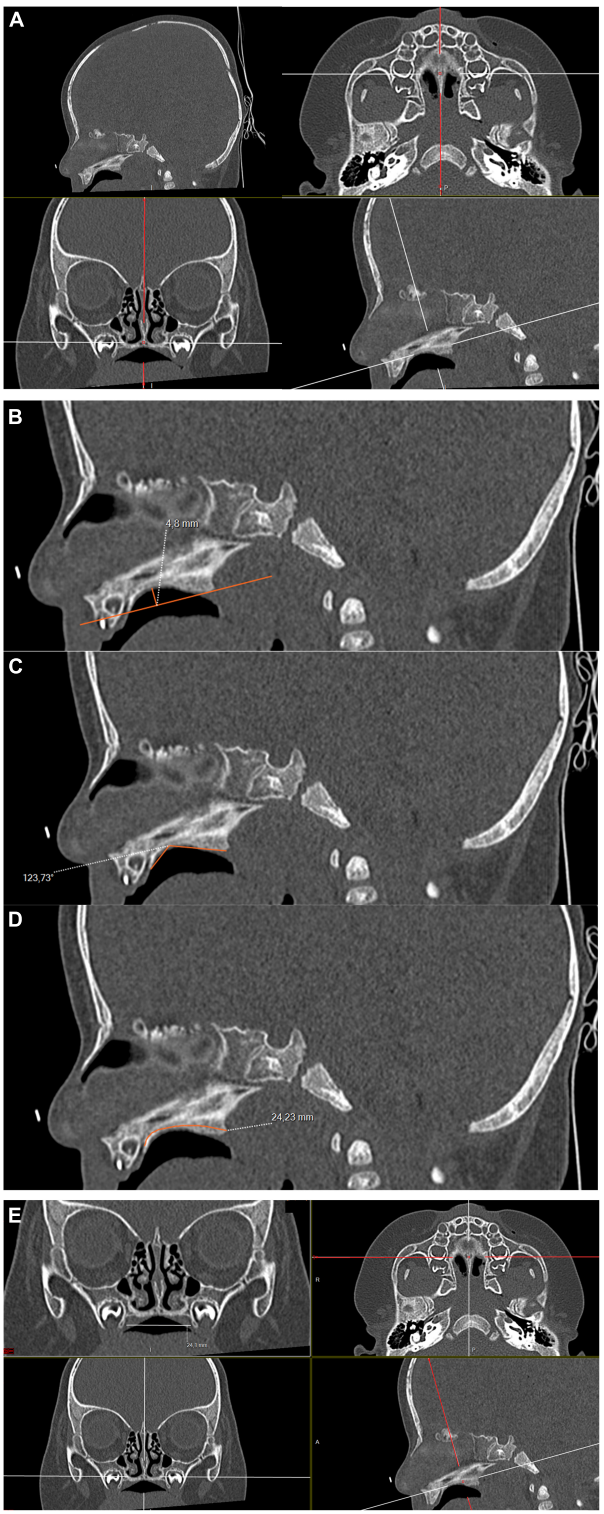

FIGURE 1 | Head CT image of a 5-month-old deceased male with no specific cause of death found after post-mortem investigations; bone filtered, double oblique multiplanar reconstruction; 100 kV, 95 mAs. **(A)** Sagittal plane used to measure the height **(B)**, the sagittal angle **(C)**, and the length of the hard palate **(D)**. **(E)** Coronal plane for the measurement of the width of the palate.

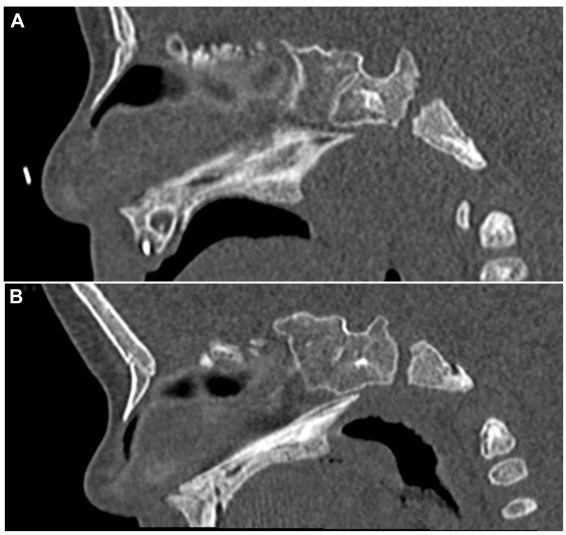

FIGURE 2 | Head CT images for palate comparison. **(A)** Deceased 5-month-old male. Anteroposterior incurvation of the palate can be noticed, with a high palatine arch. The palate was considered to be ogival. **(B)** Living 5-month-old male. CT was performed to eliminate intracranial blood. The palate is almost flat, without anteroposterior incurvation, and was considered to be non-ogival.

set to 5%, the unfavorable hypothesis of 5 uncorrelated tests, and the conservative Bonferroni's correction, a *P*-value <0.01 (0.05/5) was considered statistically significant. All analyses were performed using the R statistical software version 4.0.0, with the "survival" package (13, 14).

TABLE 1 | Study population data.

Cases (*n* = 32)	
Mean age (minimum-maximum)	5.3 months (2 days – 19 months)
Sex (female)	17/32 (53%)
Mean gestational age at birth (minimum-maximum)	38.8 WA (25–41 WA)
Position of discovery after death	
Prone	21 (65%)
Supine	4 (13%)
Lateral	2 (6%)
Unknown	5 (16%)
Cause of death	
Sudden infant death syndrome	28 (88%)
Hypertrophic cardiopathy	1 (3%)
Dilated cardiopathy	1 (3%)
Acute gastroenteritis	1 (3%)
Asphyxiating thoracic dystrophy	1 (3%)
Controls (*n* = 64)	
Mean age (min-max)	5.0 months (1 day – 19.5 months)
Sex (female)	34/64 (53%)
CT indications	
Suspicion of intracranial bleeding	43 (67%)
Convulsions	8 (13%)
Subdural enlargement or increased head circumference	3 (5%)
Skull deformation	3 (5%)
Infection (meningitis, ethmoïdis)	2 (3%)
Vomiting	2 (3%)
Hypotonia	1 (2%)
Suspicion of thrombophlebitis	1 (2%)
Staging of neuroblastoma	1 (2%)

RESULTS

Population

The study included 34 children who died between 2011 and 2018 (cases). All the children deceased from SUDI in this period benefited from a head and/or whole-body CT scan. Two of these children were excluded because of an incomplete exploration of the hard palate (n = 1) or no bone reconstruction (n = 1). The study flowchart can be found in **Supplementary Figure 1**.

The mean gestational age at birth was 38.8 weeks of amenorrhea (WA), with two children under 37 WA. The position of discovery was available in 27/32 cases (84%): supine position in 4 cases (15%), prone position in 21 cases (78%), and lateral position in 2 cases (7%). Arguments of upper airways infection were found for 11 children (34%). A specific cause of death was identified in 4/32 cases (13%): one hypertrophic cardiopathy, one dilated cardiopathy, one acute gastroenteritis in an ex-premature infant, and one asphyxiating thoracic dystrophy. Two of the children were known to have respiratory disorders while alive. The other 28 cases were considered to have died as a result of SIDS. None of the deceased children had clinical facial dysmorphia. One child was treated for gastroesophageal reflux.

The 32 deceased children were matched with 64 alive children (controls). Among them, two were excluded and replaced, one because of movement artifacts and one because of the child's death a few days later. They were replaced by two controls using the same matching criteria. CT indications were as follows: suspected intracranial bleeding after accidental or inflicted trauma (n = 43, 67%), convulsions (n = 8, 12%), subdural enlargement or increased head circumference (n = 3, 5%), suspicion of craniostenosis that was refuted by CT imagery (n = 3, 5%), infection (meningitis, ethmoids) (n = 2, 3%), vomiting (n = 2, 3%), hypotonia (n = 1, 2%), suspicion of thrombophlebitis (n = 1, 2%), and staging of neuroblastoma (n = 1, 2%).

The median age of the deceased and living children was 5.0 and 5.3 months, respectively. The average absolute value of the age difference between cases and controls was 0.41 months (0.30), with a maximum difference of 28 days. The male/female ratio was 0.9.

The clinical data of the study population are summarized in **Table 1**.

Imaging

The mean height of the hard palate was 4.1 millimeters (mm) (± 0.7) in the deceased children versus 3.2 mm (± 0.6) in the living children, with an OR (+1 SD) = 4.30 in univariable analysis (95% CI, 2.04–9.06, P = 0.0001) and an OR (+1 SD) = 3.23

TABLE 2 | Factors associated with sudden unexpected death.

	Controls (n = 64)	Cases (n = 32)	OR (95% CI)	P-value
Univariable analysis				
Age (months)	5.0 [3.0–7.0]	5.3 [3.0–7.0]	-	-
Female sex	34/64 (53%)	17/32 (53%)	-	-
Hard palate measurements			(for +1 SD)	
Sagittal angle (degrees)	142.9 ± 8.1	134.5 ± 9.3	0.28 (0.14–0.56)	0.0003
Height (mm)	3.2 ± 0.6	4.1 ± 0.7	4.30 (2.04–9.06)	0.0001
Width (mm)	23.2 ± 2.1	21.0 ± 1.9	0.15 (0.06–0.40)	0.0001
Length (mm)	23.9 ± 2.7	22.7 ± 1.8	0.50 (0.29–0.87)	0.015
Height/width ratio	14.1 ± 3.3	19.8 ± 3.7	6.10 (2.50–14.9)	<0.0001
Radiological subjective evaluation of the presence of an ogival palate (narrow, high-arch palate)	8/64 (12.5%)	19/32 (59.4%)	15.1 (3.47–65.7)	0.0003
Multivariable analysis				
Height (mm)	3.2 ± 0.6	4.1 ± 0.7	3.23 (1.41–7.37)	0.0055
Width (mm)	23.2 ± 2.1	21.0 ± 1.9	0.18 (0.06–0.60)	0.0048

CI, confidence interval; mm, millimeters; OR, Odds ratio; SD, standard deviation.
Categorical data are expressed using frequencies. (%). Quantitative data are given using mean (± SD) when the distribution was gaussian, except for age (25–75th percentile). Distribution of quantitative variables was assessed on histograms. Only the age was not considered as following a gaussian distribution. The ORs were calculated using a conditional logistic regression accounting of 2:1 matching. For quantitative variables, all ORs are expressed for a +1 SD increase after standardization $f : x \rightarrow (x - mean(x))/sd(x)$*). P-values were calculated using a Wald test.*

after adjustment on the width of the hard palate (95% CI, 1.41–7.37, P = 0.0055). The width of the hard palate was 21.0 (± 1.9) mm in the deceased children versus 23.2 (± 2.1) mm in the living children, with an OR (+1 SD) = 0.15 (95% CI, 0.06–0.40, P = 0.0001) in univariable analysis and an OR (+1 SD) = 0.18 (95% CI, 0.06–0.60, P = 0.0048) after adjustment on the height of the hard palate. The angle of the hard palate was more acute in the deceased children than in the living children, with a mean angle measured at 134.5° (± 9.3) versus 142.9° (± 8.1), respectively, and an OR (+1 SD) = 0.28 (95% CI, 0.14–0.56, P = 0.0003). The height/width ratio was higher in the deceased children than in living children at 19.8 (± 3.7) versus 14.1 (± 3.3), respectively, with an OR (+1 SD) = 6.10 (95% CI, 2.50–14.9, $P < 0.0001$). The length of the hard palate was slightly lower in the deceased children (22.7 (± 1.8)) than in the living children (23.9 (± 2.7)), with an OR (+1 SD) = 0.50 (95% CI, 0.29–0.87, P = 0.015). These results are detailed in **Table 2**. The ROC (receiver operating characteristics) curves are presented in **Figure 3**. The higher AUROC result was found for the height/width ratio, with an AUC = 0.88 (95% CI, 0.81–0.95). The AUC are resumed in **Supplementary Table 1**.

None of the children, living or deceased, had choanal stenosis. The median palatine suture was closed in 9% (3/32) of the deceased children and in 5% (3/64) of the controls; it was considered as opened in all the other children. The hard palate was subjectively considered as ogival by the senior radiologist in 59.4% (19/32) of the cases versus 12.5% (8/64) of the controls. Interobserver reproducibility of this observation was good between the senior and junior radiologists as only 8/96 discordances (8.3%) were noted. The tendency was a slightly higher estimation by the junior radiologist: alive, 15% (9/62); deceased, 63% (20/32). The ICC was 0.68 (95% CI, 0.20–0.85) for the angle, 0.80 (95% CI, 0.70–0.86) for the height, 0.79 (95% CI, 0.70–0.85) for the width, 0.66 (95% CI, 0.35–0.81) for the length, and 0.82 (95% CI, 0.74–0.88) for the height/width ratio.

DISCUSSION

Our study suggests that a high proportion of the children deceased from SUDI have a particular orofacial anatomy. Following our results, the height of the hard palate was significantly higher and the width significantly lower in the deceased children than in the living children, reinforced by the calculation of the height/width ratio, which seems to be an effective reflection of these anatomical specificities. This quantitative approach was also confirmed by a subjective evaluation of the ogival palate, which showed a significant difference in frequency between the two groups. The high significance of an ogival palate in our results supports the clinical evaluation first made by Rambaud et al. in (6) and is a first step to define it with quantitative measurements. Thus, it strongly reinforces the hypothesis that an ogival palate is associated with SUDI.

