JAMA Pediatrics | Review

Risk Factors, Protective Factors, and Current Recommendations to Reduce Sudden Infant Death Syndrome
A Review

Rebecca F. Carlin, MD; Rachel Y. Moon, MD

IMPORTANCE Sudden infant death syndrome remains the leading cause of death in infants aged 1 month to 1 year in the United States.

OBSERVATIONS While its exact cause is unknown, sudden infant death syndrome is believed to be multifactorial, ie, occurs in infants with underlying biological vulnerability who experience an exogenous stressor, such as prone/side sleeping or soft bedding, during a critical developmental period. Much genetic and physiologic evidence points to impaired arousal responses to hypercarbia and hypoxia, which ultimately leads to asphyxia. Known risk factors for infants include prone and side sleeping, soft bedding, bed sharing, inappropriate sleep surfaces (including sofas), exposure to tobacco smoke, and prematurity; protective factors include breastfeeding, pacifier use, room sharing, and immunizations.

CONCLUSIONS AND RELEVANCE Despite our improved understanding of the physiologic mechanisms that cause sudden infant death, the mainstay of risk reduction continues to be a safe sleep environment, as most infants who die suddenly and unexpectedly do so in unsafe sleep environments.

JAMA Pediatr. doi:10.1001/jamapediatrics.2016.3345
Published online December 5, 2016.

Author Affiliations: Division of General Pediatrics and Community Health, Goldberg Center for Community Pediatric Health, Children's National Medical Center, Washington, DC (Carlin); Department of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington, DC (Carlin); Division of General Pediatrics, University of Virginia School of Medicine, Charlottesville (Moon).

Corresponding Author: Rachel Y. Moon, MD, Division of General Pediatrics, University of Virginia School of Medicine, PO Box 800386, Charlottesville, VA 22908 (rym4z@virginia.edu).

Sudden infant death syndrome (SIDS) remains the third leading cause of all infant mortality in the United States (after congenital malformations and disorders related to short gestation and low birth weight) and is the leading cause of death in infants aged 1 month to 1 year, with greater than 1900 deaths per year (approximately 0.49 deaths per 1000 live births).[1] Sudden infant death syndrome is defined as the sudden death of an infant younger than 1 year that cannot be explained after a thorough investigation, including autopsy, scene investigation, and clinical history.[2] Despite advances in our understanding of the pathophysiology of SIDS, it remains a diagnosis of exclusion.

Sudden unexpected infant death (SUID) is a term that encompasses SIDS (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code R95), asphyxia (including "accidental suffocation and strangulation in bed"; code W75), and ill-defined and unknown deaths (code R99) for infants younger than 1 year. An explanation may be determined after autopsy and death scene investigation in deaths that begin with an SUID diagnosis. Examples of this include SUIDs with cardiac, metabolic, and infectious etiologies. However, because there are no consistent autopsy findings that can reliably distinguish between SIDS and unintentional suffocation, the determination of the final cause of death generally relies on the scene investigation. Indeed, with more consistent death scene investigation, there has been a diagnostic shift over the past 20 years; some deaths that would previously have been considered SIDS are now being classified into other categories, such as accidental suffocation and strangulation in bed, asphyxia, and ill-defined deaths.[3,4] Sudden unexpected infant death accounts for more than 3500 deaths annually in the United States.[1]

While SIDS rates have more than halved since the beginning of the Back to Sleep campaign (now "Safe to Sleep") in 1994, there has been no further decline since 2006. In contrast, deaths attributed to accidental suffocation and strangulation in bed and ill-defined deaths have increased in the past decade, such that the overall SUID rate has remained constant since 2000.[5]

Despite the overall decline in deaths, racial variance in SUID rates has persisted. The rate of SIDS in non-Hispanic African American infants and American Indian/Alaskan Native infants remains more than twice that of non-Hispanic white infants (0.87 and 0.96, respectively, vs 0.42 deaths per 1000 live births), while Asian American and Hispanic infants have lower rates (0.2 and 0.22 deaths per 1000 live births, respectively).[1] Similarly, rates of accidental suffocation and strangulation in bed and ill-defined deaths are 2 to 3 times higher in non-Hispanic African American and American Indian/Alaskan Native infants than in non-Hispanic white infants.[1] These disparities are present independent of socioeconomic status. Similar racial variance is observed in other Western countries. For example, in New Zealand, which has one of the highest SIDS rates among Western countries,[4] the rate in Maori natives is almost 5 times that of their European counterparts.[6]

Pathophysiology

Sudden infant death syndrome has long been believed to be multifactorial in origin. The triple risk hypothesis, which is the most widely accepted model, proposes that SIDS occurs when there is (1) a vulnerable infant in a (2) critical but unstable period of development of homeostatic control (the highest risk period is at ages 2 to 4 months, with 90% of instances occurring before age 6 months) who experiences (3) an exogenous stressor (eg, prone or side resting position, soft bedding, or in utero or environmental tobacco exposure). Based on the model, all 3 factors must be present for a death to occur.[7] Much research has focused on potential physiologic etiologies that may create vulnerability in the infant. While no studies have satisfactorily provided a complete explanation, each factor studied may play a contributory role in selected infants.

