

# Sudden infant death syndrome – epidemiology and environmental factors

Prevention is still a challenge

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Cover illustration: Le berceau, Berthe Morisot

Le berceau

Mme Pontillon, née Edma Morisot (1839-1921), soeur de l'artiste, et sa fille, Blanche Pontillon, nièce de Berthe Morisot, future Mme Pierre Forget (1871-1941)

Collection Mme Pontillon RF2849

Morisot Berthe (1841-1895)

Localisation: Paris, musée d'Orsay

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Note that the baby is sleeping on her back in her own cradle.

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*Truth, in science, can be defined as the working hypothesis best fitted to open the way to the next better one.*

*Konrad Lorenz*

*On aggression, 1966*

***To bereaved families***



# **Sudden infant death syndrome – epidemiology and environmental factors**

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### **ABSTRACT**

Sudden infant death syndrome (SIDS) is still an important cause of death in infancy despite its declining incidence. The overall aim of this thesis was to study environmental factors influencing the risk of SIDS with the goal of still further reducing preventable deaths among infants in the future.

In a prospective study (Children of Western Sweden) consisting of 5600 healthy six-months-old infants born in 2003 and 430 healthy Swedish infants born in 1991-1995, the prevalence of risk factors was compared and factors associated with prone sleeping were studied. We found that parents had complied with advice to prevent SIDS but that further change to an exclusively supine sleeping position and reducing the number of pregnant women who smoke might be beneficial. A prone sleeping position was more common if the mother was unemployed or smoked during pregnancy, and also if the child was irritable, never used a pacifier or shared a bedroom with siblings.

To identify the changes in epidemiology since the national guidelines to prevent SIDS were established in 1992-94 we studied 207 SIDS cases in 1997-2005 and compared them with controls randomly selected from the Swedish Medical Birth Register (MBR). The results showed that the incidence of SIDS had remained low in Sweden and that the age at death continued to decrease. The odds ratio for smoking continued to increase. The high incidence at weekends persisted but there was no longer any seasonality.

Bed sharing is considered to be a risk factor for SIDS and we therefore we examined bed sharing at six months of age and associated factors. The questionnaire was answered by 5605 families with a response rate of 68.5% and we found that every fifth infant shared a bed. Factors associated with bed

sharing were breastfeeding, sleeping problems and a single parent. Never using a pacifier was associated with a higher frequency of bed sharing but it was less common to bed share if the infant was bottle-fed during the first week.

In a retrospective study we investigated data from all sudden unexpected deaths in infancy (SUDI) in Sweden from 2005-2011. Medical records were obtained from hospitals and supplementary data from the Swedish MBR. Of the 261 infants, 136 were defined as SIDS and 125 as explained SUDI. We found that bed sharing was more common in SIDS than in explained SUDI. Sparse data in medical records were a problem. Bronchopneumonia, other infections and congenital anomalies were the most common causes of explained SUDI.

It is still possible to prevent more deaths in SIDS if prone and side sleeping positions, maternal smoking and bed sharing during the first months decrease. One tool for success is to have routines and documentation continuously to follow changes in the epidemiology of environmental factors, together with the possibility to communicate this and reach groups at risk with targeted information.

**Keywords:** bed sharing, epidemiology, prevention, SIDS, Sudden infant death syndrome, SUDI, Sudden unexpected death in infancy, Sweden

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## LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Alm B, Möllborg P, Erdes L, Pettersson R, Åberg N, Norvenius G, Wennergren G. SIDS risk factors and factors associated with prone sleeping in Sweden. *Arch Dis Child* 2006; 91: 915-919.
- II. Möllborg P, Alm B. Sudden infant death syndrome during low incidence in Sweden 1997-2005. *Acta Paediatr* 2010; 99: 94-98.
- III. Möllborg P, Wennergren G, Norvenius SG, Alm B. Bed-sharing among six-month-old infants in western Sweden. *Acta Paediatr* 2011; 100: 226-230.
- IV. Möllborg P, Wennergren G, Almqvist P, Alm B. Bed sharing is more common in sudden infant death syndrome than in explained sudden unexpected deaths in infancy. *Acta Paediatr* 2015; 104: 777-783.





# SAMMANFATTNING PÅ SVENSKA

**Bakgrund:** Plötslig spädbarnsdöd (SIDS) är något som de flesta föräldrar är oroliga för skall drabba just deras barn. Efter att från mitten på 70-talet och ända fram till början på 90-talet alltför barn dött i SIDS med ett maximum 1991 med 1,2 fall/1000 levande födda i Sverige visade internationella studier att den största riskfaktorn för plötslig spädbarnsdöd var om spädbarnet sov på mage. Andra betydelsefulla fynd som ökade risken var om modern rök under graviditeten, om barnet inte kunnat röra sig fritt eller blivit för varmt. En minskad risk sågs vid amning. Efter nationellt förebyggande råd, riktade till nyblivna föräldrar, introducerats 1992-1994 i Sverige har antalet fall av SIDS kraftigt minskat och stabiliserats kring ca 0,2 fall/1000 levande födda vilket är en av de lägsta siffrorna internationellt. Risk- och skyddsfaktorer har förändrats när fallen är färre och har inte studerats i Sverige på senare tid.

**Målsättning:** Genom att studera omgivningsfaktorer kopplade till SIDS och annan plötslig oväntad spädbarnsdöd få mer kunskap kring dessa faktorer betydelse, deras förändring över tid och därmed möjliggöra ytterligare förebyggande arbete för att minska risken för SIDS.

**Metod:** Två av studierna (artikel I och III) undersöker via en enkät hur de förebyggande råden har accepterats av föräldrarna, deras följsamhet till desamma och hur vanligt det är med samsovning vid 6 månaders ålder. En annan studie (artikel III) jämför förekomsten av omgivningsfaktorer kring SIDS mellan en nordisk studie från 1995 och de spädbarn som fått diagnosen SIDS 1997-2005. Den fjärde studien (artikel IV) analyserar data gällande alla spädbarn som dött plötsligt och oväntat under åren 2005-2011. Uppgifter från dödsorsaksregister, medicinska födelseregistret samt genomgång av journalhandlingar har studerats och statistiskt bearbetats.

**Resultat:** Vi konstaterar att de av Socialstyrelsen utgivna råden tagits emot mycket väl med god följsamhet från föräldrarnas sida. Endast 5,6 % av barnen läggs på mage jämfört med 31,8 % ett decennium tidigare. Däremot hade sidoläge eller sida/rygg som sovposition ökat från 25,2 % till 43,8 %.

I de fall barnet lagts på mage var det vanligare att modern var arbetslös och rökte mer sista delen av graviditeten samt att barnet delade sovrum med syskon, beskrevs som irriterat eller inte använt napp.

Den låga förekomsten av SIDS har bibehållits. Risken för SIDS var större om modern rök under tidig graviditet, om föräldrarna inte bodde ihop, om mamman var ung och fött många barn samt om barnet var för tidigt fött.

Andra fynd var att rökning under graviditeten hade ännu större betydelse som risk för SIDS när antalet SIDS fall var färre, att spädbarnets genomsnittliga ålder vid dödsfallet hade minskat, och att vi inte längre fann någon säsongsvariation.

Vi såg att vart femte barn sov i samma säng som sina föräldrar vid 6 månaders ålder. Det var vanligare med samsovning om barnet amrades, om barnet hade svårighet att somna och många nattuppvaknanden liksom om föräldern var ensamstående. Om barnet använde napp eller bröstmjölkersättning var det mindre vanligt med samsovning.

I vår kartläggning av samtliga 261 dödsfall i plötslig oväntad spädbarnsdöd fann vi att 136 barn fått diagnosen SIDS medan 125 dödsfall fick andra diagnoser. Vi fann att samsovning var 7,7 gånger vanligare bland SIDS-fallen än bland förklarade dödsfall, att magläge fortfarande var överrepresenterat bland SIDS och att rökande mamma var vanligt i båda grupperna. Dokumentationen av omgivningsfaktorer i barnets journal var påtagligt bristfällig. De vanligaste orsakerna till plötslig oväntad spädbarnsdöd där man finner förklaringar var infektioner i luftvägar, andra infektioner, medfödda sjukdomar och hjärtfel.

**Slutsats:** Förekomsten av SIDS i Sverige har sjunkit sedan förebyggande råd infördes och är bland de lägsta i världen. Följsamheten till råden är generellt god men det finns ytterligare potential att rädda liv om magläge undviks, om spädbarn inte läggs på sidan, om moderns rökning under graviditet minskar och om spädbarn under den första tiden sover i egen säng. Den tidigare säsongsvariationen sågs inte längre och inte heller några geografiska skillnader. Medianåldern (64 dagar) för SIDS hade minskat jämfört med åren när SIDS var mycket vanligare men var konstant mellan de senaste studierna. Kunskap kring vilka bakgrundsfaktorer som gör att man väljer alternativt inte väljer att följa rekommendationer möjliggör mer riktad information från MVC och BVC till riskgrupper. Dokumentationen i barnets journal är bristfällig när det gäller omgivningsfaktorer som sovläge, sovmiljö, samsovning, rökning, amning, napp och sociala faktorer, vilket försvårar uppföljning av hur olika faktorer påverkar risken för SIDS och annan oväntad död hos spädbarn. Utifrån sistnämnda resultat har ett projektarbete initierats av Socialstyrelsen för att förbättra rutiner och dokumentation kring när plötsliga oväntade dödsfall inträffar bland spädbarn.