Craniofacial modifications are widely studied for their association with OSA (15–17). The optimal functioning of the upper airway (i.e., proper suction and swallowing, as well as nasal breathing) depend on many factors among which normal growth of the facial structures is one of the most important (18). A narrow nasomaxillary complex with an ogival palate can be associated with nasal obstruction and mouth breathing. The misuse of the nasal cavities and mouth breathing may consequently lead to dysfunction of the upper airway muscles, which may exacerbate the abnormalities of craniofacial structure (18–20). An orthodontic correction of this morphotype is one of the effective treatments for OSA, especially in children and young adults (20–22). Thus, if a relation between the orofacial structure and a breathing-related sleep disorder (including OSA and upper airway resistance syndrome) has been established over the years, the physiological process which leads to the morphological variations of the upper airway is debated. Indeed, it remains unclear whether the anatomical changes are the cause

or the consequence of the obstructive sleep disorder (23, 24). The palatal morphology is resulting in different factors, which are particularly important during the first months of life (25). Feeding and sucking habits influence the growth of the palate through the forces involved in chewing and swallowing (26). Position and size of the tongue, length of the tongue frenula,

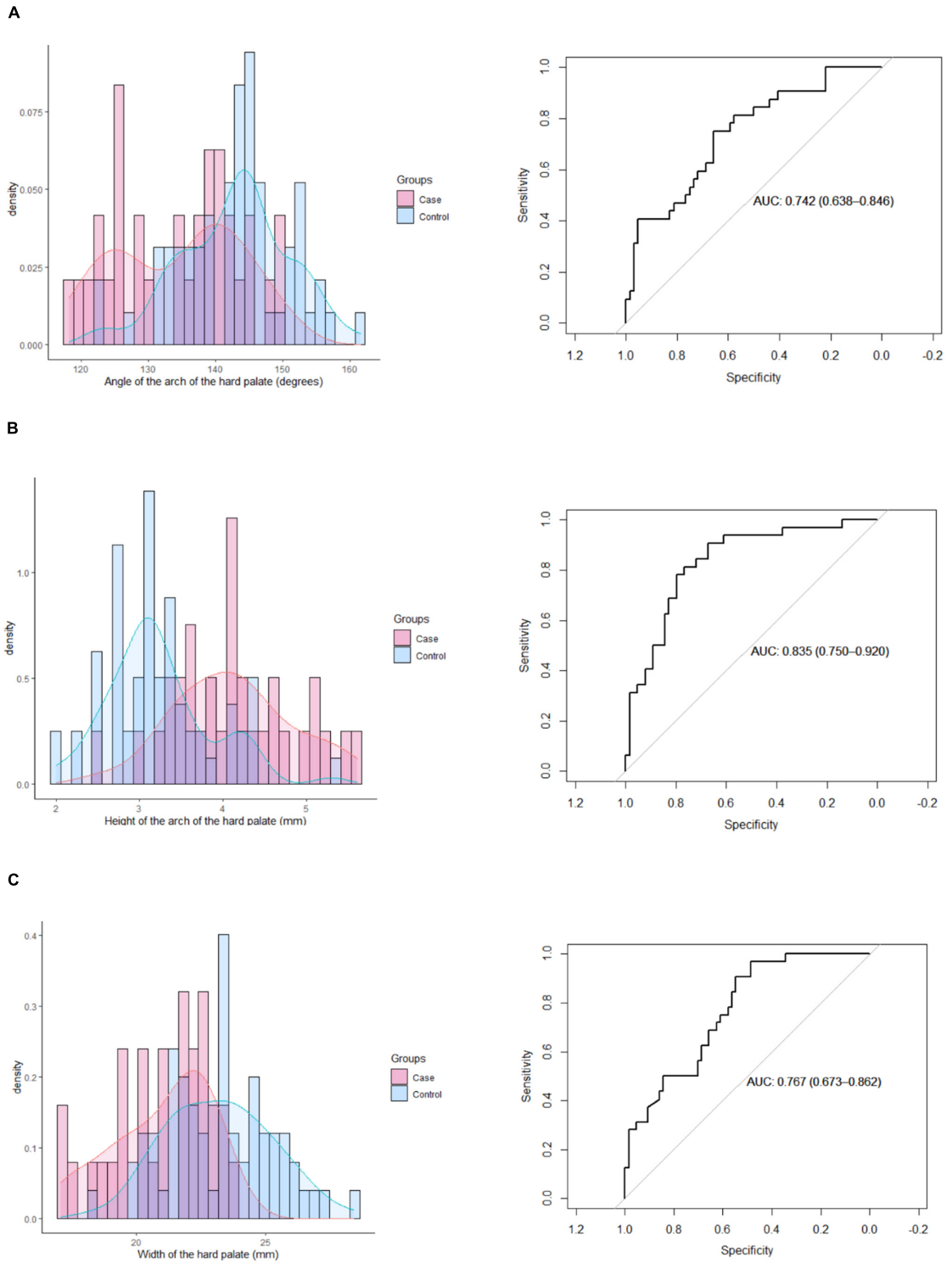

FIGURE 3 | (Continued)

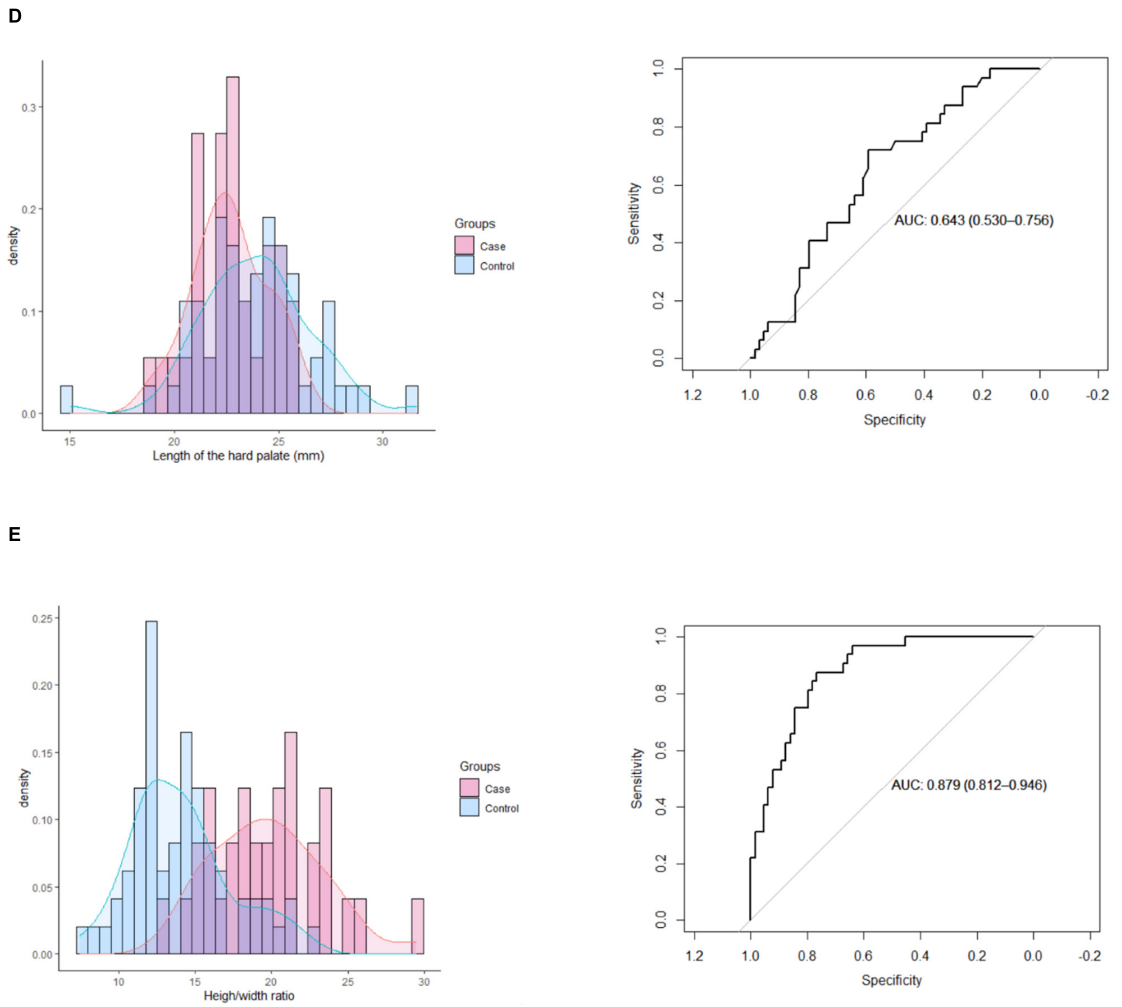

FIGURE 3 | Receiver operating characteristics curves of each parameter. **(A)** Angle of the arch of the hard palate. **(B)** Height of the arch of the hard palate. **(C)** Width of the hard palate. **(D)** Length of the hard palate. **(E)** Height/width ratio.

strengthens of the masticatory muscles of the mastication are many factors susceptible to impact the palatal development (27, 28). A high vaulted palate has also been described in preterm infants (29). It could be explained by several factors, such as immature swallowing and sucking functions and/or prolonged orotracheal intubation (29, 30). The possibility of the ogival palate as an inherited phenotype must also be considered as a strong hypothesis, as OSA in families has been previously studied (7, 31). Antenatal and neonatal studies could help foster a better understanding of the origins of this anatomical disposition.

The link between OSA and SUDI was first suggested in the 1970s (9, 32–34). The descriptions of the narrowness, obstruction, and increased resistance of the upper airway presented in the literature have suggested an association between OSA and SUDI (31, 35). Dysfunction of the central nervous system has been suspected, too, through alteration of dysautonomic functions, especially in preterm infants; however, this dysfunction is probably less predominant as a lethal process (36, 37). Mechanical asphyxiation that is secondary to an acute upper airway obstruction is indeed recognized as one of the most common mechanisms of death in very young infants, especially suspected when intrathoracic petechiae are numerous (32, 34, 38). The role of airway obstruction is reflected by the effectiveness of prevention campaigns promoting proper sleep environments and sleep position, which mainly aim to reduce possible accidental asphyxiations (39). Thus, it becomes easy to consider that an unfavorable orofacial structure may be a major predisposition for acute airway obstruction when triggered by upper airway infection, by sleeping in a prone position, and/or by using inappropriate bedding (40).

In the current literature, the studies mostly concern school-age children or adults, and the clinical presentation of OSA in very young children is poorly described (41, 42). None of the parents of the deceased children in our study spontaneously described strong signs of breathing disorders during sleep, such as snoring, agitated sleep, or mouth breathing. However, these clinical data may seem banal or insignificant by parents and they are usually not actively asked about during interviews

with parents. This information could be more easily gathered by using a standardized questionnaire that asks about OSA symptoms, as detailed by the International Classification of sleep disorders (snoring, obstructed breathing, movement arousals, neck hyperextension during sleep, inward rib-cage motion during inspiration) (43).

This study provides new perspectives to better understand and prevent SUDI. First, studying the orofacial structure in victims of SUDI may help researchers to better understand the protective role of pacifiers or dummies. Many hypotheses have been ventured: pacifiers may help to increase blood pressure during sleep but it is also supposed to enlarge the upper airways thanks to the genioglossus contraction and the mandibular movements (8, 44–46). In addition, the repeated suction and swallowing induced by the use of a pacifier could stimulate the growth and enlargement of nasomaxillary complex and the effectiveness of upper airway muscles (16, 47, 48). The correlation between palate structure and pacifier use in very young children needs to be evaluated in deceased and living children, with long-term cohort studies. Second, abnormalities in oral development could be one explanation for the increased risk of SUDI in preterm infants (49). Preterm children, especially boys, are subject to the alteration of the palatal morphology, which may be increased by lower gestational and longer orotracheal intubation (29). An attentive follow-up of palate structure, suction reflexes, and sleep breathing modality in these children could be an effective way to prevent the development of an ogival palate and may limit the risk of premature death.

Our study presents some limitations. First, the retrospective and monocentric design and the limited size of our sample limit the generalizability of the results, even if the magnitude of the effect allowed for a high statistical significance. A greater number of cases would have facilitated a subgroup analysis, especially regarding the age (less or more than one year). Second, the radiologists were not blinded to the status of the patients. A blind interpretation would have strengthened the results. Third, the choice of a case-control design might be criticized since it implies the comparison of deceased and alive children. However, we believe this design remains the best to investigate our research question with acceptable feasibility. Indeed, the incidence of the SUDI being, fortunately, low, a cohort study would need to recruit tens of thousands of children followed up at least 1 year to identify as much as the 32 presented cases, which would be difficult to implement, and ethically very arguable regarding the associated X-ray exposure. Furthermore, we are confident that the quality of the measurement remains the same, as the death of the child is not expected to modify the assessed radiological parameters. Fourth, the choice of the "controls" remains also an issue. We chose a 1:2 design as it increased the statistical power, and the representativeness of the control population, compared to a 1:1. But ideal controls would have been matched not only for the same age and sex but also with regard to their living environment and other identified risk factors for SUDI such as sleep environment.

The perspectives offered by this preliminary work are numerous. The radiological evaluations of other parameters, such as nasal piriform aperture, nasal septum deviation or mandibular position and measurement, could provide a complete description of the morphotype of children suddenly deceased. Subjective analysis of three-dimensional reconstructions of the hard palate could be very helpful to improve the evaluation of this parameter by different specialists (pediatricians, radiologists, general practitioners). Complementary studies on the correlations between CT images and clinical observations are essential in both living and deceased children to characterize possible subclinical OSA. The frequency of an ogival palate in the normal population of children under 2 years of age, which remains currently unknown, need also be determined, for a more precise interpretation of the frequency of the ogival palate in infants who died unexpectedly.