Asphyxia has long been thought to be the primary cause of death in many instances of SIDS, based both on the practices (eg, supine positioning and/or lack of soft bedding) known to be protective against SIDS and on the frequent autopsy finding of pulmonary edema, which is often seen with asphyxiation.[8,9] Infants resting in the prone position or lying with soft bedding may rebreathe exhaled carbon dioxide, potentially leading to hypercarbia and hypoxia.[10] If infants' environment does not change or infants are unable to extract themselves from the hazardous situation, they will ultimately die of asphyxia.[11]

Some researchers believe that infants who died of SIDS have an increased rate of chronic hypoxia. Several studies have demonstrated changes in surfactant on autopsies of infants who died of SIDS.[12,13] Decreased surfactant results in lower lung compliance and is suspected to lead to a chronic relative hypoxia. In utero tobacco exposure is also known to decrease lung capacity and compliance, which may lead to chronic hypoxia.[14] Elevated levels of vascular endothelial growth factor,[15] lactate,[16] and erythropoietin,[17] all of which are signs of chronic hypoxia, are documented more frequently in infants who died of SIDS compared with healthy controls. These data support the hypothesis that hypoxia occurs prior to death in these infants.

There is increasing evidence to suggest that a failure of the arousal mechanism to trigger the distressed infant to wake up may be a common pathway in SIDS. It is known that infants sleeping prone have higher arousal thresholds than those sleeping supine,[18] and this is a plausible mechanism for the increased risk seen with prone positioning.

There are other studies that suggest that decreased autonomic regulation is a possible contributing factor in SIDS. Indeed, there are known biochemical differences in the brains of infants who died of SIDS. Neuropathologic investigations have studied serotonin (specifically 5-hydroxytryptamine receptors) levels in the brainstems of infants who died of SIDS and controls, as serotonin is known to have neuroexcitatory effects in the ventrolateral medulla, leading to increased respiratory drive and arousal. Infants who died of SIDS had elevated levels of 5-hydroxytryptamine metabolites, indicating greater breakdown of serotonin, and lower densities of serotonin receptor binding sites.[19] In addition, genetic studies have demonstrated polymorphisms in the serotonin transporter protein 5-HTT, which transports serotonin intracellularly. These polymorphisms increase the promoter activity of the transporter, thus decreasing extracellular serotonin concentrations and reducing available concentrations at the synapse.[20] These findings may also contribute to impaired thermostasis and cardiac rhythm dysregulation. New work has looked at levels of the neuropeptide orexin, which is also believed to affect arousal thresholds; Hunt et al[21] recently demonstrated immunogenicity to orexin in infants who died of SIDS compared with age-matched controls, supporting the concern for impaired arousal in these infants.

Neuronal immaturity and increased rates of cell death have also been postulated to contribute to SIDS. Lavezzi et al[22] found that a marker present on mature neurons, neuronal nuclear antigen, was significantly decreased in infants who died of SIDS compared with controls, indicating increased neuronal immaturity. Others have suspected that there may be alterations in the myelination of neurons in infants who died of SIDS, although evidence for this is limited.[23] Several laboratories have looked at rates of cell death and apoptosis in infants who died of SIDS, postulating that increased cell death would lead to decreased autonomic regulation and arousal. Data over the years have been variable, depending on the markers examined. While data since 1995 revealed no increase in neuronal apoptosis and cell death in infants who died of SIDS compared with controls,[24] newer studies have indicated increased cell death specifically in the brainstems of infants who died of SIDS.[25] However, the exact contribution of brainstem apoptosis to the mechanism of death remains unclear.