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## ABBREVIATIONS

AAP	American Academy of Pediatrics
aOR	Adjusted Odds Ratio
CI	Confidence Interval
ICD-9	International Classification of Diseases version 9
ICD-10	International Classification of Diseases version 10
ISPID	International Society for the Study and Prevention of Perinatal and Infant Death
MBR	Medical Birth Register
NordSIDS	Nordic Epidemiological SIDS Study
OR	Odds Ratio
SGA	Small for Gestational Age
SIDS	Sudden Infant Death Syndrome
SUDI	Sudden Unexpected Death in Infancy

# 1. INTRODUCTION

Sudden infant death syndrome, SIDS, is rare but the consequences are catastrophic and affect the family for the rest of their lives. For the bereaved parents it is important and necessary to be taken care of in a professional and empathetic manner. No efforts should be spared to further reduce infant deaths in Sweden and to make this goal attainable we have to know the factors that are in play in this vulnerable period of infancy. Research and guidelines to prevent SIDS have to be updated to maintain the current low Swedish incidence and reduce it still further.

This thesis is a contribution to add knowledge relating to environmental factors that are involved in the risk of SIDS. The different studies focus on the adherence to national guidelines relating to supine sleeping and factors associated with prone sleeping, the changes in epidemiology during the low incidence of SIDS compared with a decade earlier, how common bed sharing is and factors that are associated with sharing a bed. The last study describes all the sudden unexpected deaths of infancy, SUDI, in Sweden from 2005-2011 and compares SIDS cases and explained deaths of infancy in terms of environmental risk factors. It also describes the diagnosis and causes of explained death in infancy.

With any new recommendations there is resistance to complying and it is essential that recommendations are evidence based. Changing practice is difficult and the communication should always be focused on the receiver. Understanding the barriers is the first step towards facilitating changes in behaviour, which is a challenge for all healthcare providers to be aware of. The message in new sleep safety recommendations must be clear and unified towards the parents and more effort and skills in communication are necessary to reach the families who are most resistant to adopting recommended practices.

Research could make a difference and it is our aim that the on-going work with the Swedish National Board of Health and Welfare and the Swedish National Board of Forensic Medicine will result in better routines when an unexpected death in infancy occurs, that data in the medical records will improve and that we will be able to study environmental factors on a yearly basis with the goal of reducing the incidence of SIDS still further.

The definition of research by David Smith expressed in “The Health Professional as Researcher, 1992”, is well suited to the area of SIDS and

especially when studying epidemiology, environmental factors and the compliance with public advice. He states that research is “the systematic gathering of reliable and valid information to aid understanding, solve problems, develop policy, and improve practice”.

## 1.1 Historical perspective

The first known description of a case of SIDS can be found in the *Old Testament*, in the *First Book of Kings*. In a story that illustrates the wisdom of King Solomon as a judge, it says: “And this woman’s child died in the night; because she overlaid it” (1 Kings, 3:19). The view that the deaths were caused by the mother lying on the top of her infant is also reflected in the old Swedish provincial laws from the 13th and 14th centuries. A woman who had overlaid her child could be punished (Norvenius 1993).

In 1855 a letter was published in *The Lancet* in which the author noted the seasonality of sudden deaths in infancy, the weekly variation and the time of discovery (Wakley 1855). He suggested that all post-mortem examinations should be “...conducted on one uniform plan...” and opposes the hypothesis that overlaying could be the cause of death. The first epidemiological study of sudden infant death is considered to be *Two hundred and fifty-eight cases of suffocation of infants* (Templeman 1892). In this article he attributed the deaths to overlaying and suffocation in connection with alcohol.

The Swedish professor Fredrik Theodor Berg, active at the Karolinska Institute in Stockholm in the mid-19th century, observed sudden infant deaths in the Public Orphanage (Allmänna Barnhuset) and questioned the role of an enlarged thymus (Norvenius 1993). This observation that the infants that died in this way had large thymus led to the conclusion that death was caused due to suffocation by this organ (Paltauf 1889). The condition was named “status thymo-lymphaticus” and remained as the most prevalent explanation for sudden infant death for almost half a century. The diagnosis was disputed when it was recognised that the enlarged thymus was in fact a normal condition in early infancy (Hammar 1926). Not until the 1950s was it concluded that: “The conception of status lymphaticus has now been almost universally abandoned...” (Barret 1954).

The hypothesis that infection was associated with sudden infant death was raised after seasonality that paralleled that of respiratory infections was shown in a Swedish study (Siwe 1934). Other studies suggested that infection with streptococci might play a role (Farber 1934) and pulmonary infections were suggested as the main cause of death by other (Werne 1942, Adams



1944). This theory of infection as a cause of sudden unexpected death in infancy has today been confirmed, but these deaths are regarded as explained SUDI to differentiate them from SIDS when no explanation is found at the autopsy.

Accidental suffocation, either by bedclothes or by the inhalation of foods, attracted attention parallel with the infection theory in the 1940s and 1950s. In a study in New York 139 cases of infants who were supposed to have died of suffocation showed that 68% of the babies were found prone and 15% in their mothers' bed (Abramson 1944). Due to these findings, the author suggested that the prone position should be abandoned. The theory of inhalation of vomit or food was proposed by Barret (Barret 1954) but he was unable to find sufficient evidence to confirm or reject it.

When child mortality due to infectious diseases declined in the mid-20<sup>th</sup> century, it became more obvious that some infants died suddenly and unexpectedly. In Sweden, cot deaths started to attract attention in the 1960s (von Sydow 1969). The incidence of cot deaths was around one per 2000 live births from 1960 to the beginning of the 1970s. The incidence then started to rise during the 1970s (Norvenius 1987). During the 1980s, the increase in SIDS incidence became worrying both in the Scandinavian countries and in other western countries.

## 1.2 Definitions

SIDS as a term was first proposed in 1969 for a distinctive subgroup of unexpected infant death that occurred during the postneonatal period with relatively consistent clinical, epidemiological and pathological features (Beckwith et al. 1970). The definition designated as the 1969 definition is "The sudden death of any infant or young child, which is unexpected by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause for death".

This definition played an important role by focusing attention on a major category of postneonatal infant death with several distinctive features, such as age distribution and apparent occurrence during sleep. However, the definition was discussed due to its limitations in terms of case history, clinical data and death scene investigation and the fact that it compromised too many different underlying causes.

It took 20 years before the next definition, designated as the 1989 definition: "The sudden death of an infant under one 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” (Willinger et al. 1991).

As a result of discussions and the call for a re-evaluation of the SIDS definition, a panel of experts met in San Diego in 2004 and proposed a new definition. It was expressed as “The death of an infant that cannot be explained, despite a thorough case investigation, including death scene investigation, autopsy and review of the clinical history” (Krous et al. 2004). In addition to this more general definition the panel also agreed on a subclassification based on specific epidemiological features. It divided the SIDS diagnosis into category I A SIDS, I B SIDS or II SIDS, depending on how the criteria were fulfilled. This categorisation has not been put into practice in Sweden among forensic examiners.

Sudden unexpected death in infancy (SUDI) is a term used to describe any sudden and unexpected death, whether explained or unexplained, including SIDS, which occurs during the first year of life (AAP 2011).

Perinatal mortality refers to the death of a foetus or neonate and is the basis for calculating the perinatal mortality rate. The World Health Organisation (WHO) defines perinatal mortality as the “number of stillbirths and deaths in the first week of life per 1000 live births, the perinatal period commences at 22 completed weeks (154 days) of gestation and ends seven completed days after birth”.

Neonatal mortality is defined as death within 28 days of birth (Mosby 2009).

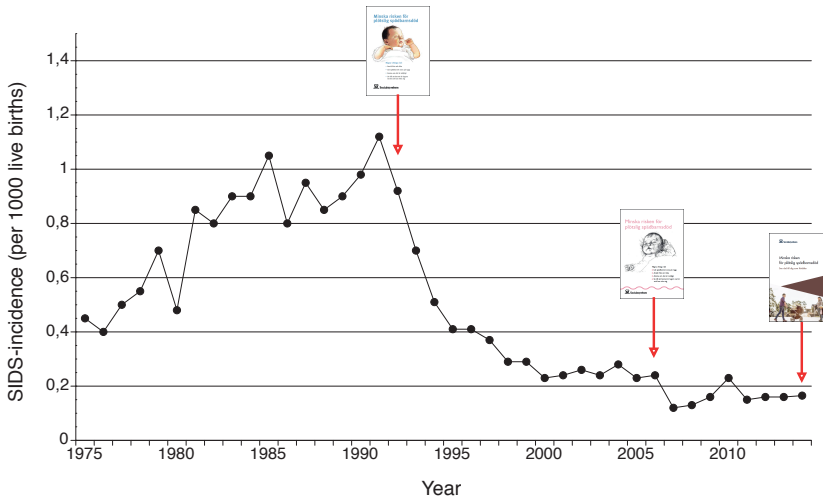
Post-neonatal mortality is a standard indicator of health, defined as the number of infants death occurring between 28 days and 11 months of life (McGraw-Hill 2002).