CONCLUSION

The facial structure of the case infants who died of SUDI seems to be different from that of living control children. More specifically, the ogival palate could be the sign of infraclinic OSAs and a narrow structure of the facial upper airways. Thus, the relationship between SIDS and OSA suggests that the orofacial structure could be a supplementary risk factor for SUDI. Recognizing this sign may be the first step in detecting and investigating possible OSAs in infants and children. Further studies are essential to confirm these results, to provide radiological and clinical correlations and to better describe the normal measurements of the nasomaxillary complex in infants. The frequency of ogival palate could consequently be described in the general population of infants. The precise pathogenesis of this anatomical disposition also needs to be determined. At the same time, a more thorough screening for craniofacial growth abnormalities may help to determine their possible involvement in breathing disorders during sleep and avoid premature deaths in very young children.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MD, CM, MW, and CR contributed to the conception and design of the study. PC, CR, and P-AG helped supervise the project. CM and MD organized the database. MW and P-AG performed the statistical analysis and realized some figures. MD and CM wrote the first draft of the manuscript with support from PC and RC. CG-G, MW, and CR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.809725/full#supplementary-material

Supplementary Figure 1 | Flow chart detailing the inclusion process and the mean age difference between cases and controls.

Supplementary Table 1 | Area under receiver operating characteristic (AUROC) for case identification, results with different hard palate measurements.

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Heart Rate Variability Analysis to Evaluate Autonomic Nervous System Maturation in Neonates: An Expert Opinion

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While heart rate variability (HRV) is a relevant non-invasive tool to assess the autonomic nervous system (ANS) functioning with recognized diagnostic and therapeutic implications, the lack of knowledge on its interest in neonatal medicine is certain. This review aims to briefly describe the algorithms used to decompose variations in the length of the RR interval and better understand the physiological autonomic maturation data of the newborn. Assessing newborns' autonomous reactivity can identify dysautonomia situations and discriminate children with a high risk of life-threatening events, which should benefit from cardiorespiratory monitoring at home. Targeted monitoring of HRV should provide an objective reflection of the newborn's intrinsic capacity for cardiorespiratory self-regulation.

Keywords: autonomic nervous system, sudden infant death syndrome (SIDS), life-threatening events, neonate, cardiac monitoring

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INTRODUCTION

Like adult pathology (1), the impact of autonomic nervous system (ANS) dysfunctions on children's health is well established. Regardless of age (2), heart rate variability analysis (HRV) is a relevant non-invasive tool of real-time or delayed evaluation of autonomic function with recognized diagnostic and therapeutic implications (3–8). Measurement tools that consider variations in the length of the RR interval, beat after beat, are widely available, and reference values according to the child's age have been published (9, 10).

This narrative review aims to overview the various HRV analysis techniques to evaluate autonomic nervous system maturation in neonates. We will also discuss the potential implications of ANS maturation studies to prevent sudden infant death syndrome and guide cardiac monitoring in neonatology units.

GENERALITIES ABOUT CARDIAC SIGNAL PROCESSING

Analysis of HRV obtained from the heart electrical signal by a monitor connected to two or three thoracic electrodes can be carried out offline (e.g., from a cardiac Holter) or in real-time from sliding windows analyzing cardiac irregularity according to a sampling frequency between 200 and 1000 Hz (11–13).

A series of R-R intervals with an accuracy from 1 to 5 ms is generated from each detected R peak. Missing or ectopic beats and artifacts are corrected using cubic interpolations (12). The curve of these intervals (tachogram) is then processed by algorithms (**Figure 1**).

Linear Analysis

In this configuration, signal analysis conventionally relies on the Fast Fourier Transform (FFT), method to assess the different frequencies in the RR series which requires the acquisition of stationary data with signal stability during the sampling period (13).

Time-Domain Analysis (12)

It is based on the means and standard deviations measurements of the short and long-term variations of the RR intervals. The standard deviation of the RR intervals (SDNN), the standard deviation of the mean of all RR intervals for 5-minute segments (SDANN), and the mean of the standard deviation of all 5-minute RR intervals (SDNNIDX) represent long-term global variations. The percentage difference between adjacent normal RR intervals greater than 50 msec (pNN50) and the square root of the mean of the sum of the differences between normal RR intervals squared (rMSSD) represent the rapid changes associated with the parasympathetic activity. The geometric indices calculated on the density distribution of the RR intervals correspond to the assignment of the number of RR intervals of the same length to each value of their length.

The Poincaré plot is a scatter plot developed by plotting each RR interval against the previous one. It is analyzed quantitatively by fitting an ellipse whose shape is plotted with the average RR interval as the ellipse's center. SD1 (short-term variability) represents the standard deviation of the Poincaré plot perpendicular to the identity line. In contrast, SD2 (long-term variability) means the standard deviation of the plot along this identity line.

Frequency Domain Analysis (12)

A frequency spectrum from 0 to 2 Hz segmented into three main bands of interest as standardized by the Task Force in 1996 (11) and defines the regulation of the human cardiac signal: very low frequencies (VLF) from 0 to 0.04 Hz reflect the long-term regulatory mechanisms (thermoregulation, vasomotor tone peripheral, renin-angiotensin system), low frequencies (LF) from 0.04 to 0.15 Hz correspond to the involvement of mainly the sympathetic system and more incidentally of the parasympathetic system, and high frequencies (HF) of 0.15 to 2 Hz in newborns correspond to the ventilatory component under the exclusive control of the parasympathetic system. Total power (Ptot) represents overall variability. Normalized indices (LFnu, HFnu) and LF/HF ratio estimate sympathetic modulation and autonomic balance.

Geometric Analysis (12)

This analysis defines the triangular index (integral of the density distribution divided by the maximum of the density distribution) and the TINN index (triangular interpolation of the RR interval histogram, i.e., the width of the base of this triangle). These measurements quantify the overall HRV primarily influenced by slow oscillations of the RR intervals.

Non-linear Analysis (12)

Transition periods are evaluated by segmentation of the signal with the wavelet transform method (14), allowing better evaluation of non-stationary signals and more refined real-time analysis. The indices resulting from this approach provide information on the complexity of autonomic regulations. We can distinguish fractal values, which quantify the repetition of the patterns displayed at different scales. Fractal values are based on trend fluctuation analysis (α1, α2, H), slope (1/f), exponent (Hurst, Higuchi, Katz, Lyapunov). Entropy values can also estimate the regularity and complexity of a pattern over different lengths (entropy indices of Shanon and its derivatives, conditional entropy, sampled and approximated entropy).

Another non-linear approach consists in measuring the deceleration (DC) and acceleration (AC) capacities of two successive RR beat sequences to estimate the vagal and sympathetic powers.

Cardiorespiratory Coupling

Other approaches to autonomic steady state analysis incorporate the link of instantaneous fluctuations between heart and respiratory rates over time using wavelet transforms. This is the cardiorespiratory coherence whose most significant reflection is represented by the physiological sinus arrhythmia caused by the respiratory cycle in the full-term baby with a healthy heart. In this case, if the child inhales and exhales, the HR increases and decreases in synchrony. In a situation of physiological stress, this coupling between heart rate and respiration could be attenuated. However, respiratory immaturity and the severity of central apneas are inversely correlated with gestational age and current treatment strategies based on caffeine and non-invasive respiratory assistance make it possible to overcome the initial stage of immature breathing. So when the full term approaches, the cardiorespiratory coupling is usually efficient. Currently the analysis of the cardiorespiratory coherence is not routinely used to guide monitoring for discharge but mainly concerns anesthesia and the perioperative period and proves to be of interest for evaluating nociception (15–17).

PHYSIOLOGICAL AUTONOMIC MATURATION

In neonatal medicine, understanding vital physiological systems during the first months of life must integrate the notion of autonomic control system maturation. Thus *in utero*, it has been established that at least 37 weeks of maturation are necessary to achieve complete autonomous maturation at birth, particularly the parasympathetic system (2, 17, 18).

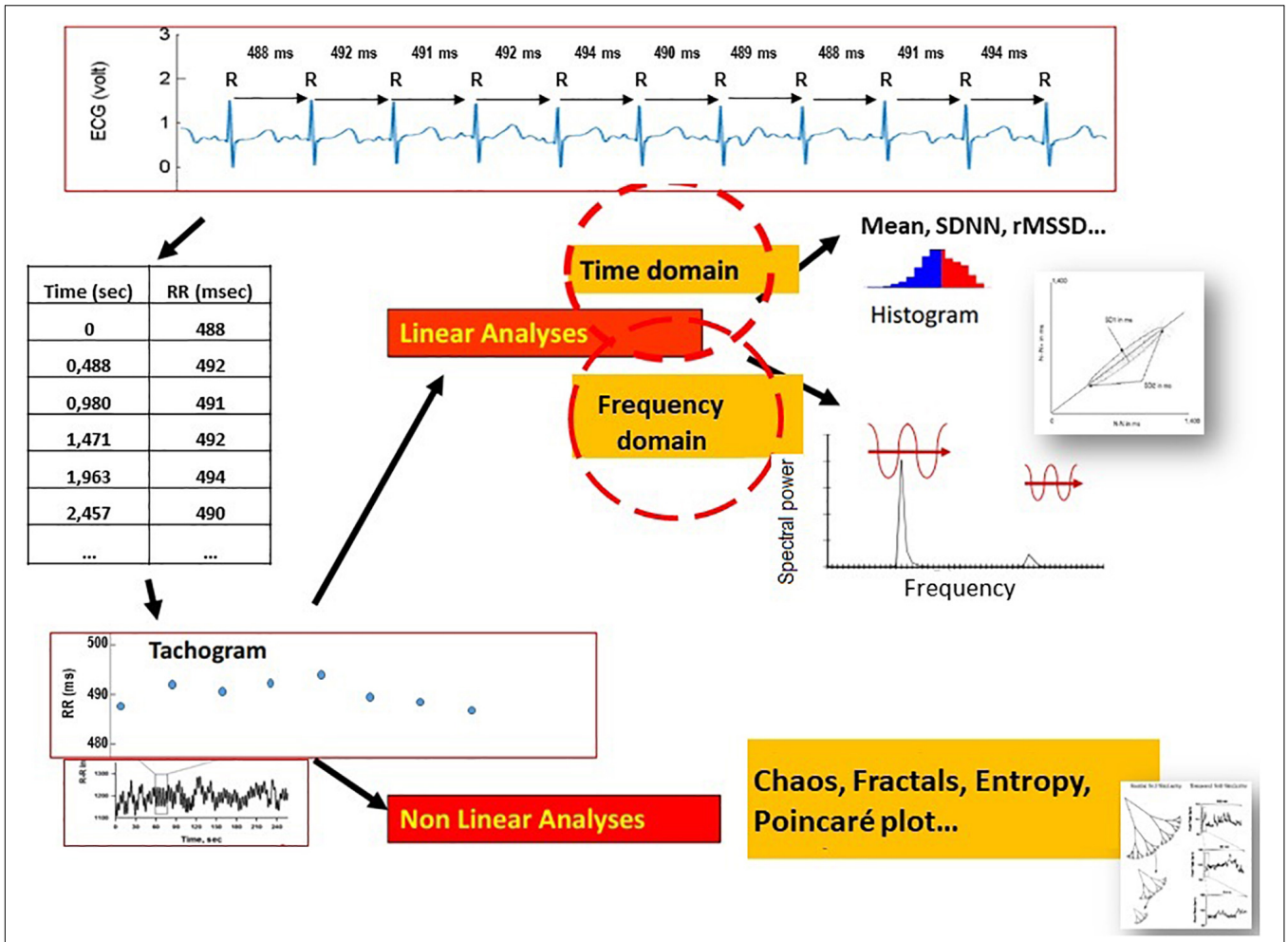

FIGURE 1 | Electrocardiographic signal decomposition and beat-to-beat measurement (ms) of the RR suite to obtain a spectrogram over a given period, processed by mathematical models adapted to linear sequences (time domain, frequency domain) or non-linear sequences (chaos, fractal, entropy, and Poincaré plot).

For premature newborns regardless of gestational age (GA)(19, 20)and including late prematurity (21), cardiac reactivity, and the baroreflex loop are altered at theoretical term compared to term newborns (22, 23) (**Figure 2**), even if with postnatal age there is a significant increase in HRV parameters, in particular for the high-frequency index (HF), recognized as a relevant indicator of parasympathetic maturation.

HRV is a good indicator for detecting and monitoring a stress level related to labor and delivery for the full-term newborn. After birth, the autonomic balance changes significantly during the first day of life. The slight sympathetic predominance observed at birth decreases in a few days in favor of the parasympathetic system, whose reactivity quickly becomes efficient (23). The rapidity of the cholinergic response (in milliseconds) compared to the thousand times slower adrenergic response (in seconds) will facilitate the onset of sudden cardiac slowdowns in response to extrinsic (noise, pain) or intrinsic (gastrointestinal reflux) stress (24). The sympathovagal balance of this neonatal period, specific to each individual, will then slowly modulate during the first months of life in favor of the parasympathetic branch, which will gradually become predominant, as described in the longitudinal *AuBE* (Autonomic Baby Evaluation) cohort (**Figure 3**). During the first 2 years of life, the healthy child benefits from a significant gain in overall autonomic maturation and gradually reaches a new equilibrium, resulting in a predominant parasympathetic activity compared to the sympathetic activity and, therefore, a fast and fine regulation gain (10).

Therefore, we must consider that this essential balance for homeostasis and cardiorespiratory control closely depends not only on wakefulness (wakefulness, calm sleep, active sleep) but also on postnatal age (25).