Cardiac arrhythmias remain another potential contributor to SIDS. Most of this work has focused on prolonged QT syndrome as a potential arrhythmogenic cause, given that it is both common and frequently asymptomatic. An increased rate of prolonged QT syndrome has been reported in families who have lost a child to SIDS. One prospective study of 34 000 infants found a higher rate of prolonged QTc syndrome in infants who ultimately died of SIDS than in those who did not.[26] Additionally, autopsies of infants who died of SIDS have found an increased rate of alterations in *SCN5A*, which results in a sodium channelopathy that is a known cause of prolonged QTc syndrome.[27]

New work has focused on the known association of SIDS with a recent viral infection, most commonly a mild upper respiratory tract infection. There is evidence of an increase in interferon-γ in infants who died of SIDS, which may alter cytokine responses, making it more difficult to fight infection.[28] Other evidence shows an increase in interleukin 6, a proinflammatory cytokine, in infants who died of SIDS.[29] The effect that this immune modulation has on the nervous system is still being investigated.

Alterations in inflammatory cytokines have sparked considerable new interest in the potential contribution of the bacterial biomes of infants who died of SIDS and how that may affect the overall inflammatory response. In 1999, Blackwell et al[30] reported that 86% of infants who died of SIDS were colonized with *Staphylococcus aureus* compared with 56% of controls. Further, Highet et al[31] found that the nasopharynges of infants who died of SIDS were more likely to be colonized with *Clostridium perfringens*, *Clostridium difficile*, *Clostridium innocuum*, and *S aureus* than controls. *S aureus* has also been found more commonly in the respiratory tracts of infants sleeping prone than those sleeping supine,[31] perhaps providing an additional explanation for the association of prone sleeping with an increased risk of SIDS.

Epidemiology: Risk and Protective Factors

It is important to note that case-control studies are the mainstay of SIDS research, as significant ethical issues preclude randomized clinical trials. Case-control studies can only determine associations of specific factors and SIDS, and causation cannot be inferred. In addition, because the controls in the case-control studies are age-matched to infants who died of SIDS and therefore can be up to age 1 year, all recommendations to reduce the risk of SIDS pertain to infants until age 1 year.

Risk Factors

Sleep Position

Although prone positioning was noted to be a risk factor in unintentional suffocation deaths in 1944,[32] the association with SIDS was first identified in 1965[33] in the United Kingdom and then corroborated in the 1970s by studies from Europe, Australia, and New Zealand. Safe to Sleep campaigns promoting the supine sleep position began in the late 1980s in other Western countries and in the United States in 1994; all were associated with significant decreases in rates of SIDS. It has now been conclusively shown that sleeping prone is associated with an increased risk of SIDS (adjusted odds ratios, 2.3-13.1).[34-36] Prone positioning is associated with increased risk of hypercapnia and subsequent hypoxia,[37-39] depressed cerebral oxygenation,[40] increased rates of overheating,[41] altered autonomic control of the infant cardiovascular system,[42] and increased arousal thresholds.[18] Studies have found the risk of side positioning (adjusted odds ratio, 2.0; 95% CI, 1.2-3.4) to be similar to the risk of prone positioning (adjusted odds ratio, 2.6; 95% CI, 1.5-4.5)[35] and that side positioning has a higher population-attributable risk than prone positioning.[36] This may be at least partially explained by the instability of the side position; infants placed on their side are more likely than those on their back to roll into the prone position.[43] Placement in or rolling to the prone position places infants at extremely high risk of SIDS.[44] Side and prone positioning are of particular concern when the infant is with a new caregiver, eg, a day care provider, who may place a usual supine sleeper in the prone position.[45] Infants should be placed in the supine position for every sleep by every caregiver.

Bed Sharing

Bed sharing (ie, sleeping on the same surface as another person) is associated with increased rates of SIDS in case-control studies.[46,47] Bed sharing was found in one analysis of infant deaths to be the most important risk factor for infants younger than 4 months.[48] The risk associated with bed sharing may be in part because of soft mattresses and other soft bedding, the risk of overheating, and the risk of overlay (ie, another individual rolling on top of the child). However, the recommendation against bed sharing is controversial, as bed sharing facilitates breastfeeding,[49,50] which is a known protective factor against SIDS.[51] Additionally, bed sharing is more common in minority groups, perhaps because of cultural traditions, and those of lower socioeconomic status, relating to space constraints. Room sharing (ie, sleeping in proximity to the infant, allowing the individual to see, hear, smell, and/or touch the infant) without bed sharing is the safest sleep arrangement.[46,47] It can also permit easy access to the infant for comforting and feeding.