Infant mortality is the statistical rate of infant death during the first year after live birth, expressed as the number of such deaths per 1000 live births in a specific area or institution in a given period (Mosby 2009). This means that neonatal mortality added to post-neonatal mortality represents the infant mortality rate.

The most accepted definition of bed sharing is when the infant sleeps on the same surface as another person (McKenna et al. 2007).

Co-sleeping is often used in the same context as bed sharing, but it is not synonymous, as co-sleeping can include bed sharing or sleeping in the same room in close proximity (McKenna et al. 1993).

### 1.3 Incidence of SIDS



**Figure 1. Incidence of SIDS in Sweden in 1975-2014 and campaigns to reduce the risk. Data from the Swedish National Board of Forensic Medicine.**

Before SIDS was accepted as an entity, at the end of the 1960s, reliable data were almost non-existent (Beckwith et al. 1970). In Sweden, one study investigated SIDS deaths between 1968-1972 in seven counties and found a mean incidence of 0.56 per 1000 live births (Pettersson et al. 1975). During almost the same period, 1966-1970, another study in the southern region of Sweden, reported 0.39 per 1000 live births (Bjerre et al. 1974).

The first Swedish study that included death certificates, police reports, autopsy protocols, medical records from maternity wards, child health-care centres and hospitals, plus available records from social welfare bureaux, was a study in 1973-1977 and 1979 (Norvenius 1987). The result was an incidence of 0.30 (true SIDS) and 0.41 (true plus possible SIDS) per 1000 live births in the examined 1873 post-perinatal deaths.

In Sweden as in many other countries the incidence increased during the 1980s to reach maximum levels at the beginning of the 1990s before the

campaign to reduce the risk, recommending a supine sleeping position, began and the decline was a fact (Wennergren et al. 1997). The maximum incidence was seen in 1991, with an incidence of 1.12 per 1000 live births, which means that 146 infants died in this year and were classified as SIDS.

Norway had an even higher incidence with 2.6 per 1000 live births in 1989 while Denmark had 1.8 per 1000 live births in the same year (Wennergren et al. 1997). The decline in incidence after the risk reducing campaigns were established was first seen in Norway (Markestad 1992), which was the first Nordic country to begin with national preventive advice in January 1990. Denmark started in December 1990 and Sweden in April 1992, with a reinforcement of the message in the spring of 1994.

The highest incidence of SIDS before the risk-reducing campaigns started was in Tasmania with 3.8 cases per 1000 live births (Dwyer et al. 1995), and in New Zealand with 4.4 cases per 1000 live births (Mitchell et al. 1994). The countries with the lowest incidence were Hong Kong with 0.3 (Lee et al. 1989) and Japan also 0.3 (Watanabe et al. 1994). After the preferred sleeping position was changed to supine and the other preventive advice was communicated, the differences between countries are smaller between countries but still exist.

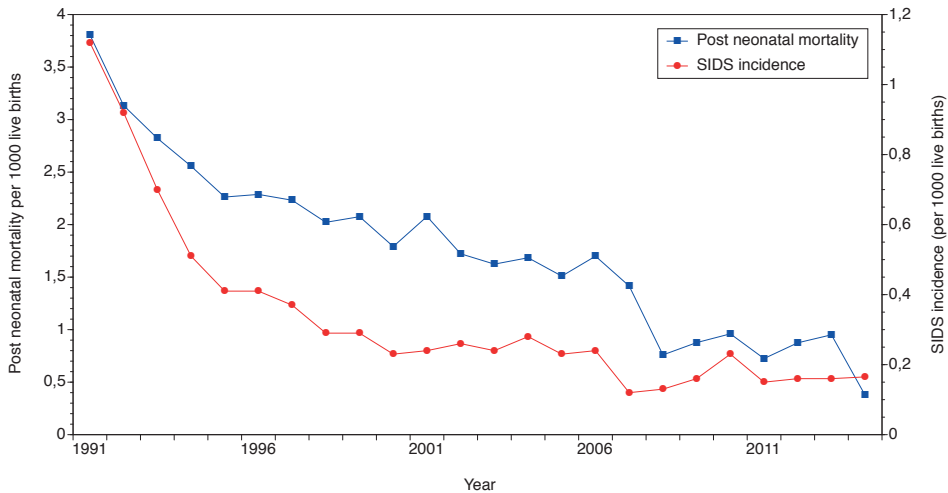
The incidence of SIDS in Sweden has remained low during the last decade and is stable at around 0.2 per 1000 live births, as can be seen in Figure 1.

An international comparison of SIDS incidence and post-neonatal mortality (death between 28 days and 11 months of life) was published in 2008, together with the year the preventive programmes were introduced in individual countries (Hauck et al. 2008). The Netherlands, Japan and Sweden reported the lowest SIDS incidence in 2005 and the lowest post-neonatal mortality rate was found in Sweden, Norway and Ireland. A recent study concluded that SIDS mortality followed trends in overall post-neonatal mortality (Goldstein et al. 2015).

It is an epidemiological problem that few countries have published reliable data on SIDS incidence and post-neonatal death and also that the data are often presented several years after the classification was made.

The question whether there is a diagnostic shift in the classification of SIDS and that other diagnoses are found according to more extensive examinations and autopsies has been discussed. This could indicate that a decrease in SIDS diagnosis would lead to an unchanged post-neonatal mortality, but we were

unable to see this in the Swedish statistics, where the incidence curve of SIDS and post-neonatal death is almost parallel (Fig 2).



**Figure 2. Post-neonatal mortality and SIDS incidence in Sweden in 1991-2014. Data from the National Board of Health and Welfare.**

## 1.4 Prevention

At the beginning of the 1970s there was a change in child-care practices, where babies were no longer put on their backs or side to sleep but in a prone position. Unfortunately, the consequence of the prone sleeping position in terms of an increase in the risk of SIDS was not understood until the second half of the 1980s (Davies 1985, Beal 1988, Engelberts et al. 1990).

The breakthrough in reducing SIDS came around 1990. Two pivotal case-control studies, one in the UK and the other in New Zealand, convincingly demonstrated that prone sleeping increased the risk of SIDS (Fleming et al. 1990, Mitchell et al. 1991). This insight rapidly spread throughout the western world and parents started to place their babies on their backs to sleep. Early in 1992, the National Board of Health and Welfare in Sweden issued

advice against prone sleeping for infants (Socialstyrelsen 1992). This resulted in a rapid decline in the incidence of SIDS (Fig 1).

Maternal smoking during pregnancy was shown to be another important risk factor for SIDS (Steele et al. 1966, Rintahaka et al. 1986, Mitchell et al. 1991, Mitchell et al. 1993a, Blair et al. 1996, Alm et al. 1998). The welcome reduction in smoking habits in Sweden especially during pregnancy in the last two decades has definitely contributed to the continuing reduction in the incidence of SIDS even if prone sleeping is rare.

The national guidelines for preventing SIDS in Sweden have been successful and today SIDS is uncommon in Sweden. The number of SIDS cases has decreased from 146 cases in 1990 to around 20 cases a year during the last decade. This means that the incidence has gone down from 1.2 to 0.2 infants per 1000 live births (Fig 1).

Since 1992, the National Board of Health and Welfare has provided advice to reduce the risk of SIDS and the first major revision was made in 2006. A major systematic review in 2013 led to new recommendations (Socialstyrelsen 2013, Wennergren 2014). A few months later, the National Board of Health and Welfare supplemented the advice with a comprehensive publication on SIDS called *Reducing the risk of cot death – a guide for healthcare professionals* (Socialstyrelsen 2014). The updated Swedish advice on reducing the risk of SIDS can be seen in Table 1 (Wennergren et al. 2015).

**The new advice from the Swedish National Board of Health and Welfare on reducing the risk of SIDS:**

- **The infant should sleep on its back.**
- **Smoking and nicotine should be avoided.**
- **The infant's face should be kept free, overheating should be avoided, and movement should not be restrained.**
- **The safest place to sleep for an infant under three months is in its own cot.**
- **Mothers should breastfeed if possible.**
- **A pacifier (dummy) can be used when the infant is going to sleep.**

**Table 1. Advice from the Swedish National Board of Health and Welfare on reducing the risk of SIDS, presented in December 2013.**

## 1.5 Gender perspectives

It is generally agreed that boys are overrepresented among cases of SIDS. In a Danish study comprising 356 children aged 0-2 years that died suddenly and unexpectedly, the ratio of males to females was 1.47 (Jacobsen et al. 1956). When the SIDS diagnosis was more defined and accepted, three different Swedish studies representing the 1970s and 1980s reported male/female ratios of between 1.34-1.5 (Norvenius 1987, Wennergren et al. 1987, Rammer 1991). A Dutch study representing the same time period also found a male/female ratio of 1.5 (l'Hoir et al. 1998b).