IMPACT ON THE DECISION TO STOP CARDIORESPIRATORY MONITORING IN NEONATAL CARE UNITS

In the neonatal unit, the decision to stop cardiorespiratory monitoring before discharge requires careful tracking of daily

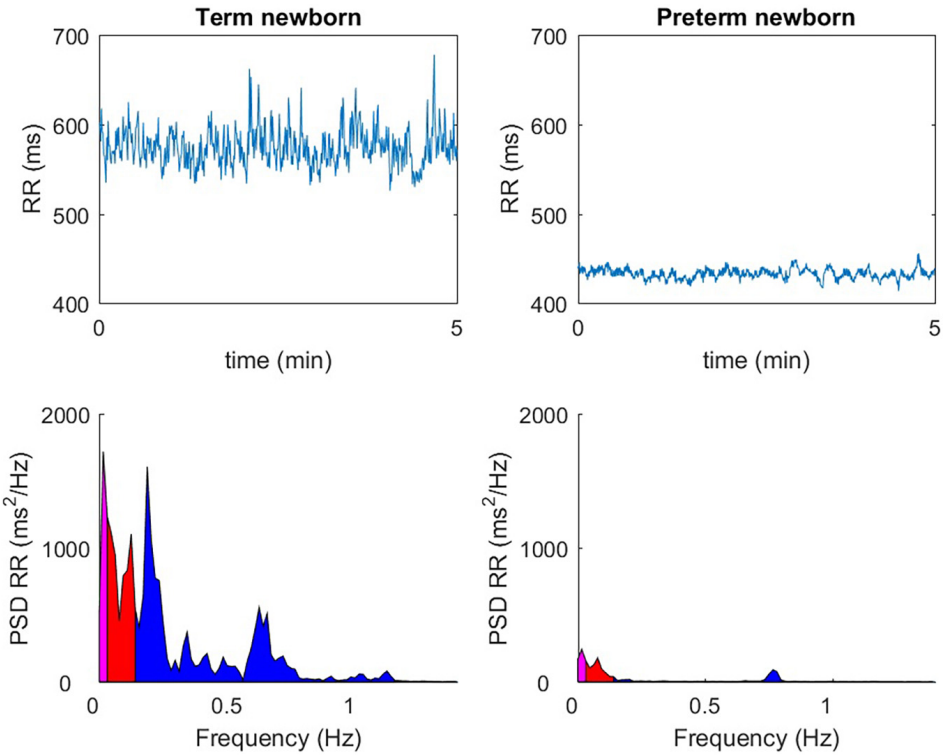

FIGURE 2 | The observable difference over 5 min in quiet sleep, between a full-term newborn (40 wGA) and a premature newborn (36 wGA), with a temporal analysis (ms) of the RR spaces (top windows), or with a frequency domain representation (ms2 / Hz) (bottom windows).

modulations of heart rate, bradycardias, and desaturations and understanding the intrinsic self-regulatory capacities of newborns, and so by extension to analyze the basal autonomic balance and the ANS reactivity.

When the corrected term is reached, the cholinergic response is very efficient and faster than the adrenergic response. This singularity implies a physiological increase in the number of daily cardiac slowdowns as the term approaches for premature children. What matters then is not to count the daily bradycardias but to have a certainty on the capacity for sympathetic self-regulation (response), which must not be deficient. In other words, when the baby approaches the theoretical term, this vagal predisposition should not be considered as a pathological element. Conversely, a lack of orthosympathetic responsiveness could increase the risk of an inadequate cardiorespiratory response after internal or environmental stress. This lack of sympathetic response would increase the risk of Sudden Infant Death Syndrome (SIDS), especially in the premature population (26, 27).

In clinical practice, the occurrence of sinus bradycardias in a child who did not have it before may be the first symptom of a new problem and requires careful clinical examination. But when the baby approaches the theoretical term, a reflection on the capacity of autonomic self-regulation of the heart and respiratory rate should make it possible to safely stop the cardiorespiratory monitor in the vast majority of cases. Thus neonatal bradycardias do not justify continuing monitoring if, although numerous, they remain isolated, asymptomatic, brief (< 10 s), not deep (> 80 bpm), and followed by rapid cardiac acceleration testifying to an adapted sympathetic response. A complimentary assessment of newborns' autonomic "capital" and their "responsiveness" makes it possible to identify children

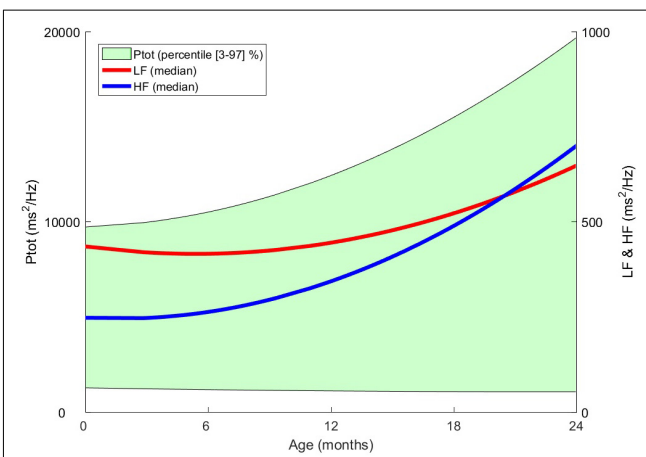

FIGURE 3 | From birth to the age of 2 years, evolution of heart rate variability indices in the frequency domain. Ptot: total power of the spectrum (ms2 / Hz), LF: low frequency (ms2 / Hz), HF: high frequency (ms2 / Hz) – Data from the *AuBE cohort*.

with a high potential for life-threatening event, who alone should benefit from cardiorespiratory monitoring at home (28–30).

This careful observation of the heart rate variability and complexity of respiratory rhythms, either in real-time or from a 24-hour cardiac Holter monitor, should become a valuable tool for considering autonomic control for neonatologists.

AUTONOMOUS MATURATION AND LIFE-THREATENING EVENTS

Autonomic imbalance in the first few months may involve inappropriate cardiorespiratory responses after internal or environmental stress (31–35).

The neonatologist's search for a congenital or acquired autonomic deregulation state as an objective risk factor for severe life-threatening event or unexpected infant death syndrom (28) should be a constant concern. In the SIDS triple risk model involving vulnerable children, exogenous stress, and critical development period, the cardiorespiratory autonomic control immaturity and abnormal arousal responses are predominant (33, 34). In an epidemiological survey of 20,000 children, Kato et al. have shown an association between central abnormalities of the cardiorespiratory response on awakening and life-threatening events and sudden death (34). In prematurity, Lucchini et al. showed a perfect correlation between the different experimental conditions of sleep-wake or prone and the multiparametric indices of HRV (30). Finally, the recent review by R. Horne (35) considers the association between cardiovascular control during infant sleep and the various components of the triple risk of SIDS, including maternal smoking.

Cardiorespiratory modulations during awakening periods are neurophysiologically mediated by the cortico-hypothalamic pathways and the cardiorespiratory nuclei of the brainstem (solitary tract, ambiguous nucleus, dorsal pneumogastric nerve). The molecular contribution of cardiorespiratory control inhibitory neurotransmitters such as GABA (γ-aminobutyric acid), adenosine, serotonin, endorphins, and prostaglandins in the genesis of apnea and bradycardia (36, 37) has been proposed in SIDS patients in particular with the identification of an abnormal serotoninergic response in the bulb and the arcuate nucleus of the hypothalamus, possibly due to genetic polymorphisms (38–40). Livolsi et al. reported overexpression of muscarinic M2 receptors in the brain, serum, and heart; and an increase in the enzymatic activity of acetylcholinesterase in case of severe life-threatening event or SIDS (41, 42).

All of these neurobiological considerations converge toward autonomic dysfunction as a preponderant element in the occurrence of SIDS.

ACQUIRED DYSAUTONOMIA IN NEONATOLOGY

Studying the autonomic status of the child also has a predictive potential in many clinical situations frequent in the neonatal period, such as sepsis (43), anoxia (44), retinopathy of prematurity (45), and growth deficit (46). The pathogenic link between acute inflammation and dysautonomia during the neonatal period deserves to be refined even if it has been shown in case of chronic inflammatory diseases or diabetes (47, 48) an impairment of autonomic control and an increased risk of cardiovascular disease.

As part of routine care, analysis of HRV assessed in a non-linear domain could be of interest to predict extubation failure in very low birth weight premature infants (49).

It should also be remembered in a full-term neonatal model without pulmonary disease that in the case of non-invasive ventilation, the application of a continuous positive nasal pressure modifies the heart and respiratory rate variability by reducing the parasympathetic efferent activity without change in sympathetic efferent activity (50).

CONCLUSION

The main interest of an HRV analysis from continuous monitoring is to obtain an objective reflection of the intrinsic capacity of the newborn to achieve perfect cardiorespiratory self-regulation. A state of congenital or acquired dysautonomia could be a central prerequisite for the occurrence of deleterious and life-threatening events.

The challenge of a real-time HRV assessment must be continued and complemented by clinical studies. It should make it possible to better target children at risk of SIDS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HP conceptualized and wrote the article. PF, VP, and AG participated in certain studies described in the review, and refined the final manuscript with regard to recent data from the literature. All authors contributed to the article and approved the submitted version.

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Missed Opportunities: Healthcare Encounters Prior to Sudden Unexpected Infant Death

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Introduction: Sudden unexpected infant death (SUID) is the leading cause of death in children 28 days to 1 year of age. The study aim was to identify opportunities for healthcare professionals to provide families with education on sleep and prevention of SUID.

Methods: We performed a retrospective chart review of SUID infants over 10 years (12/2010–12/2020). The study included patients 0–12 months who presented to single institution with SUID (including asphyxia, suffocation, and SIDS). Baseline descriptive characteristics, sleep patterns (location, position, co-sleeping, presence of pillows/blankets), and prior healthcare encounters (type, duration, frequency, timing) were described.

Results: Thirty-five infants met inclusion criteria. Twenty-three percent of families routinely practiced unsafe sleep, while 63% practiced unsafe sleep at the time of SUID. All unsafe sleep behaviors increased during the SUID event compared to routine, including inappropriate location (60%), co-sleeping (46%), and inappropriate position (37%) at the time of SUID. There were 54 total healthcare encounters (mean 1.5 per patient +/− 2.1) prior to SUID. Primary care physicians (57%) and NICU (29%) were the most frequent prior healthcare encounters, however visits spanned multiple specialties. Twenty-six percent had a healthcare encounter within 7 days of their death.

Discussion: We demonstrated the frequency and variability in healthcare encounters among SUID infants prior to their death. Majority of infants had prior healthcare encounters, with 26% seen by healthcare professionals within 7 days of their death. These results highlight the important role healthcare professionals across all specialties have the potential to play in educating families about safe sleep and SUID.

Keywords: SUID (sudden unexpected infant death), SIDS (sudden infant death syndrome), safe sleep, infants, healthcare encounters

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INTRODUCTION

Sudden infant death syndrome (SIDS), a sub-category of sudden unexpected infant death (SUID), is the leading cause of death in infants 28 days to 1 year of age (1, 2). Although infant deaths from SUID are likely multifactorial, cases are often associated with unsafe sleep practices. Several factors have been identified as protective against SUID, including: supine position while sleeping, using a

firm sleep surface, breastfeeding, offering a pacifier, room-sharing without bed-sharing, elimination of soft objects from the bed or under the infant, prevention of overheating, and avoidance of tobacco, alcohol, and illicit drugs (3–5). Given these associations, pediatricians recommend the pivotal aspects of infant safe sleep as the ABCs: Alone, on the Back, and in an empty Crib (6).

Healthcare professionals are uniquely positioned to educate new parents about infant safe sleep at every encounter. Safe sleep initiatives have historically targeted nursery care and neonatal intensive care unit (NICU) hospitalizations, with nursery-based safe sleep programs successfully resulting in reduced average SUID rates post-intervention (7). Studies addressing safe sleep during outpatient primary care physician visits, inpatient general pediatric admissions, and emergency room visits are limited, however promising new data shows that parent knowledge and practice of infant safe sleep are influenced by in-hospital interventions, with parents more likely to place their infants in a supine position and use a crib following intensive hospital educational efforts (8, 9). Studies have begun to look at how modeling safe sleep practices and educating parents in the hospital result in improved patient outcomes (8), yet this area is only beginning to evolve.

The 2016 American Academy of Pediatrics (AAP) Taskforce update on SIDS stated that healthcare providers should model safe sleep practices in the hospital (10). They further stress that providers should receive education on infant safe sleep and hospital policies should meet safe sleep standards (10). Prior to quality improvement efforts, only 0% to 32% of hospitalized infants slept in a safe environment (11–13). Improved adherence to safe sleep standards and modeling of safe sleep practices provide an opportunity to educate parents throughout their hospitalization. Although the historical approach of targeting nursery and NICU care for population-wide safe sleep initiatives remains important, directing SUID prevention initiatives toward the most frequent types of healthcare interactions may increase educational opportunities and better capture at-risk patients prior to their death. There is a paucity of published data on where and how infants interact with the healthcare system prior to SUID. Therefore, this study aimed to identify opportunities for healthcare professionals to provide families with education on safe sleep and prevention of SUID.

METHODS

We performed a retrospective chart review of infants whose death was attributed to SUID over the last 10 years (December 2010 – December 2020) at a single tertiary care institution in the United States of America. The study population included patients aged 0–12 months who were declared deceased and assigned an ICD-9 or ICD-10 diagnosis of SIDS, SUID, death not otherwise specified (NOS), asphyxia, accidental suffocation and strangulation in bed (ASSB), suffocation, shaken infant syndrome, hypoxic ischemic encephalopathy, cardiac arrest, respiratory arrest, or unresponsive. Due to institutional admission practices, infants whose death occurred during a NICU or cardiac intensive care unit (CICU) encounter were excluded, leaving patients who presented to the emergency room (ER) or pediatric intensive care unit (PICU) (**Figure 1**). Infants whose cause of death was attributed to a known, underlying complex or chronic disease (e.g., genetic conditions, congenital syndromes, immunologic deficiencies, liver disease, etc.) were excluded. Deaths attributed to acute but identifiable non-sleep related causes (e.g., non-accidental trauma, sepsis, drowning, aspiration, etc.) were excluded. Finally, we excluded one infant who was identified as having a cardiac arrest attributed to unsafe sleep positioning and resultant suffocation, but was revived and survived to discharge.