The risk of SIDS while bed sharing is highest when one or both parents are smokers, when the mother smoked during pregnancy, when the infant is born prematurely or with low birth weight, when the adult bed sharer has ingested alcohol or arousal-altering medications or drugs, when bed sharing occurs on a sofa or couch, when there is soft bedding, when infants bed share for the entire night, and when infants are younger than 11 weeks.[36,46,52] There is no increase in SIDS risk for infants who are held or fed in bed with an awake caregiver and are then placed into their own space to sleep before the caregiver goes to sleep.[36]

Soft Bedding

The use of soft bedding, including blankets, pillows, sheep skins, bumper pads, and positioners, in the infant sleep environment has been associated with a 5-fold increase in SIDS, independent of infant sleep position, and a 21-fold increase when the infant is prone.[34] The Consumer Product Safety Commission has also reported an increased risk of unintentional suffocation and asphyxia deaths with soft bedding use.[53] Soft bedding may also contribute to the risk associated with overheating and head covering. The presence of soft bedding was found in one analysis of infant deaths to be the most important risk factor for infants older than 4 months, as these older infants may roll into soft bedding and be unable to extract themselves.[48] Wearable blankets or sleep clothing are acceptable alternatives to loose blankets or sheets.

Sleep Surfaces

The safest sleep surface for an infant is a firm, tight-fitting crib mattress. Cribs, bassinets, and playpens may be acceptable sleep locations if they meet these criteria.

Sofas are one of the most dangerous sleep surfaces, with odds ratios of SIDS as high as 66.9.[47] One investigation found that 12.9% of sleep-related deaths studied occurred on a sofa or couch and that infants who died on sofas were more likely to be sleeping with an adult, on their side, and exposed to prenatal smoking; in addition, the sofa was more likely to be a new rather than a usual sleep location.[54] These deaths were also more likely to be coded as unintentional suffocation. It has been proposed that the soft cushiony surfaces and sloping edges of the sofa may predispose to these unintentional deaths. Parents should be cautioned to never place an infant for sleep on a couch, sofa, or equally cushioned surface. Parents should also take care to never fall asleep with an infant on such surfaces.

It is also not uncommon for infants to be placed for sleep in car seats, strollers, swings, infant carriers, and slings, often because the infant falls asleep more quickly or because of concerns about gastroesophageal reflux. One study found that the average infant spends 5.7 hours per day in a car seat or similar sitting device.[55] This is particularly concerning in young infants who do not have sufficient head control to support their airway adequately in these devices, as this can lead to unintentional deaths.[56] Additionally, particularly when placed on high or soft surfaces, car seats are prone to falling and flipping, potentially leading to injury or suffocation if the infant lands face down.[57] When using slings, it is recommended that infants' heads remain outside the sling and visible to parents as a precaution against suffocation.[58]

Maternal Smoking

Both in utero and environmental tobacco smoke exposure have been linked in a dose-dependent fashion to an increased risk of SIDS.[59-61]

In addition to reducing lung compliance and volume, in utero exposure is neurotoxic, leading to impaired arousal mechanisms and decreased heart rate variability in response to stress, compromising a distressed infant's ability to respond appropriately to the environment.[62,63] While it can be difficult to separate the effects of environmental smoke exposure on infants from prenatal exposure, environmental smoke exposure is also thought to decrease lung compliance and volume.

One analysis estimated that one-third of instances of SIDS could be prevented if tobacco smoke exposure was eliminated.[64] In addition, differences in nicotine metabolism among ethnic groups may explain some of the racial and ethnic disparity in infants who died of SIDS, as non-Hispanic African American parents are more likely to be slower metabolizers[65]; smoking may thus have a relatively stronger effect on non-Hispanic African American infants.[65] Indeed, a recent study found that increases in cigarette taxes led to a decrease in infant mortality, with an increased effect on non-Hispanic African American infants compared with non-Hispanic white infants.[66]

Prematurity

Premature and low-birth-weight infants are 4 times more likely to die of SIDS than their full-term counterparts.[67,68] Much of this risk may be derived from an immature autonomic system, leading to impaired arousal mechanisms and an increased risk of hypercarbia. Although premature infants are at increased risk for apnea of prematurity, there is no evidence that these apnea episodes precede SIDS deaths, and thus, apnea monitors are not recommended for SIDS prevention.[69] However, it has been shown that preterm infants are at equal or increased risk of SIDS when placed prone and are more likely to be placed prone at home, presumably because they were more likely to have been placed prone in the hospital.[70] Premature infants should be placed supine as soon as they are clinically stable, preferably by 32 weeks postmenstrual age, and early enough so that they can become accustomed to the supine position before hospital discharge.

Protective Factors

Breastfeeding

Multiple studies have shown that breastfeeding or giving expressed breast milk to infants is protective against SIDS.[51] While the decrease in SIDS is most pronounced in infants who are exclusively breastfed, breast milk consumption to any extent and for any duration is protective.[51] Parents are encouraged to feed the infant breast milk as much as possible and for as long as possible.