In a Swedish study representing all SIDS cases in Sweden in 1997-2005 the ratio of males to females was 1.39 (Paper II). The latest study in Sweden representing all SIDS and SUDI cases from 2005 to 2011 concludes that there is still an over-representation of boys in both the SIDS group and the SUDI group (Paper IV) but no significant differences between the groups. In a large British case-control study consisting of 325 cases of SIDS and 72 explained SUDI the ratio for male gender in SIDS was OR 1.66 (95% CI 1.26-2.18) and for explained SUDI 1.57 (95% CI 0.86-2.88) (Leach et al. 1999). A German study reported an over-representation of boys (60.1%) in the SIDS group, but, contrary to other results it did not find this in the explained SUDI group (Vennemann et al. 2007).

## 1.6 Socio-economic characteristics

The fact that infant deaths are over-represented in the lower social classes was reported back in 1892 (Templeton 1892). In the Scandinavian countries, several studies have shown that unexpected death in infancy is more common in socially disadvantaged families (Jacobsen et al. 1956, Biering-Sørensen et al. 1979, Rintahaka et al. 1986, Norvenius 1987).

In the 1990s, studies from the USA confirmed the relationship between social factors and SIDS (Malloy et al. 1995, Taylor et al. 1996). This was also the case in Scandinavia (Arntzen et al. 1995, Daltveit et al. 1998) and in New Zealand (Ford et al. 1995).

A case-control study in Germany found that it was more common among the controls for the infant to be placed prone in the low socio-economic group (calculated by using school education, present work position, and income) compared with middle and upper groups (Vennemann et al. 2009). This study showed an association between SIDS and lower socio-economic status, OR 3.00 (95% CI 1.35-6.69).

A case-control study from the UK comprising 325 cases of SIDS and 1588 matched control infants showed that the socio-economic factor of unemployment (lone parent or both parents) was present in half the SIDS families (49%) compared with fewer than a fifth of control families (Leach et al. 1999).

Attendance at prenatal care could be a socio-economic proxy. Studies have shown that case mothers made their first prenatal visit later than control mothers (Steele et al. 1966) and that they have also been found to make fewer prenatal visits than controls (Jørgensen et al. 1979, Rintahaka et al. 1986).

## 1.7 Other characteristics

### 1.7.1 Maternal age and parity

Young mothers have been shown to be overrepresented among SIDS cases in several studies. A study from Canada found that mothers of cases were younger at the time of marriage and younger at the time of first pregnancy and delivery (Steele et al. 1966). This has since been confirmed in studies from Northern Ireland (Frogatt et al. 1971), Denmark (Jørgensen et al. 1979), the USA (Lewak et al. 1979), Finland (Rintahaka et al. 1986), Sweden (Norvenius 1987) and the Netherlands (l'Hoir et al. 1998).

A German study (Vennemann et al. 2005) showed that maternal age at delivery of < 20 years was a significant risk factor, OR 18.71 (95% CI 6.00-58.32). In our material studying SIDS cases 1997-2005 in Sweden (Paper II), we found young mother (<19 years) was a significant risk factor, OR 5.64 (95% CI 2.79-11.40).

The reason why young mothers are over-represented could perhaps be socio-economic background especially educational level and poorer adherence to advice for preventing SIDS. As mentioned before, it is more common for young mothers not to obtain regular prenatal care in the same way as older ones and there is epidemiological evidence that there is a link between prenatal care and the risk of SIDS (Kraus et al. 1989, Stewart et al. 1995, Paris et al. 2001).

High parity as a risk factor for SIDS has been studied in several studies and a relationship has been shown in most. In Sweden a study from the 1970s found that sudden infant death was more common among infants with siblings (Peterson et al. 1975). In Denmark, Jørgensen (Jørgensen et al. 1979) also found this relationship as did Malloy in the USA (Malloy et al. 1995).



In the New Zealand study (Mitchell et al. 1991), the OR was highest for the third-born, but, in our material during a low incidence of SIDS we were able to see an almost linear increase up to four or more pregnancies in the multivariate analysis (Paper II).

Multiple births were regarded as a risk factor for SIDS in several studies before the campaign to promote supine sleeping position (Rintahaka et al, 1986, Norvenius 1987). In our study of SIDS cases and controls during low incidence we were unable to find any significance for multiple birth in the multivariate model (Paper II).

### **1.7.2 Prematurity and small for gestational age**

The fact that prematurity or low birth weight can be identified as SIDS characteristics has long been known (Frogatt et al. 1968, Wennergren et al, 1987, Øyen et al. 1995, Schellscheidt et al. 1997). Low birth weight can be a consequence of prematurity, but it is also caused by intrauterine growth retardation (Kraus et al. 1989, Buck et al. 1989). Smoking during pregnancy is a well-known and well-studied risk factor for intrauterine growth retardation (Øyen et al. 1995, Cooke 1998).

In the German GeSID study, birth weight of less than 1500 g was a significant risk factor adjusted for smoking and other factors with an aOR of 10.67 (95% CI 2.10-54.17) but not gestational age of less than 30 weeks (Vennemann et al. 2005). In our material we also found that birth weight and gestational age, as well as small for gestational age (SGA) were significant in a univariate model but in a multivariate model, SGA was no longer significant (Paper II).

### **1.7.3 Age**

The age at which sudden infant death occurs was studied before the definition of SIDS was established. In 1892, the first scientific study comprising 258 infants was presented and it concluded that 76% had died before three months and 95% within six months (Templeman 1892). The fact that unexpected infant death has a peak incidence between one and six months has been reported from many countries, such as Denmark (Jacobsen et al. 1956), the UK (Emery 1959, Carpenter et al. 1965), Canada (Steele et al. 1966), the USA (Bergman et al. 1972) and Sweden (Norvenius 1987, Rammer 1991).

After the risk-reducing campaign was set up in Sweden, we were able to show that the median age of SIDS had decreased to 64 days during the time

period 1992-2005 (Paper II) and that it is still 64 days in our study in 2005-2011 (Paper IV). The average age of the explained SUDI infants was higher in a study from the UK (Leach et al. 1999) but showed no significance in another European study (Vennemann et al. 2007).

### **1.7.4 Seasonality and geographical variation**

Seasonality, with a higher incidence during the winter, has been a characteristic of SIDS that has been reported in many studies (Norvenius 1987, Wennergren et al. 1987, Douglas et al. 1996, Chang et al. 2008). The question of whether the explanation is due to the fact that infections, especially respiratory tract infections, are much more common during the winter months has been discussed.

After the intervention campaigns had been set up, the seasonal peak appeared to have disappeared (Mitchell 1997, l'Hoir et al. 1998a, Alm et al. 2001, Malloy et al. 2004). One suggested explanation of why this seasonal variation appears to disappear in low incidence periods is that factors such as upper-tract infections and over heating from warm clothes can be modified by the supine sleeping position (Paper II).

In Sweden, as well as in New Zealand, studies showed that SIDS were more common in the colder regions of each country when the SIDS incidence was rising (Norvenius et al. 1993, Mitchell et al. 1994). After the risk-reducing campaign started in New Zealand, there was a significantly greater decline in incidence on the South Island (colder region) than on the North Island (Mitchell 1997). The same phenomenon is described in Sweden where we were no longer able to find significant geographical variations (Paper II). As mentioned in parallel with seasonality, this indicates that the new advice on not sleeping prone and avoiding overheating could be an explanation of this outcome.

### **1.7.5 Day of the week**

The fact that SIDS is more common at weekends has been described in several studies (Emery 1959, Rintahaka et al. 1986, Norvenius 1987, Mitchell et al. 1988). Explanations offered to account for the weekend effect on SIDS have included restricted access to medical care over the weekend (Murphy et al. 1986), and differences between the baby's routines during the week and over the weekend (Kaada et al. 1990). Alcohol consumption is known to be higher at weekends and the combination of alcohol, bed sharing and new sleeping environment can considerably increase the risk of SIDS (Blair et al. 2014).

In an epidemiological study analysing all SIDS cases in the United States in 1989-1991, no over-representation of deaths at weekends compared with Monday to Friday was found (Spiers et al. 1999). When the authors split the file on years of education as a socio-economic marker they found significant differences in that SIDS was more common at weekends among mothers with less education. The authors discussed whether this was due to the fact that known risk factors, such as smoking and bed sharing, are more common in the less well educated group.

In our Swedish material investigating SIDS cases in 1997-2005, we were still able to conclude that the weekends were over-represented, in line with earlier studies (Paper II).