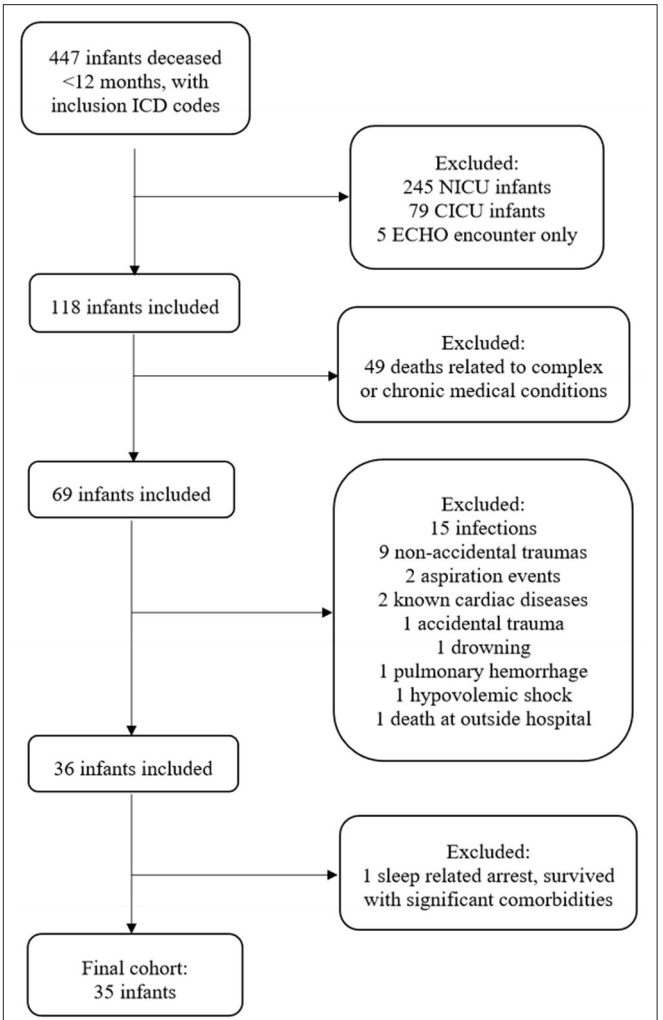

FIGURE 1 | Flowchart of infant inclusion and exclusion, 2010–2020.

Abbreviations: SIDS, sudden infant death syndrome; SUID, sudden unexpected infant death; ABCs, Alone, on the Back, in an empty Crib; NICU, neonatal intensive care unit; AAP, American academy of pediatrics; NOS, not otherwise specified; ASSB, accidental suffocation and strangulation in bed; CICU, cardiac intensive care unit; ER, emergency room; PICU, pediatric intensive care unit; EHR, electronic health record; PCP, primary care physician; DCFS, department of children and family services; LOS, length of stay.

A single investigator (KS) reviewed all patient charts that met inclusion criteria. Baseline descriptive characteristics, sleep patterns, and prior healthcare encounters were manually extracted from the electronic health record (EHR) for all patients who met inclusion criteria. Due to the retrospective nature of this study, data collection was reliant on manual review of clinical notes from the infant's final hospital encounter. Extraction of data (demographics, sleep patterns, healthcare encounters) was dependent on providers charting the presence or absence of clinical variables at the time of SUID. These variables were described in physician or social work notes and were based on parental report at the time of SUID event. Clinical notes reviewed for this study included: ER notes, history and physicals, progress notes, child protection team notes, social work notes, and death summaries.

Appropriate infant sleep patterns were defined as: in a crib/bassinette, supine position, absence of co-sleeping, and absence of pillows/blankets. Infants were determined to not meet AAP safe sleep guidelines if one or more of the above safe sleep definitions were not met. For demographics and sleep patterns, failure to document presence or absence of a variable was coded as "unknown." Prenatal care was summarized as "adequate," "delayed," or "unknown" per physician or social worker documentation in their clinical note(s). Prior healthcare encounter was defined as any visit with a physician, nurse practitioner, or physician's assistant for a sick or well visit after discharge from the newborn nursery. Outpatient visits with the primary care provider (PCP) and urgent care were included. Emergency room visits, admissions to the general pediatric inpatient ward, admissions to the NICU, and admissions to the PICU were included. Only healthcare encounters that occurred in our EHR or were documented as having occurred in our clinical notes were included. We did not have access to encounters related to prenatal care, newborn nursery visits, or immunization-only visits, except as were documented in clinical notes at the time of SUID event as having previously occurred. For healthcare encounters, absence of documentation of previous exposure was coded as "no known exposure."

RESULTS

Demographics

A total of 35 infants met inclusion criteria, with a median age of 67 days (interquartile range [IQR] 48–112). There was a median of two adults in the home (IQR 2–3) and two minors in the home (IQR 1–3). Forty-three percent of caregivers reported receiving adequate prenatal care, while caregiver prenatal care status was unknown for 52% of the cohort. The majority (63%) of patients were fully immunized and 29% of patients were born premature at <37 weeks gestation. Although infrequent, known exposures to smoke (14%), alcohol (9%), and drugs (6%) were reported. Finally, 20% of our cohort had prior Department for Children and Family Services (DCFS) involvement, with 11% of families experiencing a prior child death (**Table 1**). DCSF cases involved prior fractures ($n = 2$), inadequate supervision ($n = 2$), death of previous infant ($n = 2$), and drug exposure at birth (n=1). Prior child death was attributed to SUID event while sleeping ($n = 2$), gas leak ($n = 1$), and gang violence ($n = 1$). Of note, one of these prior child deaths was an infant already in our cohort, as one family had two infants die from separate sleep-related events during the study period.

TABLE 1 | Demographics of infants with SUID from 2010–2020 ($n = 35$).

	Number (%)
Gender	
Female	10 (28.6%)
Male	25 (71.4%)
Age at SUID event	
0–30 days	5 (14.3%)
30–60 days	9 (25.7%)
60–90 days	10 (28.6%)
90–120 days	6 (17.1%)
>120 days	5 (14.3%)
Race and Ethnicity	
African American	18 (51.4%)
Asian	1 (2.9%)
Caucasian	11 (31.4%)
Hispanic	4 (11.4%)
Other	1 (2.9%)
Gestation (weeks)	
Term (>37)	22 (62.9%)
Late preterm (34–36.6)	5 (14.3%)
Moderate preterm (32–33.6)	3 (8.6%)
Very preterm (28–31.6)	1 (2.9%)
Extreme preterm (<28)	1 (2.9%)
Unknown	3 (8.6%)
Multiples	
Twin	5 (14.3%)
Singleton/ unknown	30 (85.7%)
Vaccine status	
Fully immunized	22 (62.9%)
Partially immunized	1 (2.9%)
Unimmunized	2 (5.7%)
Unknown	10 (28.6%)
Prenatal care	
Adequate prenatal care	15 (42.9%)
Delayed prenatal care	2 (5.7%)
Unknown	18 (51.4%)
Exposures	
Known smoke exposure	5 (14.3%)
Known alcohol exposure	3 (8.6%)
Known drug exposure	2 (5.7%)
Other risk factors	
DCFS involved previously	7 (20%)
Prior child death	4 (11.4%)

SUID, sudden unexpected infant death; DCFS, department of children and family services.

TABLE 2 | Overview of the infant sleep environment ($n = 35$).

	Routinely *n* (%)	At time of SUID *n* (%)
Overall safe sleep		
Yes	11 (31.4%)	8 (22.9%)
No	8 (22.9%)	22 (62.9%)
Unknown	16 (45.7%)	5 (14.3%)
Location		
Crib/bassinette	11 (31.4%)	9 (25.7%)
Adult bed	6 (17.1%)	12 (34.3%)
Couch	1 (2.9%)	4 (11.4%)
Car seat	0 (0.0%)	1 (2.9%)
Held	0 (0.0%)	3 (8.6%)
Rock 'n play	0 (0.0%)	1 (2.9%)
Unknown	17 (48.6%)	5 (14.3%)
Position		
Supine	3 (8.6%)	7 (20%)
Prone	2 (5.7%)	6 (17.1%)
Side	0 (0.0%)	3 (8.6%)
Held	0 (0.0%	4 (11.4%)
Unknown	30 (85.7%)	15 (42.9%)
Sleep details		
Co-sleeping	8 (22.9%)	16 (45.7%)
Presence of pillows/blankets	3 (8.6%)	7 (20%)

SUID, sudden unexpected infant death.

Sleep Patterns

Thirty-one percent of families routinely met the ABCs of safe sleep, however only 23% were in a safe sleep environment at the time of SUID (**Table 2**). All unsafe sleep behaviors were increased at the time of SUID compared to routine sleep patterns, with the highest incidences being inappropriate location (60% during the event vs. 20% during routine practice), co-sleeping (46% during the event vs. 23% during routine practice), and inappropriate position (37% during the event vs. 6% during routine practice) (**Table 2**).

Healthcare Encounters

Our cohort had 54 documented healthcare encounters (mean of 1.5 encounters per patient ± 2.1) prior to SUID (**Table 3**). Encounters with the primary care physician (57%) and NICU (29%) were the most frequent prior healthcare encounters, however visits spanned multiple specialties (**Table 3**). Of those who were admitted to the NICU previously, average length of stay (LOS) was 19 days (IQR 11–39). Inpatient general pediatric admissions had an average LOS of 2 days (IQR 2–2.5) and the single patient with prior PICU admission had a LOS of 19 days. Notably, 26% of our cohort had a documented healthcare encounter within 7 days of their death; the majority of these infants (78%) were seen by their primary care physician during this period.

DISCUSSION

Despite AAP recommendations for infant safe sleep practices, families frequently practice unsafe sleep behaviors, with studies showing only 80% of families routinely place their infant supine, 60% practice room-sharing without bed-sharing, 40% avoid soft bedding, and 30% use a separate bed surface (14). Rates of unsafe sleep practices in SUID are further increased relative to the general population, supporting the relationship between SUID and unsafe sleep (15, 16). Our study supports this association, with similar unsafe sleep practices described during routine sleep in our cohort compared to general Unites States population data (14), and further increased at the time of SUID (15–17). With a well-documented relationship between SUID and unsafe infant sleep, promoting infant safe sleep practices is essential.

Several studies have examined infant safe sleep counseling by healthcare professionals, with overall trends not adhering to AAP recommendations. In the first decade after the Back to Sleep guidelines were published (18), 50–80% of physicians caring for pregnant women and infants routinely discussed SIDS, with only 40% recommending exclusively placing an infant supine to sleep (19). More recent survey data shows that 20% of parents report not receiving advice from doctors on infant sleep position, and over 50% report not receiving advice on sleep location (20). Furthermore, parental report of physician advice was frequently inconsistent with AAP guidelines, including >25% of parents reporting inconsistent recommendations for sleep position or location (20). Importantly, healthcare provider safe sleep advice is associated with increased infant safe sleep practices (14). While knowledge acquisition has been the foundation for the majority of prior safe sleep educational initiatives, recent literature suggests that future efforts would benefit from more targeted and tailored approaches that emphasize understanding, trust, and credibility (21). Ongoing efforts should address previously identified barriers based in culture, tradition, family support, available resources, and concerns for infant comfort and safety (22).

Historically, SUID and safe sleep educational efforts were focused on the NICU and newborn nursery encounters (7). Our results suggest a need to re-balance these efforts to include outpatient primary care practices (the most frequent presentation in our cohort) and inpatient hospitalizations (where length of stay provides multiple opportunities for education and modeling). By describing the frequency and locations of healthcare encounters prior to SUID, our study builds on existing literature to emphasize the importance of safe sleep counseling at every opportunity. Increased education for physicians on existing AAP safe sleep guidelines, including education on modeling and delivery of safe sleep advice, may increase safe sleep practices at home. Additionally, our findings highlight the breadth of healthcare professionals (e.g., neonatologists, hospitalists, outpatient providers, and emergency medicine physicians) who interact with families prior to SUID. All of these healthcare professionals have the opportunity to educate families about SUID and potentially improve safe sleep practices in the home.

Our result of 1.5 mean healthcare encounters per patient is likely a gross underestimate. While our study comments on

TABLE 3 | Healthcare encounters prior to SUID.

	Total # visits	Average # visits per patient	Exposure anytime ($n = 35$)	Exposure within 7 days of death ($n = 35$)	Median LOS in days (IQR)
Any encounter[a]	54	1.5 ± 2.1	26 (74.3%)	9 (25.7%)	
PCP	36	1.0 ± 1.7	20 (57.1%)	7 (20%)	
ER	4	0.1 ± 0.4	3 (8.6%)	1 (2.9%)	
NICU	10	0.3 ± 0.5	10 (28.6%)	1 (2.9%)	19 (11, 39.3)
Inpatient pediatrics	3	0.1 ± 0.3	3 (8.6%)	1 (2.9%)	2 (2, 2.5)
PICU	1	0 ± 0.2	1 (2.9%)	1 (2.9%)	19

[a]*Includes PICU, NICU, Inpatient pediatrics, ER, and PCP encounters; does not include prenatal visits, immunizations-only visits, newborn nursery care, or subspecialty outpatient care encounters.*

SUID, sudden unexpected infant death; PCP, primary care physician; ER, emergency room; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; LOS, length of stay.

the presence or absence of prenatal care (if known) prior to SUID, we did not include prenatal encounters when calculating average number of visits per patient. Prior studies describe an average of 8–12 prenatal care visits per mother, making this encounter type a recurrent interaction for families and another potential target for interventions (23). Additionally, newborn nursery visits (spanning 24–72h after birth for most infants) were not included in our results due to the inability to reliably extract this data. On our medical campus, the birthing center is part of a separate Women's Hospital, and therefore nursery visit encounters were unavailable for review. Prenatal care and nursery visits are major opportunities for parental safe sleep education due to the frequency of visits and duration of newborn stay.