Pacifier Use

A recent meta-analysis of pacifier (dummy) use in infants found a strong protective effect.[71] Proposed mechanisms include increased arousability, increased sleeping blood pressure, and increased low frequency heart rate variability and decreased high frequency heart rate variability, indicating improved autonomic control.[72] Use of pacifier at onset of sleep is protective, even when the pacifier falls out of the mouth after the infant falls asleep.[73,74] A pacifier can be introduced in formula-fed infants as soon as desired. Because there is some concern that pacifier use may interfere with breastfeeding, introduction of the pacifier to breastfed infants should be delayed until breastfeeding has been well established.

Immunizations

Case-control studies and analyses of the US Vaccine Adverse Event Reporting System have shown no positive association between immunizations and subsequent SIDS. While one recent meta-analysis found that the risk of SIDS is halved by immunization,[75] others have not found this level of protection.[76] Fear of subsequent SIDS should not be a reason for nonimmunization.

Current Recommendations

The American Academy of Pediatrics publishes recommendations to reduce the risk of SIDS.[77] These include supine placement on a firm surface without soft bedding, bumpers, or positioners; room sharing without bed sharing; avoidance of overheating; pacifier use; avoidance of maternal smoking, alcohol, and illicit drug use during and after pregnancy; and avoidance of monitors and other products that are marketed to prevent SIDS. Breastfeeding as much as possible and for as long as possible is recommended. The guidelines also recommend routine prenatal care for expectant mothers and immunization for infants. Medical personnel (including neonatal intensive care unit personnel) are urged to promote and model SIDS guidelines both in the hospital and in office visits, and the media are urged to use safe sleep guidelines in their marketing campaigns. Finally, the recommendations call for additional research on SIDS.

Direction of Future Research

Despite our improved understanding of the pathophysiology of SIDS, additional work focusing on physiologic pathways and genetic features that may increase vulnerability for SIDS is needed. Research on the immature brain and arousal mechanisms has led to new hypotheses and discovery of biological markers believed to contribute to the final pathway of SIDS; however, further research is needed to identify how specific infections and the immune system may affect both neurologic development and arousal mechanisms as well as how ineffective arousal mechanisms can be altered to avert these deaths. Ultimately, a better understanding of the pathophysiology of these systems may aid in not only identifying at-risk infants but also identifying potential biologic targets for SIDS prevention.

Currently, the mainstay of prevention continues to be a safe sleep environment, as most infants who die suddenly and unexpectedly do so in unsafe sleep environments. Therefore, future research must also focus on the interplay between pathophysiology and known environmental and behavioral risk factors, specifically how environmental exposures, such as sleep position, exposure to smoking, and sleep location, alter typical physiologic responses. Finally, additional research must focus on more effective educational campaigns and strategies. Particular attention should focus on high-risk groups, such as non-Hispanic African American and Native American/Alaskan Native parents, for whom prior campaigns have been less effective. It is likely that a combination of epidemiologic, physiologic, and genetic research will be needed to identify trends, determine predispositions, and modify both intrinsic and extrinsic risks.

ARTICLE INFORMATION

Accepted for Publication: August 27, 2016.

Published Online: December 5, 2016. doi:10.1001/jamapediatrics.2016.3345

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank Elena Lagon, BS (University of Virginia School of Medicine), and Melissa Long, MD (Children's National Medical Center and George Washington School of Health Sciences), for their careful reading and editing of the manuscript. Neither were compensated for their work.

REFERENCES

1. US Centers for Disease Control and Prevention. Infant deaths: linked birth/infant death records. http://wonder.cdc.gov/lbd.html. Accessed May 5, 2016.

2. Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. *Pediatr Pathol*. 1991;11(5):677-684.

3. Shapiro-Mendoza CK, Tomashek KM, Anderson RN, Wingo J. Recent national trends in sudden, unexpected infant deaths: more evidence supporting a change in classification or reporting. *Am J Epidemiol*. 2006;163(8):762-769.

4. Taylor BJ, Garstang J, Engelberts A, et al. International comparison of sudden unexpected death in infancy rates using a newly proposed set of cause-of-death codes. *Arch Dis Child*. 2015;100(11):1018-1023.

5. Mathews TJ, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2015;64(9):1-30.

6. New Zealand Ministry of Health. Infant health. http://www.health.govt.nz/our-work/populations/maori-health/tatau-kahukura-maori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/infant-health. Accessed August 3, 2016.

7. Filiano JJ, Kinney HC. A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model. *Biol Neonate*. 1994;65(3-4):194-197.