### **1.7.6 Immunisation**

Almost all children are vaccinated according to national vaccination programmes and it has been questioned whether an increased risk of SIDS is associated with vaccinations. It is easy to understand this worry, as the peak incidence of SIDS is in the same time period as the first vaccination is often administered. Some studies have indicated an association (Torch 1982, Baraff et al. 1983) but four case-control were unable to find an association (Taylor et al. 1982, Hoffman et al. 1987, Griffin et al. 1988, Flahault et al. 1988). Two studies suggested a temporal relationship but only in a specific subgroup analysis (Jonville et al. 1995, Walker et al. 1997).

Studies in New Zealand (Mitchell et al. 1995) found an increased risk if the infant was not immunised with an OR of 2.1 (95% CI 1.2-3.5) and also case-control studies in France (Jonville-Bera et al. 2001) and the United Kingdom (Fleming et al. 2001) also found that vaccines had a be protective effect on SIDS. It has been argued that this protective effect can be explained by confounding factors, such as maternal, birth, social and infant medical factors.

In a meta-analysis where confounding factors were considered, there was a multivariate summary OR for immunisations and SIDS of 0.54 (95% CI 0.39-0.76) indicating that the risk of SIDS is halved by immunisation (Vennemann et al. 2007). In conclusion, there is evidence that there is no causal relationship between immunisations and SIDS and that vaccinations may have a protective effect.

## 1.8 Environmental factors

### 1.8.1 Sleeping position

A large number of studies show that the back is the safest sleeping position for babies (Fleming et al. 1990, Mitchell et al. 1991, Ponsonby et al. 1995, Wennergren et al. 1997, Brooke et al. 1997). Being placed on the side involves a greater risk than being placed supine (Li et al. 2003, Vennemann et al. 2005). The side position as such does not appear to carry an increased risk of SIDS but is a less stable position (Skadberg et al. 1998). The increased risk occurs if the baby rolls into a prone position (Carpenter et al. 2004). If the baby is not used to sleeping prone, the risk is much higher if it falls over from the side position. In a case-control study the adjusted odds ratio (aOR) for unaccustomed prone sleeping was 45.4 (95% CI 23.4-87.9) (Carpenter et al. 2004).

#### Mechanisms

Why is there an increased risk of SIDS when the infant is placed prone to sleep? There is no definitive answer, but one explanation could be that the infant's respiration is obstructed when the face meets the mattress or soft bedding (Thompson et al. 2006). Another important physiological reason could be that the face is crucial for heat and temperature regulation. When the infant is placed prone the regulation is impaired and has less ability to emit heat (North et al. 1995, Tufnell et al. 1995). Another shown mechanism that can interact during sleep is that both full-term and premature babies appear to have less ability for an arousal reaction when placed prone (Horne et al. 2001, Horne et al 2002).

### 1.8.2 Smoking and nicotine

Several studies have shown that smoking during pregnancy increases the risk of SIDS (Steele et al. 1966, Mitchell et al. 1993a, Blair et al. 1996, Schellscheidt et al. 1997, Alm et al. 1998, Mitchell et al. 2006, Blair et al. 2009). The risk is dose dependent and increases exponentially (Alm et al. 1998). In a meta-analysis the odds ratio was 2.86 (95% CI 2.77-2.95) for smoking during pregnancy before the “back-to-sleep” campaign and 3.93 (95% CI 3.78-4.08) after the advice that a supine sleeping position is the safest (Mitchell et al. 2006). The authors conclude that about one third of SIDS cases could be avoided if there was no smoking during pregnancy.

There is also an interaction between sharing a bed and smoking during pregnancy, which considerably enhances the risk of SIDS (Carpenter et al. 2013). A Norwegian case-control study found that sharing a bed with a

smoking mother was associated with a 16-fold increase in the risk of SIDS (Stray-Pedersen et al. 2005). In Sweden, the use of snuff, as well as nicotine chewing gums, is not unusual among pregnant women and, due to the nicotine as the active substance, the national guidelines recommend avoiding all nicotine substances during pregnancy. Because of the dose-response relationship between smoking and the risk of SIDS, it is important, in the communication with smokers and other nicotine users, to emphasise the fact that the risk is lower if it is possible to reduce the use (Alm et al. 1998).

Infants that have been exposed to nicotine *in utero* have been shown to have fewer wake-up periods during REM sleep, indicating an impaired arousal ability (Horne et al. 2004, Richardson et al. 2009).

Another question is whether passive exposure to smoking increases the risk of SIDS, even if the child has not been exposed during pregnancy, but studies have not been able to answer this question. Experimental studies have shown that nicotine can affect respiration and circulation, indicating that it should be avoided (Edner et al. 2007, Cohen et al. 2010). A Swedish study has been able to demonstrate a relationship between maternal snuff use and cigarette smoking with neonatal apnoea (Gunnerbeck et al. 2011).

## Mechanisms

One mode of action appears to be that babies who have been exposed to smoking as foetuses appear to have impaired arousability (Horne et al. 2004, Richardson et al. 2009). Impaired arousal of this kind could explain why the risk of SIDS is greater in the babies of smoking mothers, when the mother and the baby sleep in the same bed (Carpenter et al. 2004, Carpenter et al. 2013). Animal models have studied how arterial oxygen receptors are affected when exposed to nicotine and discussed in the area of possible mechanisms related to SIDS (Holgert et al. 1995).

Maternal smoking also appears to affect the autonomic nervous control of cardiovascular function and blood pressure (Cohen et al. 2010). This impairs the baby's ability to maintain autonomic balance, *i.e.* homeostasis.

### 1.8.3 Alcohol and other drugs

It is an epidemiological challenge to investigate how different drugs affect the foetus and risk of death in infancy due to substance abuse, which often includes several substances in addition to smoking. A study from Denmark based on prospective data on maternal alcohol use found a significant relationship between maternal binge drinking and postneonatal infant mortality, including SIDS (Strandberg-Larsen et al. 2009). One study found

an association between SIDS and heavy alcohol consumption in the two days before the death (Alm et al. 1999).

The triad of smoking, alcohol and bed sharing increases the risk of SIDS exponentially and this has been shown in several studies (Blair et al. 1999, Fleming et al. 1996, Carpenter et al. 2004, James et al. 2003). A meta-analysis of five case-controls studies concludes that the risks associated with bed sharing are greatly increased when combined with parental smoking, maternal alcohol consumption and/or drug use (Carpenter et al. 2013). The same study showed that the use of any illegal drug including cannabis increases the risk of SIDS 11-fold, even when the baby shares a room but not a bed.

Confounding factors are even more difficult to compensate for when the mother is addicted to cocaine, but a meta-analysis that investigated an association between *in utero* cocaine exposure and SIDS found an increased risk of SIDS (Fares et al. 1997).

## **Mechanisms**

There is a higher risk of neglect if a parent or care-giver is drug dependent. If a person's consciousness is affected it is difficult to interpret the infant's signals and this is especially important in a bed sharing situation. It is not just the arousal of the infant that is important but also that of the parent!

There is a strong connection between having a drinking problem or other abuse, together with also being a smoker. The studies showing the risk of impaired arousal and effect on the autonomic nervous system when exposed to nicotine *in utero* is discussed above (Chapter 1.8.2)

### **1.8.4 Head covering and overheating**

If the infant's head is covered with bedding there is an increased risk of SIDS. This has been shown in a meta-analysis (Blair et al. 2008), as well as in a German case-control study (Schlaud et al. 2010). Several studies have shown an increased risk of SIDS if the baby becomes overheated with a thick and warm quilt or other bed clothing affecting the thermal regulation (Fleming et al. 1990, Ponsonby et al. 1992, Fleming et al. 1996, Williams et al. 1996, Vennemann et al. 2009).

Head covering during sleep is of particular concern and is not an uncommon finding when SIDS has occurred. In a systematic review, the pooled mean

prevalence of head covering among SIDS victims was 24.6% compared with 3.2% among control infants (Blair et al. 2008).

Overheating, a well-known risk factor for SIDS, is also discussed as a consequence of swaddling (van Gestel et al. 2002) and swaddling as a risk factor is described in 1.8.5.

## **Mechanisms**

Infants sleeping in a prone position run a higher risk of overheating than do supine-sleeping infants (Ponsonby et al. 1993). The convection of heat is better when the face is placed supine and the risk of the airways being obstructed is lower compared with prone sleeping.

If the infant's head is covered by bedding, a large pillow and so on, the respiration is affected and the baby re-breathes carbon dioxide, so that oxygen saturation falls, thereby increasing the risk of apnoea, which can lead to respiratory arrest and SIDS.

### **1.8.5 Swaddling**

Swaddling as an infant-care practice is a tradition that has been used in some form or other in many cultures since ancient times (Lipton et al. 1965). There has been a debate about whether swaddling or firm wrapping provides protection from SIDS, due to low SIDS incidence in populations where swaddling is common, or whether it is a risk factor (Beal et al. 1991, van Sleuwen et al. 2003).

One study showed that bedding firmly could reduce the risk of SIDS, but the authors concluded that it was probably an effect of a reduced risk of head covering or the inability of infants to roll into a prone position (Wilson et al. 1994). Another study showed that swaddling increased the risk of SIDS considerably, from three-fold to 12-fold, if the infant slept in a prone position, but the risk was unchanged if the infant slept in a supine/lateral position (Ponsonby et al. 1993). In a case-control study of SIDS performed in the UK, swaddling was significantly more common among SIDS cases than among age-matched controls (Blair et al. 2009).