Other limitations worth noting are that our study was conducted at a single academic center, therefore limiting our sample size. Due to the retrospective nature of this study, data extraction was reliant on clinical notes documenting safe sleep and demographic information at the time of SUID. In many patient charts, the data was incompletely documented, resulting in missing variables. Institutional quality improvement efforts should include development of a standardized and comprehensive data collection tool to use following a suspected sleep-related death. Additionally, the nature of using a single institution's EHR limited the total healthcare encounter estimates as we were unable to view encounters from healthcare facilities outside our network. Next, variability in ICD code designation at the time of death may have resulted in missing SUID patients. Autopsies primarily occurred at the county level and results were unavailable for review. Therefore, cause of death, if identified on autopsy, was not available to report.

This topic would benefit from a larger scale, multi-center study to more thoroughly describe healthcare interactions prior to SUID. By better describing where families present in the healthcare system prior to their child's death, we can better target educational efforts for healthcare providers, improve advice for families, and direct future policy change. Additionally, future quality improvement efforts would benefit from investigation of family attitudes toward safe sleep/SUID education provided by healthcare professionals at various encounters in the first year of life. With increased understanding of family attitudes surrounding healthcare provider education, we can deepen our communication and build trust with families. Heightened awareness and knowledge of the SUID cohort may result in improved emphasis on safe sleep education and modeling by healthcare professionals across specialties. Hopefully, one day this translates into optimized safe sleep practices for families at home and reduced incidence of SUID.

CONCLUSION

We created a local database of infants who died from SUID, demonstrating the frequency and variability in healthcare encounters among these infants prior to death. The majority of infants had prior healthcare encounters, with 26% of our cohort seen by healthcare professionals within 7 days of their death. These results highlight the important role healthcare professionals across all specialties have the potential to play in educating families about safe sleep and SUID risk factors. Increased emphasis on this education during all infant encounters may be an opportunity to reduce the risk of SUID.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KS conceptualized and designed the study, collected the data, carried out the initial analysis and interpretation of data, drafted the initial manuscript, and reviewed and revised the manuscript. CB conceptualized and designed the study, carried out the initial analysis and interpretation of data, and reviewed and revised the manuscript for important intellectual content. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Maternal Smoking, Alcohol and Recreational Drug Use and the Risk of SIDS Among a US Urban Black Population

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Background: Rates of sudden infant death syndrome (SIDS) are twice as high among Black infants compared to white infants in the US. While the contribution of sleep environment factors to this disparity is known, little is known about the risk of SIDS among Black infants in relation to maternal prenatal smoking, alcohol and drug use as well as infant smoke exposure.

Objective: To assess the contribution of maternal substance use during pregnancy and the potential interactions with infant bedsharing in a high-risk, urban Black population.

Methods: The Chicago Infant Mortality Study (CIMS) collected data on 195 Black infants who died of SIDS and 195 controls matched on race, age and birthweight. Risk of SIDS was calculated for maternal smoking, alcohol and drug use, adjusting for potential confounding variables and other risk factors for SIDS. Interactions between these substance use variables and bedsharing were also calculated.

Results: Infants were more likely to die from SIDS if the mother smoked during pregnancy (aOR 3.90, 95% CI 1.37–3.30) and post-pregnancy (aOR 2.49, 95% CI 1.49–4.19). There was a dose response seen between amount smoked during pregnancy and risk of SIDS. Use of alcohol (aOR 2.89, 95% CI 1.29–6.99), cocaine (aOR 4.78, 95% CI 2.45–9.82) and marijuana (aOR 2.76, 95% CI 1.28–5.93) were associated with increased risk of SIDS. In the final, multivariable model controlling for sociodemographic factors and covariates, maternal smoking (aOR 3.03, 95% CI 1.03–8.88) and cocaine use (aOR 4.65, 95% CI 1.02–21.3) during pregnancy remained significant. There were significant, positive interactions between bedsharing and maternal smoking during pregnancy and post-pregnancy, alcohol use and cocaine use.

Conclusion: Maternal use of tobacco, alcohol and cocaine during pregnancy is associated with significantly increased risk of SIDS in a Black, urban population. Reducing substance use and eliminating disparities in SIDS, sudden unexpected infant death (SUID) (also known as sudden unexpected death in infancy or SUDI) and infant mortality need to involve more than individual level education, but instead will require a comprehensive examination of the role of social determinants of health as well as a multi-pronged approach to address both maternal and infant health and wellbeing.

Keywords: pregnancy, sudden infant death syndrome (SIDS), smoking, cocaine, alcohol, racial disparities, marijuana, sudden unexpected infant death (SUID)

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INTRODUCTION

Black-white disparities in infant mortality and sudden infant death syndrome (SIDS) in the United States are well known and longstanding. Many would argue that it is a national "tragedy and disgrace" and eliminating these disparities must be a priority (1). Data from 2014 to 2018 show that non-Hispanic Black infants died from SIDS at a rate of 72.7/100,000 live births compared with a rate of 36.7/100,000 live births among non-Hispanic white infants (2). While some locales have been successful in reducing sleep related infant deaths and narrowing the racial disparity, such as the B'More for Healthy Babies initiative in Baltimore (3), other locales have seen not only persistent but widening gaps.

Sudden unexpected infant death (SUID) also known as sudden unexpected death in infancy (SUDI) includes deaths from SIDS, accidental suffocation and strangulation in bed (ASSB) and undetermined causes of death, which previously may have been classified as SIDS (4). In the US, a diagnostic shift occurred between 1999 and 2001, when many medical examiners and coroners began classifying SUID deaths as ASSB or undetermined rather than SIDS (4). Between 1999 and 2015, rates of SIDS in the US decreased by 35% and rates of ASSB increased by 183% (while there were no significant reductions in overall SUID), possibly reflecting a shift in the preferred use of the term ASSB (5). To demonstrate the widening racial/ethnic disparity in SUID, the SUID rate in Illinois for Black infants (3.3/1,000 live births) compared with white infants (0.5/1,000 live births) was almost seven times higher in 2018 (6). While SUID rates among infants born to white and Hispanic mothers have remained stable since 2000 in Illinois, the SUID rate among infants born to Black mothers has increased by 38% since 2009 (7).

Risk factors for SIDS include unsafe sleep circumstances, such as placing infants prone to sleep, with soft bedding, or sharing a sleep surface with other adults or children. The Chicago Infant Mortality Study (CIMS) identified these as significant risk factors in the largely Black population studied (8–10). In addition to infant care practices that increase the risk for SIDS, parental use of tobacco, alcohol or recreational drugs have been shown to also be associated with risk. The relationship between maternal smoking in pregnancy and postpartum passive smoke exposure of infants has been well documented by numerous studies worldwide over the past 3 decades. In a comprehensive review of maternal smoking during pregnancy and risk for SIDS, the pooled relative risk of studies conducted before the Safe to Sleep campaigns (which included recommendations to avoid smoking in pregnancy) was 2.86 (2.77–2.95); the RR of studies conducted after these campaigns was 3.93 (3.78–4.08) (11). It is estimated that up to one-third of SIDS deaths could be prevented if mothers did not smoke during pregnancy. More recent studies continue to show the strong association between prenatal maternal smoking and SIDS as well as a dose effect (12). The New Zealand 2017 SUDI (Sudden Unexpected Death in Infancy) Nationwide Case Control Study found a strong interaction between maternal smoking in pregnancy and bedsharing; infants exposed to both risk factors had a large increased risk of SUDI (SUID) (aOR = 32.8, 95% CI 11.2–95.8) compared with infants not exposed to either risk factor (13). The risk of SIDS is also particularly high when an infant bed shares with an adult smoker, even when the adult is not smoking in bed (OR 2.3–21.6) (10).

The risk of SIDS associated with maternal alcohol and drug use have been less well studied, and results are less consistent. In addition, it is difficult to separate out the effects of individual substances on the risk of SIDS, since multiple substances are often used. Studies of maternal alcohol use during pregnancy have found a six-fold increased risk of SIDS with periconceptional use (aOR 6.2, 1.6–23.3), an eight-fold increased risk with binge drinking in the first trimester (aOR 8.2, 1.9–35.3) (14), a four-fold increased risk with drinking past the first trimester (aOR 3.95, 0.44–35.83) (15) and a seven-fold increased risk when mothers had a diagnosis of alcoholism during pregnancy (adjusted hazard ratio 6.92) (16).

Studies of recreational drug use and SIDS generally focused on individual drugs or drugs in combination. A meta-analysis of 5 studies found that cocaine-exposed infants had a four-fold increased risk of SIDS compared with drug-free infants (unadjusted OR 4.10, 3.17–5.30) (17). Among infants born to maternal drug users, the incidence of SIDS did not differ by race or ethnicity.

To our knowledge, only one published study found a positive association between maternal marijuana use and SIDS. Infants of mothers who used marijuana post-partum had an increased risk of SIDS only when used at night (aOR 2.35, 1.6–4.05), but not during the day (18). As with smoking, parental alcohol and/or recreational drug use in combination with bedsharing places the infant at particularly high risk for SIDS (10).

Very limited research has focused on substance use risk factors for SIDS and SUID within the Black community. The purpose of the current analyses is to examine the risks between maternal smoking, passive smoke exposure, alcohol and drug use and SIDS, based on findings from the Chicago Infant Mortality Study. Additionally, recommendations are made to address the persistent Black-white disparities in SIDS and SUID, with particular attention to social determinants of health (SDOH). SDOH include individual level factors (income, education, marital status, food security, access to healthcare, housing security, experiences with racism and racial discrimination) and community level factors (crime, housing stock, air pollution, toxin exposure, segregation), all of which can affect maternal and child health outcomes (19). Many studies support the potential influence of SDOH on racial/ethnic disparities in preterm birth, but fewer studies have investigated their role in infant deaths (19).

METHODS

The Chicago Infant Mortality Study

This study involves secondary data analysis from the Chicago Infant Mortality Study (CIMS). The methodology for CIMS is described in detail in previous publications (8, 20, 21). Briefly, CIMS was a population-based, case-control study examining risk factors for SIDS among a largely Black population in Chicago. All Chicago resident infant deaths from November 1993 to April 1996 that were classified as SIDS per the Medical Examiner's office (cases) were matched to living controls based on (in order

of priority) maternal race/ethnicity, age at death/interview and birth weight. Data for cases were collected through the death scene investigation which included approximately 400 questions detailing the circumstances before death; the sleep environment of the child when last put down and found; the infant's and family's medical history; the mother's prenatal alcohol, tobacco, and drug use history; and other factors pertinent to determining the cause of death (20). Additionally, standardized autopsy procedures were followed by the Medical Examiners, including gross and microscopic examination, laboratory, toxicology and radiology studies (20). The Medical Examiner determined cause of death based on the autopsy, death scene investigation and review of medical history. One in four cases were reviewed blindly by an external review team, including a forensic pathologist and a pediatric pathologist experienced in sudden infant death. Diagnoses that differed from those of the Medical Examiner or each other were discussed by a multidisciplinary committee to establish the final diagnosis. SIDS was defined as "the sudden death of an infant under 1 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 (22)." Two weeks after the death, the infant's caretaker completed a standardized in-home follow-up interview to address items not included in the death scene investigation (e.g., routine infant sleep practices).

Potential control infants meeting matching criteria were identified through review of birth certificates at the Chicago Department of Public Health. Parents of potential controls were sent a letter in the mail inviting their participation. Controls were enrolled on a first-come basis and interviews with their mothers took place in the home. The death scene investigation and follow-up interview questionnaires were reworded to apply to living infants. Control infants' mothers received a small stipend ($25-$35 over the course of the study) for participating.

Variables

Sociodemographic Variables

Key sociodemographic variables from CIMS included maternal age, education, marital status and quality of prenatal care based on the Kessner index (23). Maternal age was categorized as under 25 and 25+ years. Education was grouped into two categories: less than high school and high school diploma or greater. Mothers' marital status was dichotomous: married/non-married. Index of prenatal care was categorized as adequate, intermediate or inadequate. Infants' gestational age in weeks was also included to account for any effect of prematurity. Infant sex was also included.

Tobacco, Alcohol and Drug Use

Mothers indicated whether they had smoked during pregnancy and post-pregnancy. Additional measures determined amount smoked during and post-pregnancy, which were grouped as: less than half a pack per day, half a pack to one pack per day and more than one pack per day. Participants also indicated whether they were exposed to other smokers during and post-pregnancy. Alcohol use and binge drinking (≥4 drinks on one occasion) were included. Women also indicated whether they had used cocaine or marijuana during their pregnancy.

Covariates

Because of the relationship between sleep environment and SIDS (8, 20), we controlled for use of a soft sleep surface, pillow use, prone sleeping position and bedsharing. All of these variables referred to infants' environment during their last sleep.