8. Hunt CE, Hauck FR. Sudden infant death syndrome. *CMAJ*. 2006;174(13):1861-1869.

9. Valdes-Dapena M. The sudden infant death syndrome: pathologic findings. *Clin Perinatol*. 1992;19(4):701-716.

10. Kemp JS, Nelson VE, Thach BT. Physical properties of bedding that may increase risk of sudden infant death syndrome in prone-sleeping infants. *Pediatr Res*. 1994;36(1, pt 1):7-11.

11. Kinney HC, Thach BT. The sudden infant death syndrome. *N Engl J Med*. 2009;361(8):795-805.

12. Carroll JL, Loughlin GM. Sudden infant death syndrome. *Pediatr Rev*. 1993;14(3):83-93.

13. Stray-Pedersen A, Vege A, Opdal SH, Moberg S, Rognum TO. Surfactant protein A and D gene polymorphisms and protein expression in victims of sudden infant death. *Acta Paediatr*. 2009;98(1):62-68.

14. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics*. 2004;113(4 suppl):1007-1015.

15. Jones KL, Krous HF, Nadeau J, Blackbourne B, Zielke HR, Gozal D. Vascular endothelial growth factor in the cerebrospinal fluid of infants who died of sudden infant death syndrome: evidence for antecedent hypoxia. *Pediatrics*. 2003;111(2):358-363.

16. Butterworth J, Tennant MC. Postmortem human brain pH and lactate in sudden infant death syndrome. *J Neurochem*. 1989;53(5):1494-1499.

17. Le Cam-Duchez V, Coquerel A, Chevallier F, et al. Erythropoietin blood level is increased in sudden infant death. *Biol Neonate*. 1999;76(1):1-9.

18. Horne RS, Ferens D, Watts AM, et al. The prone sleeping position impairs arousability in term infants. *J Pediatr*. 2001;138(6):811-816.

19. Paine SM, Jacques TS, Sebire NJ. Review: neuropathological features of unexplained sudden unexpected death in infancy: current evidence and controversies. *Neuropathol Appl Neurobiol*. 2014;40(4):364-384.

20. Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML. Association of the serotonin transporter gene with sudden infant death syndrome: a haplotype analysis. *Am J Med Genet A*. 2003;122A(3):238-245.

21. Hunt NJ, Waters KA, Rodriguez ML, Machaalani R. Decreased orexin (hypocretin) immunoreactivity in the hypothalamus and pontine nuclei in sudden infant death syndrome. *Acta Neuropathol*. 2015;130(2):185-198.

22. Lavezzi AM, Corna MF, Matturri L. Neuronal nuclear antigen (NeuN): a useful marker of neuronal immaturity in sudden unexplained perinatal death. *J Neurol Sci*. 2013;329(1-2):45-50.

23. Sarnat HB, Flores-Sarnat L. Synaptogenesis and myelination in the nucleus/tractus solitarius: potential role in apnea of prematurity, congenital central hypoventilation, and sudden infant death syndrome. *J Child Neurol*. 2016;31(6):722-732.

24. Sawaguchi T, Patricia F, Kadhim H, et al. Pathological data on apoptosis in the brainstem and physiological data on sleep apnea in SIDS victims. *Early Hum Dev*. 2003;75(suppl):S13-S20.

25. Machaalani R, Waters KA. Neuronal cell death in the sudden infant death syndrome brainstem and associations with risk factors. *Brain*. 2008;131(pt 1):218-228.

26. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med*. 1998;338(24):1709-1714.

27. Ackerman MJ, Siu BL, Sturner WQ, et al. Postmortem molecular analysis of *SCN5A* defects in sudden infant death syndrome. *JAMA*. 2001;286(18):2264-2269.

28. Moscovis SM, Gordon AE, Al Madani OM, et al. Genetic and environmental factors affecting TNF-α responses in relation to sudden infant death syndrome. *Front Immunol*. 2015;6:374.

29. Vege A, Rognum TO, Scott H, Aasen AO, Saugstad OD. SIDS cases have increased levels of interleukin-6 in cerebrospinal fluid. *Acta Paediatr*. 1995;84(2):193-196.

30. Blackwell CC, MacKenzie DA, James VS, et al. Toxigenic bacteria and sudden infant death syndrome (SIDS): nasopharyngeal flora during the first year of life. *FEMS Immunol Med Microbiol*. 1999;25(1-2):51-58.

31. Highet AR, Berry AM, Bettelheim KA, Goldwater PN. Gut microbiome in sudden infant death syndrome (SIDS) differs from that in healthy comparison babies and offers an explanation for the risk factor of prone position. *Int J Med Microbiol*. 2014;304(5-6):735-741.