It has also been suggested that swaddling could increase the risk of developmental hip dysplasia (Kutlu et al. 1992) and acute respiratory infections due to the restrictive effect on respiration (Yurdakok et al. 1990). Overheating, a well-known risk factor for SIDS, is also discussed as a consequence of swaddling (van Gestel et al. 2002).

The fact that swaddling can induce longer sleep periods and a more tranquil behavioural state is confirmed in several studies (van Sleuwen et al. 2006, Franco et al. 2005). In some countries, especially the Netherlands, this has led to swaddling becoming more popular, but as clinicians, we were not able to observe this trend in Sweden.

In a statement from the ISPID Physiology Working Group the recommendations are as follows.

- Parents should be aware of the potential risks of swaddling their infant, and particularly of the use of heavy materials for swaddling.
- Infants must never be placed prone (on their stomach) when swaddled.
- Current research suggests that it is safest to swaddle infants from birth and not to change infant-care practices by beginning to swaddle an infant at three months of age when the SIDS risk is greatest.
- Secondary care-givers should be made aware of their infants' usual sleeping environment and practices.

## **Mechanisms**

The findings of increased infant sleeping time when swaddled suggests that swaddling reduces the frequency of awakening compared with no swaddling. Since the hypothesis of SIDS pathogenesis involves an impaired ability to be aroused from sleep in response to a life-threatening respiratory or cardiovascular challenge, this could represent an increased risk. Studies have shown that infant swaddling minimises arousals from sleep, crying time, spontaneous startles and the progression to full arousal (van Sleuwen et al. 2006, Gerard et al. 2002). In contrast, other studies have shown that swaddled infants are more sensitive to auditory challenges and are aroused more easily in active sleep (Franco et al. 2005, Kahn et al. 1992).

Studies performed in Australia have examined both arousal responses to external stimuli and spontaneous arousal from sleep in infants who were routinely swaddled at home and those who were not (Richardsson et al. 2009). The infants were studied at the age of one month and three months; swaddled and unswaddled. The result was a decrease in total arousability when infants were swaddled, together with a reduction in the frequency and duration of cortical arousals. However, when the usual care practice of the infants was considered, swaddling had no effect on the arousability of infants



who routinely slept swaddled, but in the swaddling “beginners” a significant decrease in both total arousability and frequency was observed.

The combination of swaddling and prone position is regarded as a high-risk sleeping environment for SIDS (Ponsonby et al. 1993). The finding that the prone sleeping position is even more dangerous if a baby is not used to it (Mitchell et al. 1999), as well as swaddling when this is not the daily routine, is important in communication with parents.

The ISPID recommendations (above) comment on the fact that it is important not to introduce swaddling routines, as many mothers start to work when the infants are about three months old and secondary care-givers are introduced. The age of three months is in the period of peak incidence for SIDS and the authors therefore emphasise this in their advice.

In Sweden, it is unusual for secondary care-givers to be introduced before the baby turns one year, due to the generous Swedish parental leave.

### **1.8.6 Bed sharing**

The fact that bed sharing is a riskfactor for SIDS if the mother has smoked during pregnancy, consumed alcohol or other drugs, as well as with sleeping together on a sofa, has been scientifically acknowledged for a decade (Carpenter et al. 2004, Tappin et al. 2005, Blair et al. 2009). A great deal of interest has focused on the question of whether there is also a higher risk of SIDS generally in connection with bed sharing and this has resulted in several studies and meta-analyses. A Norwegian case-control study showed that bed sharing was a significant risk factor for SIDS in infants aged 0-2 months with an aOR of 5.3 (95% CI 1.3-22.0) but not for older infants (Stray-Pedersen et al. 2005). A meta-analysis of 11 studies that investigated the association of bed sharing and SIDS revealed a summary OR of 2.88 (95% CI 1.99-4.18) with bed sharing (Vennemann et al. 2011).

An extensive study based on individual data from a large number of case-control studies demonstrated that this also applies to breastfed infants and when the mother does not smoke, does not use alcohol or if other known risk factors are not present (Carpenter et al. 2013). The risk was highest for infants under three months, aOR 5.1 (95% CI 2.3-11.3). Including all cases of SIDS (n=1472) in this analysis and comparing them with the matched controls (n=4679) the aOR for bedsharing was 2.7 (95% CI 1.4-5.3). As expected this study also confirms the much higher risk of SIDS if smoking and/or the consumption of alcohol are present. The current advice in Sweden

(Table 1), presented in December 2013, is that the safest place for an infant under three months of age is to sleep in its own bed.

The fact that it is safer if the infant sleeps in the same room as the parents instead of sleeping in a separate room has been reported in different studies (Scragg et al. 1995, Carpenter et al. 2004, Tappin et al. 2005). Room sharing facilitates feeding, comforting and monitoring the infant. It also makes it easy to breastfeed in bed if wanted, but, when the infant starts to sleep, it is placed in its own bed. AAP concludes in its recommendation that room sharing without bed sharing, or having the infant sleep in the parents' room but on a separate sleep surface (crib or similar surface) close to the parents' bed is the safest (AAP 2011).

Another important issue is that the condition and construction of beds vary in terms of quality, size and softness, but beds are designed to match the adults' needs and comfort and not for infant safety. This means that the bed environment can be a hidden trap and exposes the infant to additional risks of accidental injury and death, such as suffocation, asphyxia, entrapment, falls and strangulations (Scheers et al. 2003, Ostfeld et al. 2006, Hayman et al. 2015, Scheers et al. 2015).

The risk of bed sharing in relation to SIDS is highest during the first months of life and, if the baby is born premature and/or with a low birth weight, the risk is even higher (Blair et al. 2006). When the baby turns three months there appears to be less evidence that bed sharing is a risk but these epidemiological findings are calculated at group level and do not represent a biological individual interface (Carpenter et al. 2013). The same study showed that, if the infant has been exposed to nicotine *in utero* the risk is higher, at least during the first half year of life.

The co-bedding of twins and other infants of multiple gestation is a common practice, both in a hospital setting and at home (Hutchison et al. 2010). It is important to take account of the fact that twins and higher order multiples are often born prematurely and with a low birth weight, putting them at an increased risk of SIDS (Malloy et al. 1995, Sowter et al. 1999). There is also greater potential for overheating and re-breathing while co-bedding and size discordance might increase the risk of accidental suffocation (Tomashek et al. 2007). Most co-bedded twins are placed on their sides rather than supine which increases the risk of falling over into a prone position (Hutchison et al. 2010). In hospital, twins and other multiple babies are often co-bedded and this might encourage parents to continue this practice at home (Tomashek et al. 2007). The recommendation from the AAP is to provide separate sleep

areas for these infants to reduce the risk of SIDS and accidental suffocation (AAP 2011).

One criticism of the advice not to bedshare during the first few months has been that it makes breastfeeding more difficult. It has been shown in one of our studies, that there is a positive association between bedsharing and breastfeeding (Paper III. 2011). This might also be interpreted as implying that there is interplay between breastfeeding and bed sharing, and that in reality breastfeeding promotes bed sharing and that bed sharing facilitates breastfeeding. In a case-control study, the authors concluded that the risk of SIDS while bed sharing was similar, regardless of breastfeeding status, which indicates that the benefits of breastfeeding do not outweigh the increased risk associated with bed sharing (Ruys et al. 2007).

Another criticism has been that the risks associated with bed sharing are linked to specific hazardous circumstances. In a recent analysis conducted in the UK, it was found that the risk associated with bed sharing was higher but not significant in the absence of hazards such as sharing a bed with a smoker or with a person who had consumed alcohol or sleeping together on a sofa (Blair et al. 2014). One reflection on this result is that it represents just one country and that there are cultural differences between the UK and Sweden in relation to alcohol consumption, smoking habits and the use of sofas. The SIDS incidence is also higher in the UK than in the Scandinavian countries and Germany, where other major studies have been conducted with other results. In Sweden, bed sharing was significantly higher in SIDS than in explained SUDI, OR 7.77 (95% CI 2.36-,25.57) in a study comprising 261 cases of sudden unexpected death in infancy in 2005-2011 (Paper IV. 2015).

There is no evidence from epidemiological studies that bed sharing should be protective effect on SIDS and accidental suffocation for any subgroups of the population. In Sweden, as in other countries, there are devices (for example, “babinest”) that are marketed to make bed sharing safe, but we have no studies to confirm this statement and it is still possible that a body limb, blanket or pillow could obstruct the infant’s head and airways. For ethical reasons it is not possible to perform randomised studies in this area and, as the outcome of SIDS is definite and catastrophic, we believe that no advice should be given if it is not evidence based.

## **Mechanisms**

The reason why bed sharing increases the risk of SIDS is not fully understood, but it is possible that the infant’s airways are obstructed by the

parent's body or limb. The head can also be covered by a blanket or pillow (Blair et al. 2008, Schlaud et al. 2010, Carpenter et al. 2013).