Statistical Analysis

Analyses were conducted using data from the 195 Black SIDS infants and 195 Black control infants. Initially we used the Cochran-Mantel-Haenszel statistic to determine differences in sociodemographic variables, maternal tobacco, alcohol and drug use and additional covariates between the cases and controls. Conditional logistic regression to account for matching was used to obtain unadjusted odds rations (ORs) and corresponding 95% confidence intervals (CIs), and odds ratios adjusted for the four sociodemographic variables (maternal age, education, marital status and Kessner index). A multivariable, conditional logistic regression model was constructed to determine the influence of tobacco, alcohol and drug use while controlling for sociodemographic variables and other covariates. Variables that remained significant after adjusting for sociodemographic factors were included in the final analysis. Due to collinearity between the smoking variables, we only included the measure reflecting maternal smoking during pregnancy.

Interactions were examined between the bedsharing and tobacco, alcohol and drug use variables, as previous literature suggests bedsharing is linked with other risk factors for infant death (13). Variables significant in univariable analyses were included. Significance was determined at $p < 0.05$. All analyses were conducted using R 4.1.1.

RESULTS

Cases and controls were similar based on matched factors, i.e., mean age for cases and controls (84.9 and 82.1 days, respectively) and birth weight (6.1 pounds and 6.3 pounds) were not significantly different. There were significant differences between cases and controls on non-matched factors. Mean gestational age in cases was 37.4 (SD = 3.1) and 38.3 (SD = 2.4) in controls ($p < 0.01$). Cases were more likely to have mothers with less than high school education, inadequate prenatal care and who were not married. All were significant at $p < 0.05$ (**Table 1**). Based on previous research (8, 20), maternal age, marital status, education, and adequacy of prenatal care were chosen to represent sociodemographic factors and were therefore used in subsequent analyses for adjustment purposes.

There were several differences in tobacco, alcohol and drug use between cases and controls after controlling for sociodemographic variables. Infants were more likely to die from SIDS if the mother smoked during pregnancy (aOR 3.90, 95% CI 2.35, 6.12) and post-pregnancy (aOR 2.49, 95% CI 1.49–4.19). There was a dose response seen between amount smoked during pregnancy and risk of SIDS, with the odds ratio increasing from 3.14 (95% CI 1.66–6.07) for smokers of less than a half pack of

TABLE 1a | Unadjusted and adjusted ORs for demographic and sleep variables.

Characteristic	SIDS cases N = 195[a]	Controls N = 195[a]	OR (95% CI)[+]	OR (95% CI)[±]
Infant sex				
Female	83/(43%)	97/(50%)	Reference	Reference
Male	112/(57%)	98/(50%)	1.34 (0.89, 1.99)	1.34 (0.87, 2.09)
Maternal age				
25 and over	63/(32%)	78/(40%)	Reference	
Less than 25	132/(68%)	117/(60%)	1.39 (0.92, 2.11)	–
Education				
High school or greater	89/(46%)	139/(71%)	Reference	
Less than high school	106/(54%)	56/(29%)	**2.95 (1.94, 4.49)**	–
Kessner Index of prenatal care				
Adequate	73/(37%)	113/(58%)	Reference	
Inadequate	70/(36%)	22/(11%)	**4.92 (2.84, 8.79)**	
Intermediate	52/(27%)	60/(31%)	1.34 (0.83, 2.15)	–
Marital status				
Married	13/(6.7%)	43/(22%)	Reference	
Not married	181/(93%)	152/(78%)	**3.93 (2.04, 7.59)**	–
Soft sleep surface				
No	94/(48%)	153/(78%)	Reference	Reference
Yes	101/(52%)	42/(22%)	**3.91 (2.51, 6.09)**	**3.32 (2.07, 5.36)**
Pillow use				
No	145/(74%)	170/(87%)	Reference	Reference
Yes	50/(26%)	25/(13%)	**2.34 (1.38, 3.98)**	**2.19 (1.24, 3.94)**
Prone sleep position				
No	82/(42%)	111/(57%)	Reference	Reference
Yes	113/(58%)	84/(43%)	**1.82 (1.21, 2.72)**	**1.95 (1.26, 3.03)**
Bedsharing				
No	82/(42%)	123/(63%)	Reference	Reference
Yes	113/(58%)	72/(37%)	**2.34 (1.57, 3.53)**	**2.17 (1.37, 3.30)**

[a]*n / (%).*
[+]*Statistically significant ORs are indicated in bold.*
[±]*Adjusted for maternal age, marital status, education, and index of prenatal care.*

TABLE 1b | Unadjusted and adjusted ORs for smoking variables.

Characteristic	SIDS cases N = 195[a]	Controls N = 195[a]	OR (95% CI)[+]	OR (95% CI)[±]
Smoked during pregnancy				
No	91/(47%)	151/(77%)	Reference	Reference
Yes	104/(53%)	44/(23%)	**3.92 (2.53, 6.08)**	**3.90 (2.35, 6.12)**
Smoked during pregnancy <1/2 ppd[b]				
No	90/(65%)	152/(87%)	Reference	Reference
Yes	49/(35%)	22/(13%)	**3.76 (1.13, 6.62)**	**3.14 (1.66, 6.07)**
Smoked during pregnancy ≥1/2 ≤1 ppd				
No	90/(73%)	152/(92%)	Reference	Reference
Yes	33/(27%)	13/(8%)	**4.28 (1.24, 8.57)**	**5.18 (2.40, 11.89)**
Smoked during pregnancy >1 ppd				
No	90/(83%)	152/(96%)	Reference	Reference
Yes	19/(17%)	7/(4%)	**4.58 (1.85, 11.33)**	**5.67 (2.03, 17.55)**
Smoked post-pregnancy (mother)				
No	108/(58%)	153/(78%)	Reference	Reference
Yes	78/(42%)	42/(22%)	**2.63 (1.67, 4.12)**	**2.49 (1.49, 4.19)**
Smoked post-pregnancy (mother) <1/2 ppd				
No	108/(71%)	153/(83%)	Reference	Reference
Yes	45/(29%)	31/(17%)	**2.05 (1.22, 3.46)**	**1.85 (1.02, 3.39)**
Smoked post-pregnancy (mother) ≥1/2 ≤1 ppd				
No	108/(82%)	153/(97%)	Reference	Reference
Yes	24/(18%)	5/(3%)	**6.80 (2.51, 18.38)**	**7.78 (2.86, 25.31)**
Smoked post-pregnancy (mother) >1 ppd				
No	108/(92%)	153/(96%)	Reference	Reference
Yes	9/(8%)	6/(4%)	2.12 (0.73, 6.14)	1.92 (0.62, 6.32)
Exposed to other smokers while pregnant (mother)				
No	76/(39%)	107/(55%)	Reference	Reference
Yes	119/(61%)	88/(45%)	**1.90 (1.27, 2.84)**	**4.00 (2.55, 6.36)**
Exposed to other smokers post-pregnancy (mother)				
No	70/(36%)	142/(73%)	Reference	Reference
Yes	125/(64%)	53/(27%)	**4.78 (3.11, 7.35)**	1.43 (0.92, 1.23)
Number of smokers exposed to during pregnancy (mother)				
None	57/(29%)	124/(65%)	Reference	Reference
One	71/(36%)	43/(23%)	**3.59 (2.21, 5.91)**	**3.59 (2.21,5.91)**
More than one	67/(34%)	23/(12%)	**6.33 (3.64, 11.37)**	**6.34 (3.64, 11.37)**

[a]*n/(%).*
[b]*ppd, packs per day.*
[+]*Statistically significant ORs are indicated in bold.*
[±]*Adjusted for maternal age, marital status, education, and index of prenatal care.*

cigarettes per day to 5.67 (95% CI 2.03–17.55) for smokers of more than 1 pack per day. This was also seen in smoking post-pregnancy, as the odds ratio for smokers of less than half a pack of cigarettes per day (aOR 1.85, 95% CI 1.02–3.39) increased for smokers of half a pack to one pack of cigarettes per day (aOR 7.78, 95% CI 2.86–25.31). Exposure to other smokers while pregnant (aOR 4.00, 95% CI 2.55–6.36) was associated with increased risk of SIDS, while maternal exposure to other smokers post-pregnancy was not significant (aOR 1.43, 95% CI 0.92–1.23). The risk of SIDS increased as the number of smokers pregnant women were exposed to increased (for more than one other smoker, aOR 6.34, 95% CI 3.64–11.37). Use of alcohol (aOR 2.89, 95% CI 1.29–6.99), cocaine (aOR 4.78, 95% CI 2.45–9.82) and marijuana (aOR

TABLE 1c | Unadjusted and adjusted ORs for alcohol and drug variables.

Characteristic	SIDS cases N = 195[a]	Controls N = 195[a]	OR (95% CI)[+]	OR (95% CI)[±]
Drank alcohol during pregnancy				
No	138/(82%)	156/(95%)	Reference	Reference
Yes	31/(18%)	9/(5%)	**3.89 (1.79, 8.46)**	**2.89 (1.29, 6.99)**
Binge drinking during pregnancy				
No	136/(92%)	190/(98%)	Reference	Reference
Yes	12/(8%)	4/(2%)	**4.19 (1.32, 13.27)**	2.86 (0.91, 10.99)
Cocaine use during pregnancy				
No	133/(68%)	180/(92%)	Reference	Reference
Yes	62/(32%)	15/(8%)	**5.59 (3.04, 10.26)**	**4.78 (2.45, 9.82)**
Marijuana use during pregnancy				
No	159/(82%)	184/(94%)	Reference	Reference
Yes	36/(18%)	11/(56%)	**3.79 (1.87, 7.67)**	**2.76 (1.28, 5.93)**

[a] *n/(%).*
[+] *Statistically significant ORs are indicated in bold.*
[±] *Adjusted for maternal age, marital status, education, and index of prenatal care.*

2.76, 95% CI 1.28–5.93) during pregnancy were associated with increased risk of SIDS.

In the final, multivariable model controlling for sociodemographic factors, gestational age, and covariates, maternal smoking (aOR 6.15, 95% CI 1.55, 24.4) and cocaine use (aOR 8.91, 95% CI 1.05, 75.6) during pregnancy remained significant (**Table 2**). Maternal alcohol and marijuana use during pregnancy were no longer significant. Sleep environment variables were significantly associated with SIDS. During last sleep, use of a soft sleep surface (aOR 9.01, 95% CI 2.83, 28.7), pillow use (aOR 6.74, 95% CI 1.39, 32.6), prone sleeping position (aOR 3.72, 95% CI 1.37, 10.1) and bedsharing (aOR 3.30 95% CI 1.04, 10.4) were associated with infant death.

There was a significant, positive interaction between bedsharing and smoking during pregnancy indicating the combined presence of both factors had a greater effect than would be expected by simply multiplying the effects alone. After adjusting for the four confounding variables, the OR was 8.4 (95% CI 4.06–17.38). There were also significant, positive interactions between bedsharing and amount smoked. The adjusted odds ratio for smoking half a pack to one pack of cigarettes per day was 8.56 (95% CI 2.93–24.97) and increased to 25.73 (95% CI 4.67–41.77) for smokers of greater than one pack per day. Additionally, there was a significant, positive interaction between smoking post-pregnancy and bedsharing (aOR 4.72, 95% CI 2.35–9.46). Smoking half to one pack of cigarettes per day post-pregnancy demonstrated a significant interaction with bedsharing (aOR 14.44, 95% CI 3.74–55.79). There was a significant positive interaction between bedsharing and exposure to other smokers post-pregnancy (aOR 7.58, 95%, 3.92–14.65), alcohol use (aOR 6.39, 95% CI 2.01–20.37) and cocaine use (aOR 14.43, 95% CI 4.62–45.04).

TABLE 2 | Multivariable analysis of risk factors for SIDS.

Characteristic	OR[a]	95% CI[a]	*p* value
Maternal age			
25 and over	Reference		
Less than 25	1.44	0.50, 4.14	0.5
Education			
High school or greater	Reference		
Less than high school	4.72	1.48, 15.1	0.009
Kessner Index of prenatal care			
Adequate	Reference		
Inadequate	2.15	0.65, 7.06	0.2
Intermediate	1.22	0.35, 4.16	0.8
Mother's marital status			
Married	Reference		
Not married	1.70	0.38, 7.68	0.5
Soft sleep surface			
No	Reference		
Yes	9.01	2.83, 28.7	<0.001
Pillow Use			
No	Reference		
Yes	6.74	1.39, 32.6	0.018
Prone sleeping position			
No	Reference		
Yes	3.72	1.37, 10.1	0.010
Bedsharing			
No	Reference		
Yes	3.30	1.04, 10.4	0.042
Smoked during pregnancy			
No	Reference		
Yes	6.15	1.55, 24.4	0.010
Cocaine use during pregnancy			
No	Reference		
Yes	8.91	1.05, 75.6	0.045
Marijuana use during pregnancy			
No	Reference		
Yes	1.74	0.29, 10.6	0.5
Drank alcohol during pregnancy			
No	Reference		
Yes	0.44	0.07, 2.99	0.4

[a] *OR, odds ratio; CI, confidence interval.*
All variables in the multivariable model are shown in the table.

DISCUSSION

In our study of 195 Black infants who died from SIDS and 195 matched controls, we found that maternal smoking during pregnancy, maternal passive smoke exposure during

pregnancy, and post-partum infant smoke exposure were all strongly associated with an increased risk of SIDS, controlling for socio-demographic variables. In the final multivariable model, we included only maternal smoking in pregnancy, since the smoking variables are highly correlated with each other. Smoking remained a significant risk factor. This is consistent with studies conducted before and after campaigns were launched in countries around the world to emphasize back sleeping and other practices to reduce the risk of SIDS. CIMS was conducted during the period (1993–1996) when non-prone sleep recommendations were being made on a national basis. The American Academy of Pediatrics advised against prone sleeping in 1992, endorsed by the national Back to Sleep Campaign (now called Safe to Sleep) in 1994, revised in 1996 to recommend back sleeping only. While most attention was focused on infant sleep position, the campaigns generally also included advice to avoid smoking during pregnancy and exposure of the infant to environmental smoke. Reductions in SIDS rates as a result of campaigns have been largely credited to reductions in prone sleeping rates, but there is also evidence that campaigns have resulted in reductions in maternal smoking in pregnancy (24).