32. Abramson H. Accidental mechanical suffocation in infants. *J Pediatr*. 1944;25:404-413. doi:10.1016/S0022-3476(44)80005-1

33. Carpenter RG, Shaddick CW. Role of infection, suffocation, and bottle-feeding in cot death: an analysis of some factors in the histories of 110 cases and their controls. *Br J Prev Soc Med*. 1965;19:1-7.

34. Hauck FR, Herman SM, Donovan M, et al. Sleep environment and the risk of sudden infant death syndrome in an urban population: the Chicago Infant Mortality Study. *Pediatrics*. 2003;111(5, pt 2):1207-1214.

35. Li DK, Petitti DB, Willinger M, et al. Infant sleeping position and the risk of sudden infant death syndrome in California, 1997-2000. *Am J Epidemiol*. 2003;157(5):446-455.

36. Fleming PJ, Blair PS, Bacon C, et al; Confidential Enquiry into Stillbirths and Deaths Regional Coordinators and Researchers. Environment of infants during sleep and risk of the sudden infant death syndrome: results of 1993-5 case-control study for confidential inquiry into stillbirths and deaths in infancy. *BMJ*. 1996;313(7051):191-195.

37. Kanetake J, Aoki Y, Funayama M. Evaluation of rebreathing potential on bedding for infant use. *Pediatr Int*. 2003;45(3):284-289.

38. Kemp JS, Livne M, White DK, Arfken CL. Softness and potential to cause rebreathing: differences in bedding used by infants at high and low risk for sudden infant death syndrome. *J Pediatr*. 1998;132(2):234-239.

39. Patel AL, Harris K, Thach BT. Inspired CO(2) and O(2) in sleeping infants rebreathing from bedding: relevance for sudden infant death syndrome. *J Appl Physiol (1985)*. 2001;91(6):2537-2545.

40. Wong FY, Witcombe NB, Yiallourou SR, et al. Cerebral oxygenation is depressed during sleep in healthy term infants when they sleep prone. *Pediatrics*. 2011;127(3):e558-e565.

41. Tuffnell CS, Petersen SA, Wailoo MP. Prone sleeping infants have a reduced ability to lose heat. *Early Hum Dev*. 1995;43(2):109-116.

42. Yiallourou SR, Walker AM, Horne RS. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. *Sleep*. 2008;31(8):1139-1146.

43. Willinger M, Hoffman HJ, Wu K-T, et al. Factors associated with the transition to nonprone sleep positions of infants in the United States: the National Infant Sleep Position Study. *JAMA*. 1998;280(4):329-335.

44. Mitchell EA, Thach BT, Thompson JMD, Williams S. Changing infants' sleep position increases risk of sudden infant death syndrome: New Zealand Cot Death Study. *Arch Pediatr Adolesc Med*. 1999;153(11):1136-1141.

45. Moon RY, Patel KM, Shaefer SJ. Sudden infant death syndrome in child care settings. *Pediatrics*. 2000;106(2, pt 1):295-300.

46. Carpenter RG, Irgens LM, Blair PS, et al. Sudden unexplained infant death in 20 regions in

Europe: case control study. *Lancet*. 2004;363(9404):185-191.

47. Tappin D, Ecob R, Brooke H. Bedsharing, roomsharing, and sudden infant death syndrome in Scotland: a case-control study. *J Pediatr*. 2005;147(1):32-37.

48. Colvin JD, Collie-Akers V, Schunn C, Moon RY. Sleep environment risks for younger and older infants. *Pediatrics*. 2014;134(2):e406-e412.

49. Blair PS, Heron J, Fleming PJ. Relationship between bed sharing and breastfeeding: longitudinal, population-based analysis. *Pediatrics*. 2010;126(5):e1119-e1126.

50. Huang Y, Hauck FR, Signore C, et al. Influence of bedsharing activity on breastfeeding duration among US mothers. *JAMA Pediatr*. 2013;167(11):1038-1044.

51. Hauck FR, Thompson JM, Tanabe KO, Moon RY, Vennemann MM. Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. *Pediatrics*. 2011;128(1):103-110.

52. Vennemann MM, Hense HW, Bajanowski T, et al. Bed sharing and the risk of sudden infant death syndrome: can we resolve the debate? *J Pediatr*. 2012;160(1):44-48.e2.

53. Chowdhury RT; Consumer Product Safety Commission. Nursery product-related injuries and deaths among children under age five. https://www.cpsc.gov/s3fs-public/pdfs/nursery10.pdf. Accessed November 15, 2016.