Another risk factor is if the infant is placed in a side position, which is not a stable position. In this position, the infant can be accidentally turned to the prone position by the adult, thereby considerably increasing the risk of SIDS, and even more if the baby is not used to a prone sleeping position (Skadberg et al. 1998, Carpenter et al. 2004)

Several studies have shown that bed sharing leads to a higher infant body temperature and thereby increases the risk of thermal stress (Williams et al. 1996, Vennemann et al. 2009). Another possibility is that the infant's small jaw can be pushed backwards so that the tongue closes the upper airway (McIntosh et al. 2009).

Moreover, if there is a connection between a change in sleep patterns and bed sharing, this could act as an external trigger and increase the risk of SIDS (Kahn et al. 2000). In a study comparing sleep characteristics in two-month-old infants, where the infants in one group slept on their own and the infants in the other group shared a bed, there were more reports of disturbed sleep among the infants that shared a bed (Kelmanson. 2010).

One possible additional explanation of why the risks associated with bed sharing are higher during the first few months is that the infant's immature motor skills and muscle strength make it difficult to escape potential threats, such as being trapped in a position when the airways are blocked (Vennemann et al. 2011).

### **1.8.7 Bedding**

Bedding is an important environmental factor to which little attention has sometimes been paid among all the other advice for preventing SIDS and other unexpected deaths. Many parents with good intentions want to make it extra comfortable by softening the surface with blankets and pillows. It is also not unusual for the parent who is sharing a bed with the infant to create barriers with pillows and blankets to prevent the infant from falling out of the bed or couch. However, the kind of soft bedding described above can increase the potential for suffocation and re-breathing (Chiodini et al. 1993, Kemp et al. 1995, Kemp et al. 1998, Patel et al. 2001, Kanatake et al. 2003, Sakai et al. 2008).

Sheepskins, quilts, pillows, comforters and other soft surfaces are hazardous when placed under the infant or left loose around the infant and can increase

the risk of SIDS as much as five-fold, independent of sleep position (Wilson et al. 1994, Markestad et al. 1995, Beal et al. 1995, Scheers et al. 1998, L'Hoir et al. 1998b, Hauck et al. 2003).

If the infant is placed prone with soft bedding, the risk of SIDS increases 21-fold (Hauck et al. 2003). It is possible to question whether deaths in which the infant is found covered with blankets, pillows and extra bedding should be diagnosed as SIDS or if accidental suffocation is the most relevant diagnosis (Kemp et al. 2000).

According to the American Academy of Pediatrics, the best way to organise safe bedding is for the infant to sleep on a firm surface without any soft or loose bedding. If a blanket is used, it should be thin and tucked under the mattress so as to avoid head or face covering (AAP 2011).

Bumper pads and similar products are frequently used in order to protect infants from injury. Initially, bumper pads were developed to prevent head entrapment between crib slats, but, due to newer standardisation, this should no longer be possible. When investigated, several deaths due to bumper pads have occurred (Thach et al. 2007). The authors found that deaths attributed to bumper pads were the result of three mechanisms – suffocation against soft, pillow-like bumper pads; entrapment between the mattress or crib and firm bumper pads; and strangulation from bumper pad ties. The same article also found that bumper pads only prevent minor injuries and another study of crib injuries concluded that the potential benefits of preventing minor injury with bumper pad use were far outweighed by the risk of serious injury, such as suffocation or strangulation (Yeh et al. 2011).

A recent study also reports an increase in infant deaths attributed to crib bumpers, although the recommendation from the AAP in 2011 were against the use of crib bumpers (Scheers et al. 2015). The authors claim that, despite the data, crib bumpers remain popular and are frequently used.

Wedges and other positioning devices to keep the infant in a side or supine position are not frequently used in Sweden, but they are available on the market. The potential risk of using devices of this kind is that they are frequently made of soft, compressible materials, which might increase the risk of suffocation. Another risk is that, if the baby is placed in the side position and slips out of the restraints and rolls over into a prone position, the risk of SIDS is increased.

Spending time in a car seat is not uncommon for many infants (Callahan et al. 1997). It goes without saying that a tested car seat placed backwards is the safest place for a baby when travelling by car. Because these and other sitting devices are practical and convenient, they are used more when travelling. However, a young infant has poor head control and often flexes its head while in a sitting position. Studies have shown that infants younger than one month of age might run an increased risk of upper airway obstruction and oxygen desaturation (Merchant et al. 2001, Bass et al. 2002). There have also been several reports of suffocation deaths resulting from car seats or other baby carriers overturning after being placed on a bed, mattress or sofa (Pollack-Nelson et al. 2000, Wickham et al. 2002, Desapriya et al. 2008, Parikh et al. 2010).

## **Mechanisms**

The common mechanism if a person's head is covered by a pillow, blanket or other bedding attributes is for his/her respiration to be affected due to re-breathing and desaturation. The pCO<sub>2</sub> rises and bradycardia, leading to respiratory and cardiac arrest, is the worst-case scenario.

Another possibility is that the infant's mouth and nose are obstructed against a bumper pad or other device or that the infant is trapped between the mattress and loose bedding, leading to suffocation. Strangulation from bumper pad ties or bedding devices is also a potential cause of death.

### **1.8.8 Breastfeeding**

The fact that breastfeeding is associated with a reduced risk of SIDS is concluded in two meta-analyses. In the first, the aOR was 0.64 (95% CI 0.51-0.81). It comprised six studies that met the criterion of "any breastfeeding" compared with "never breastfed" (Ip et al. 2009). In the other, the aOR was 0.55 (95% CI 0.44-0.69), (Hauck et al. 2011). There are always methodological and statistical problems because of the positive association between both breastfeeding and a high educational level and breastfeeding and better socio-economic status. However, the two above-mentioned meta-analyses were adjusted for known associations.

## **Mechanisms**

One explanation of why breastfeeding has a risk-reducing effect could be that the antibodies in the breast milk reduce the risk of virus infections, a factor that is often present in cases of SIDS (Helweg-Larsen et al. 1999). A systematic review, concluding that breastfeeding protects from infectious diseases during infancy, speaks in favour of this explanation (Duijts et al.

2009). It has recently been demonstrated that interleukin-1 B, which is produced during infection, induces the release of prostaglandin E2, which impairs respiration via receptors in the brainstem (Hofstetter et al. 2007, Siljehav et al. 2012).

Another possibility is that breastfed infants appear to have a lower threshold for arousal and that their sleep is less deep (Franco et al. 2000, Horne et al. 2004).

### **1.8.9 Pacifier**

Many studies have found that the use of a pacifier when the baby is going to sleep reduces the risk of SIDS (Mitchell et al. 1993b, Arnestad et al. 1997, Fleming et al. 1999, L'Hoir et al. 1999, Hauck et al. 2003, Carpenter et al. 2004, Hauck et al. 2005, Mitchell et al. 2006). A recent review of pacifier use and SIDS, from the Physiology and Epidemiology Working Groups of ISPID, supported the consistent evidence that pacifier use reduces the risk of SIDS (Horne et al. 2014). The authors of the ISPID review asked whether the association between the lack of a pacifier being used by the infant for the final sleep and SIDS could be a marker of something as yet unmeasured.

The size of the protective effect has been estimated in two meta-analyses as a reduction in SIDS incidence of about 50-60% if a pacifier is used (Hauck et al. 2005, Mitchell et al. 2006). Other studies have reported equivalent or even larger protective associations (Li et al. 2006, Vennemann et al. 2009).

To our knowledge, there is no study that indicates that a pacifier could be a risk factor for SIDS.

Much criticism has pointed to the possibility that a pacifier could affect breastfeeding negatively. Observational studies have found a correlation between pacifiers and reduced breastfeeding duration (Aarts et al. 1999, Scott et al. 2006). However, well-designed randomised clinical trials have found that pacifiers do not appear to cause shortened breastfeeding for term and preterm infants (Kramer et al. 2001, Collins et al. 2004). The link between a pacifier and a shortened duration of breastfeeding in observational studies probably reflects a number of complex factors, such as breastfeeding difficulty or intent to wean (O'Connor et al. 2009).

A meta-analysis of two randomised, controlled studies was unable to find any significant difference in the duration of breastfeeding between pacifier users and non-users (Jaafar et al. 2012). It could be that the pacifier merely satisfies the baby's need to suck, especially if the baby is not breastfed. The Swedish

preventive advice recommends starting with a pacifier after breastfeeding is established, if this is the parents' choice. Our conclusion is that both breastfeeding and use of a pacifier have a protective effect on SIDS (Alm et al. 2016)

It has also been observed that some dental malocclusions have been found more frequently among pacifier users than non-users, but, when studied, dentists found that it generally disappeared (Larsson 1986). A 1.2-to two-fold increase in the risk of otitis media associated with pacifier use has been shown, but this is a mainly a problem between two and three years of age and not in the time period when the risk of SIDS is the highest (Niemelä et al. 2000).