In the US, rates of maternal smoking during pregnancy have declined among all racial/ethnic groups over the period 2010–2017. Black pregnant women smoke at lower rates than white and American Indian/Alaska Native women (25). However, women with lower education are more likely to smoke within racial/ethnic groups. Healthy People 2030 provides data driven national objectives to improve the health and well-being of American people over the next decade (26). The target for smoking abstinence during pregnancy is 95.7%; in 2019 it was 94%. Thus as a nation, the target is within reach. However, compared to white smokers, Black smokers had significantly lower odds of being asked about tobacco use by healthcare providers (aOR 0.70), being advised to quit (aOR 0.72), or having used tobacco-cessation aids during the past year in a quit attempt (aOR 0.60), after controlling for sociodemographic and healthcare factors (27). Research has shown that advice from a health professional to quit smoking does motivate people to quit, thus these lower rates of counseling about smoking cessation can impact smoking among Black pregnant women (28).

We found an almost three times increased risk for SIDS when mothers drank alcohol or binge drank alcohol during pregnancy, controlling for sociodemographic factors. This became non-significant in the larger multivariable model. These results are consistent with other studies where the results were less convincing of a relationship between maternal alcohol use during pregnancy and SIDS (16, 29, 30). Since alcohol use is highly correlated with smoking, alcohol use appears to be contributing less to SIDS risk. In the Safe Passage Study, there was a higher risk of alcohol use combined with smoking beyond the first trimester than either alone (15).

Generally, pregnant women consume less alcohol than non-pregnant women, but racial/ethnic differences have been found regarding drinking behavior during pregnancy. Black women are less likely to reduce alcohol consumption or binge drinking during pregnancy than white women (31). We were unable to find any research investigating if there are differences in counseling about alcohol use during pregnancy by race/ethnicity, but unplanned pregnancies are higher among Black women (32), and unintended pregnancy is associated with later entry into care and higher rates of alcohol and drug use (33). Individual- and neighborhood-level economic disadvantage was shown to predict lower alcohol treatment completion for Blacks and in urban areas in the US, there is a higher density of alcohol outlets in Black and other minority neighborhoods compared with white neighborhoods (34).

Finally, our data show that maternal cocaine and marijuana use during pregnancy increased the risk of SIDS three- to five-fold, respectively, after adjusting for sociodemographic variables. Cocaine use remained significant in the multivariable model while marijuana use became non-significant. Findings from other studies of cocaine use and SIDS are inconsistent, although most did report a positive association similar to ours (17). Cocaine use was very high among CIMS case mothers, and more prevalent that alcohol or marijuana use in this sample. A report from the National Drug Intelligence Center described the very active drug trade in Cook County, Illinois (where Chicago is located), and heroin and cocaine were estimated to be used by about 6% of the population, 80% of which was cocaine and 12% was cocaine plus heroin (1995 data) (35). Thus, cocaine was very available at the time of the study. Unfortunately, more recent reports indicate that drug activity has not abated in Chicago, and that cocaine and other illicit drugs are still very much available (36). It is therefore essential that this threat to maternal and infant health be given the necessary attention regarding assessment and treatment.

The weight of evidence to date indicates that marijuana use is not associated with increased risk of SIDS. However, this may be a reflection of a number of other factors such as inadequate power to detect an effect and the correlation of marijuana use with other substances including tobacco. It is estimated that about 8% of women in the US reported using marijuana in the past month and 4% of pregnant women reported use in the past month (37). As more states have liberalized use of recreational and medicinal marijuana, there is growing perception of its safety. At the same time the concentration of delta-9-tetrahydrocannabinol, the active ingredient in marijuana, has increased and this chemical crosses the placenta. The research on adverse maternal and child health outcomes has had mixed results but there is evidence that maternal marijuana use can cause increased neonatal infectious or neurologic morbidity and developmental and behavioral difficulties in children. Based on these potential adverse outcomes, it is recommended that women be screened for marijuana use when planning for or early in pregnancy, and be advised to quit.

We found significant interactions between smoking in pregnancy and bedsharing in risk for SIDS. Adjusting for sociodemographic factors, the OR was 8.40 (95% CI 4.06–17.38) and increased to 25.73 (95% CI 4.67–41.77) for mothers smoking more than one pack per day. While not as high as the odds ratio found for this interaction in the New Zealand SUDI Nationwide Case Control Study, the investigators also reported a very increased risk of SUID (SUDI) among infants exposed to both maternal smoking in pregnancy and bedsharing (aOR = 32.8, 95% CI 11.2–95.8) (15). We also found an interaction

for maternal smoking post pregnancy and bedsharing, as well as a dose effect. Additionally, there were significant positive interactions between bedsharing and maternal pregnancy alcohol use and cocaine use; to our knowledge this is the first report of these associations. Women who plan to bedshare or who are bedsharing with their infants need to be advised of the high increase in risk for their infants if they are also smoking (or if their infants are exposed to other smokers), or were using alcohol or cocaine during pregnancy. The approach to counseling and motivating changes in these behaviors is extremely challenging and requires inputs on several levels. New paradigms for education and outreach among high risk Black families are very much needed to assist with smoking, alcohol and drug use cessation. This is discussed in greater detail under Addressing Social Determinants of Health to Overcome Racial Disparities below.

Limitations

As with all studies of SIDS, our study was necessarily retrospective and constrained in size by the relative rarity of the outcome. Recall bias may occur if mothers of SIDS infants recall exposures more thoroughly than mothers of unaffected, healthy infants, thus resulting in an apparent association when there is none. However, prospectively collected data on sleep position have confirmed results from previous retrospective studies, indicating that recall bias has not been a major problem in case-control studies of SIDS (38, 39). It has been shown that the length of time lapsed between the exposure and the recall has a greater influence on recall accuracy (39). In this study, parents of both SIDS victims and control infants were interviewed about their infant's sleep position within a short time of the sleep period. Thus, we do not believe that recall bias was a problem in this study.

Although the CIMS dataset is the largest comprehensive case-control dataset of SIDS in the United States and with the largest number of Black participants, over 2 decades have passed since the study's completion. Nevertheless, we believe that our results remain relevant due to the similarity in prevalence of several of the risk factors, such as bedsharing and soft bedding, to current US prevalences, as well as the similarity in many of our results (10). A study analyzing 4,929 infants in the Centers for Disease Control and Prevention's SUID case registry who died 2011–2017 (37% of whom were Black infants) found that for the 1,548 cases classified as explained, suffocation or unexplained, possible suffocation, 74% were attributed to soft bedding, 20% to overlay, 7% to wedging, and 5% to other (40). The CDC analyzed 2015 data on non-supine sleep position, soft bedding and bedsharing at 6 weeks postpartum from the Pregnancy Risk Assessment Monitoring System (PRAMS) (41). PRAMS is a state-specific and population-based surveillance system that monitors self-reported behaviors and experiences before, during, and shortly after pregnancy among women with a recent live birth. Overall, 20% of mothers reported placing their infants non-prone for sleep; Black infants had the highest prevalence of all racial/ethnic groups (38% compared with 16% of white infants). Almost two-thirds (61%) of respondents reported bedsharing with their infant and 39% of respondents reported using soft bedding in the sleep environment. Bedsharing was more common among Black infants (77%) compared with white infants (53%), as was use of soft bedding (41 vs. 33%, respectively). It is therefore likely that our results are still relevant to Black communities despite the amount of time that has elapsed since data collection.

CIMS cannot directly address the reasons for the Black-white disparities in SIDS, as the focus of the study was to determine if the risk factors identified in other studies, largely conducted outside of the US in non-Black populations, were similar for American Black infants; the methodology thus included matching cases to controls on race/ethnicity. In our first publication of CIMS results, we looked at the risk of prone positioning at last sleep comparing Black with all other infants (20). Because the prone prevalence was high among all cases but low for white control infants compared with Black control infants, the odds ratios for prone sleeping were higher for the white infants. However, when taking into account the overall higher rates of prone sleeping among Black infants, the population attributable risk for this factor was found to be 19% compared to 12% for the other infants. Over time, as noted above, the gap in prone positioning has widened greatly between Black and non-Black infants, as have the differences in bedsharing. Thus sleep position and bedsharing, in conjunction with smoking and substance use, likely explains at least in part the persistent racial/ethnic disparities in SIDS and SUID rates. New case-control studies are needed to identify which risk factors may vary according to race/ethnicity to help further understand these persistent disparities.

Another limitation is that the small cell sizes for substance use limit the precision of the estimates, resulting in wide confidence intervals. Thus, the data should be interpreted with caution.

Interventions to Address Maternal Smoking, and Alcohol and Drug Use in Pregnancy

An in-depth discussion of interventions to assist women who are contemplating pregnancy or who are pregnant in stopping the use of tobacco, alcohol and recreational drugs is beyond the scope of this paper, however, we would like to provide a few basic principles; a summary of several interventions can also be found in a paper by Hauck and Tanabe (42). A systematic review found that a medical professional's advice to quit smoking modestly increases the quit rate over no advice (28). This would require that obstetrical clinicians inquire about tobacco use (in all its forms including e-cigarettes and vaping) in pregnancy routinely and systematically spend a few minutes asking about the patient's motivation to quit and counseling her on the benefits of quitting for both her health and the health of her infant. Provision of resources such as contact information for smoking cessation programs/quit lines via phone or internet and follow-up are advised. The American College of Obstetrics and Gynecology Committee on Obstetric Practice recommends consideration of pharmacologic intervention in addition to behavioral and psychosocial intervention (43). Other interventions that have been used include health education, feedback, financial incentives and support from friends or partners (44).

There is limited evidence to identify programs that are effective in aiding pregnant women to stop using alcohol. A randomized controlled trial comparing brief counseling by the obstetrical provider compared with 6 intensive nurse-provided education sessions resulted in similar reductions in alcohol and drug use during pregnancy (45). A computer-tailored intervention was found to be more effective in reducing alcohol use compared with midwife delivered counseling or routine care (46). State policies, such as mandatory warning signs, priority treatment for substance abuse programs and prohibitions on criminal prosecution have not been found to be effective (47).

Few studies have identified successful treatment approaches for women using cocaine in pregnancy. One, utilizing contingency management therapy (positive reinforcement with monetary vouchers), was more successful in reducing cocaine use compared with a community reinforcement approach (48). Interventions focused on marijuana use in pregnancy have not been studied to our knowledge, but motivational interviewing, cognitive behavioral therapy and contingency management have been found to be effective in women using marijuana in general (49).

We were unable to identify studies of any smoking, alcohol or drug cessation programs that specifically target Black women. On the contrary, research has shown that Black communities have been victims of corporate activity, "through producing and promoting products harmful to health. The tobacco industry's disease-promoting activities are among the most powerful corporate influences on inner city health. Such activities have included targeted marketing, thwarting and undermining tobacco control efforts, deceptive scientific practices, and influencing policymakers and community leadership groups (50)." Among these corporate activities during the past several decades, the tobacco industry targeted inner cities populated predominantly by low-income Black residents with highly concentrated menthol cigarette marketing (50). A study of advertisements for tobacco and alcohol products in a sample of 24 Black and 11 general audience newspapers in 24 cities identified a greater number of alcohol product advertisements in the Black newspapers and less alcohol and tobacco control advertising (51).

Addressing Social Determinants of Health to Overcome Racial Disparities

It is apparent that overcoming racial disparities in SIDS/SUID/SUDI and infant mortality requires a multi-pronged approach that digs deeply into understanding the social determinants of health underlying these disparities. Taylor and coauthors describe comprehensive policy recommendations to eliminate racial disparities in maternal and infant mortality, based on the theory of targeted universalism—"an equity framework that employs targeted strategies to achieve a universal goal, namely meeting the needs of all populations, but having an intentional focus on those most in need—Black women and families (1)."

These recommendations target five areas: (1) improve access to critical services by strengthening existing health programs and supporting reproductive health care, screening and treating women at risk for preterm birth, eliminating maternity care deserts, and offering Black women tools to navigate the health care system; (2) improve the quality of care provided to pregnant women by training providers to address racism and build a more diverse health care workforce, creating standardized assessments for mothers and infants, and adopting new models of care and link payment to quality; (3) address maternal and infant mental health by identifying barriers to accessing maternal mental health services, dismantling care barriers with a comprehensive approach and screening for and addressing infant and early childhood mental health issues; (4) enhance supports for families before and after birth by investing in and expanding access to policies and programs that support families' basic needs, investing in community programs that offer one-stop comprehensive services, simplifying enrollment across public benefit programs, investing in home visiting and funding community-based education and communications initiatives to support families; and (5) improve data collection and oversight by standardizing birth and death certificate data, mandating and funding fetal and infant mortality review committees, and ensuring equity in the review process (1). We would propose that this framework be used in all countries and locales where racial/ethnic disparities in SIDS and SUID/SUDI exist.

CONCLUSIONS

We found that maternal use of tobacco, alcohol and cocaine during pregnancy is associated with significantly increased risk of SIDS in a Black, urban population. Reducing substance use and eliminating disparities in SIDS, SUID and infant mortality need to involve more than individual level education, but instead will require a comprehensive examination of the role of social determinants of health, as well as development of a multi-pronged approach to address both maternal and infant health and wellbeing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials; further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board for Health Sciences Research, University of Virginia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FH developed the study idea and drafted the first version of the manuscript. SB conducted the data analysis and drafted the methods and results portions of the manuscript. Both authors reviewed and edited the final version of the manuscript.

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