54. Rechtman LR, Colvin JD, Blair PS, Moon RY. Sofas and infant mortality. *Pediatrics*. 2014;134(5):e1293-e1300.

55. Callahan CW, Sisler C. Use of seating devices in infants too young to sit. *Arch Pediatr Adolesc Med*. 1997;151(3):233-235.

56. Batra EK, Midgett JD, Moon RY. Hazards associated with sitting and carrying devices for children two years and younger. *J Pediatr*. 2015;167(1):183-187.

57. Parikh SN, Wilson L. Hazardous use of car seats outside the car in the United States, 2003-2007. *Pediatrics*. 2010;126(2):352-357.

58. Bergounioux J, Madre C, Crucis-Armengaud A, et al. Sudden deaths in adult-worn baby carriers: 19 cases. *Eur J Pediatr*. 2015;174(12):1665-1670.

59. MacDorman MF, Cnattingius S, Hoffman HJ, Kramer MS, Haglund B. Sudden infant death syndrome and smoking in the United States and Sweden. *Am J Epidemiol*. 1997;146(3):249-257.

60. Schoendorf KC, Kiely JL. Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy. *Pediatrics*. 1992;90(6):905-908.

61. Haglund B, Cnattingius S. Cigarette smoking as a risk factor for sudden infant death syndrome: a population-based study. *Am J Public Health*. 1990;80(1):29-32.

62. Fifer WP, Fingers ST, Youngman M, Gomez-Gribben E, Myers MM. Effects of alcohol and smoking during pregnancy on infant autonomic control. *Dev Psychobiol*. 2009;51(3):234-242.

63. Richardson HL, Walker AM, Horne RS. Maternal smoking impairs arousal patterns in sleeping infants. *Sleep*. 2009;32(4):515-521.

64. Dietz PM, England LJ, Shapiro-Mendoza CK, Tong VT, Farr SL, Callaghan WM. Infant morbidity and mortality attributable to prenatal smoking in the U.S. *Am J Prev Med*. 2010;39(1):45-52.

65. Pérez-Stable EJ, Herrera B, Jacob P III, Benowitz NL. Nicotine metabolism and intake in black and white smokers. *JAMA*. 1998;280(2):152-156.

66. Patrick SW, Warner KE, Pordes E, Davis MM. Cigarette tax increase and infant mortality. *Pediatrics*. 2016;137(1):137.

67. Malloy MH, Hoffman HJ. Prematurity, sudden infant death syndrome, and age of death. *Pediatrics*. 1995;96(3, pt 1):464-471.

68. Sowter B, Doyle LW, Morley CJ, Altmann A, Halliday J. Is sudden infant death syndrome still more common in very low birthweight infants in the 1990s? *Med J Aust*. 1999;171(8):411-413.

69. Ramanathan R, Corwin MJ, Hunt CE, et al; Collaborative Home Infant Monitoring Evaluation (CHIME) Study Group. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. *JAMA*. 2001;285(17):2199-2207.

70. Oyen N, Markestad T, Skaerven R, et al. Combined effects of sleeping position and prenatal risk factors in sudden infant death syndrome: the Nordic Epidemiological SIDS Study. *Pediatrics*. 1997;100(4):613-621.

71. Alm B, Wennergren G, Möllborg P, Lagercrantz H. Breastfeeding and dummy use have a protective effect on sudden infant death syndrome. *Acta Paediatr*. 2016;105(1):31-38.

72. Yiallourou SR, Poole H, Prathivadi P, Odoi A, Wong FY, Horne RS. The effects of dummy/pacifier use on infant blood pressure and autonomic activity during sleep. *Sleep Med*. 2014;15(12):1508-1516.

73. Franco P, Scaillet S, Wermenbol V, Valente F, Groswasser J, Kahn A. The influence of a pacifier on infants' arousals from sleep. *J Pediatr*. 2000;136(6):775-779.

74. Weiss PP, Kerbl R. The relatively short duration that a child retains a pacifier in the mouth during sleep: implications for sudden infant death syndrome. *Eur J Pediatr*. 2001;160(1):60-70.

75. Vennemann MM, Höffgen M, Bajanowski T, Hense HW, Mitchell EA. Do immunisations reduce the risk for SIDS? a meta-analysis. *Vaccine*. 2007;25(26):4875-4879.

76. Kuhnert R, Schlaud M, Poethko-Müller C, et al. Reanalyses of case-control studies examining the temporal association between sudden infant death syndrome and vaccination. *Vaccine*. 2012;30(13):2349-2356.

77. Moon RY; Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: updated 2016 recommednations for a safe infant sleeping environment. *Pediatrics*. 2016;138(5):e20162938. doi:10.1542/peds.2016-2938