### **Mechanisms**

There is no widely accepted causal explanation why a pacifier reduces the risk of SIDS. One speculation is that the sucking activates muscles in the mouth and pharynx, thereby promoting the patency of the upper airways (Kahn et al. 2002). Another mechanism could be that the pacifier keeps the airway open mechanically (Tonkin et al. 2007). One theory is that the use of a pacifier modifies the infant's cardiac autonomic control during sleep (Franco et al. 2004).

It has also been suggested that the use of a pacifier increases the arousability from sleep (Franco et al. 2000), but subsequent studies were not able to confirm this finding (Hanzer et al. 2009, Odoi et al. 2014).

## **1.9 Plagiocephaly**

The use of a supine sleeping position has increased the incidence of acquired cranial asymmetry (van Vlimmeren et al. 2007, McKinney et al. 2009, Cavalier et al. 2011). The asymmetry falls into three main groups: plagiocephaly (skewed occipital flattening, fig.3), brachycephaly (symmetrical occipital flattening) and combined plagiocephaly-brachycephaly.





**Figure 3. Plagiocephaly (published with the parents' permission)**

The advice in Sweden for parents and the factual material for healthcare professionals focus on how to prevent the development of acquired cranial asymmetry. The most important factor to prevent plagiocephaly is that the position of the head should be varied already from birth (Peitsch et al. 2002). This emphasises the fact that advice should already be given on a maternity ward (Chizawsky et al. 2005). If the child has a favourite side, sometimes because of skewness with intrauterine causes and vaginal delivery, it should actively be placed on the other side (Nield et al. 2007).

The risk of acquiring skull asymmetry is also further reduced if the baby spends time awake in the prone position (Bialocerkowski et al. 2008).

There has been a debate about whether a pillow could have a preventive effect when the infant is placed supine to lower the risk of acquired skull asymmetry. One small study speaks in favour of this opinion, but further studies are needed to confirm this (Wilbrand et al. 2013).

## 1.10 Apparent life-threatening events

An apparent life-threatening event, ALTE, is when a child is found seemingly lifeless, without respiration, cyanotic, pale and hypotonic. This was formerly called near-SIDS or aborted SIDS. To help the infant to breathe again, it needs to be heavily stimulated and sometimes assisted ventilation is required.

After the event the child is often tired and sleepy but sometimes unaffected. In the majority of cases, this happens during sleep, but, in rare cases, it can happen when the child is awake (Kahn et al. 2004). Some studies claimed that the risk of SIDS is higher if the infant had previously had apnoeas or been cyanotic or pale during sleep (Kahn et al. 2004, Mitchell et al. 2001), but subsequent studies have not confirmed this association (Berkowitz 2012).

Life-threatening events are much more common than SIDS. One study from New Zealand reported 9.4 events per 1000 infants (Mitchell et al. 2001) compared with a SIDS incidence of 2.1 per 1000 live births in the same

country. A comprehensive medical investigation is vital after a life-threatening event because it can be the first sign of a disease affecting the heart, lungs, metabolism or neurological system (Berkowitz 2012). In about half these events, a medical reason or diagnosis is found and the remainder have an unclear origin.

In recent years, there have been several reports of ALTE affecting newborn babies on the maternity ward (Dageville et al. 2008, Andres et al. 2011, Poets et al. 2012, Pejovic et al. 2013). Many of the events have occurred immediately after birth during early breastfeeding attempts. When placed skin to skin, the newborn baby can have problems keeping its airways free. This has resulted in death by accidental suffocation (Paper IV). To avoid these accidents, it should be stressed that, when a newly born baby is placed skin to skin to promote breastfeeding, checks must be made to ensure that breathing is free. In the USA, the guidelines recommend a supine position already the first hours after delivery (AAP 2011).

## **1.11 Hypotheses of SIDS**

As a result of epidemiological research, the incidence of SIDS has been dramatically reduced. In spite of this, we still do not know the exact mechanism, or mechanisms that cause the deaths. Several hypotheses have been presented during the last few decades.

### **1.11.1 Apnoea**

For many years, the dominant hypothesis of SIDS was that the infant unexpectedly stopped breathing (apnoea), leading to asphyxia and asystole and that home apnoea monitors could be a strategy for preventing SIDS (Steinschneider et al. 1972). An experimental study registered cardiorespiratory events defined as apnoea and obstructive breathing recorded on home monitors and found that these events are quite common, even in healthy term infants. Extreme events were only common in preterm infants and their timing suggests that they are not likely to be the immediate precursors of SIDS (Ramanathan et al. 2001).

A meta-analysis strengthened this message and did not support the home monitoring of apnoea as a preventive strategy (Strehle et al. 2012). The conclusion is the result of group analyses and it does not exclude the possibility that certain infants could react in a sensitive way, leading to desaturation and asphyxia after apnoea and pulse fall. One problem with electronic monitoring is that it does not always detect obstructive apnoea.

There could be breathing movements, even if there is an obstruction in the upper airways and the child is not sufficiently breathing and saturated.

### **1.1.1.2 Imbalance in the autonomic system**

The autonomic nervous system is a control system that acts largely unconsciously and regulates bodily functions such as control of respiration, digestion, cardiac regulation, vasomotor activity and certain reflex actions such as coughing, sneezing, swallowing and vomiting. There are two branches in the autonomic nervous system: the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous system is regarded as the “fight or flight” system, and it is activated by stress and activates the muscles; the heart rate goes up and makes glucose available as energy.

The parasympathetic nervous system is a more slowly activated dampening system and the most important nerve is the vagus nerve (cranial nerve X) which reduces both heart and respiration rate. Experimental studies have shown that fetuses and newborn infants react in a special way according to stress, with less muscle activity, a reduction in heart rate and a decline in saturation. This is a physiological advantage if the umbilical cord is obstructed during labour or in the uterus to better cope with asphyxia. It has been suggested that infants could react in this way if stressed and that a heavy fall in heart frequency could lead to heart stoppage (Kaada 1986).

This hypothesis has not been verified, but other studies have shown that even exposure to passive smoking during pregnancy could alter the response in cardiovascular function when body position is changed (Cohen et al. 2010).

### **1.1.1.3 Arousal and auto-resuscitation**

SIDS occurs during sleep and it is therefore essential to study arousal mechanisms and the infant’s ability to react if there is an obstruction of the airways. The normal physiological reaction when there is an obstruction in the airways is that the saturation falls and pCO<sub>2</sub> increases. This leads to the activation of the sympathetic nervous system, with increased heart and respiration rate, and an increase in blood pressure. This is what we call an arousal reaction. Newborns react less to activate this protective system and a study conducted among 20000 infants showed that the arousal mechanisms were less prominent among infants that subsequently died of SIDS compared with the others (Kato et al. 2003). The infants that had been exposed to nicotine through maternal smoking in pregnancy were most affected.

### 1.11.4 Genetics and ethnicity

Twins have a doubled risk of SIDS, but there is no difference between monozygotic or heterozygotic twins, which implies that it is the environmental factors that are most important (Mitchell et al. 2010). It has also been shown that siblings run a higher risk, which can probably be attributed to sharing the same environmental risk factors both intrauterinely and postnatally (Beal et al. 1988).

There are differences in the incidence of SIDS associated with socio-economic status, education level, infrastructure for communicating health messages, cultural traditions relating to bed sharing, breastfeeding and sleeping position. In a study from the USA, the highest incidence of SIDS was found among Native Americans and Afro-Americans and the lowest among infants with parents originating from China and Japan, even when corrected for socio-economic factors (Hunt et al. 2004).

The CDC (Centers for Disease Control and Prevention) in the United States presented data on SUDI and ethnicity in 2010-2013 (CDC 2013). The death rates for American Indians/Alaska Natives were more than twice those of non-Hispanic white infants. The lowest death rate was found among Hispanic infants and Asian/Pacific Islander infants. In all subgroups, SIDS was the main cause of sudden unexpected deaths, representing about half the cases.

Our interpretation is that, with today's knowledge, there is no evidence that the explanation of these ethnic differences is not genetic but instead a proxy for socio-economic living conditions and existing cultural habits affecting risk factors for SIDS.

Genetic risk factors definitely play a role in explained SUDI in metabolic disease such as MCAD, medium-chain acyl-coenzyme A dehydrogenase deficiency (Weese-Mayer et al. 2007, Opdal et al. 2011). The prevalence of long-QT syndrome, a genetic condition increasing the risk of asystole, in SIDS has been studied and cases have been found with this diagnosis (Ackerman et al. 2001, Arnestad et al. 2007). It has been suggested that different genotypes, such as the interleukin-6-genotype (IL6-174GG), are associated with SIDS in a Caucasian Australian cohort (Moscovis et al. 2006), but this could not be found as a factor in a study from Norway (Opdal et al. 2007). The explanation of these contrary results could be only a few investigated SIDS cases and differences in the distribution of the IL6-174GG polymorphism in different ethnic groups.

Other mutations involving the development of the autonomic nervous system, immunological system and inborn errors of metabolism have been described in the discussion of causes of SIDS (Van Norstrand et al. 2010, Opdal et al. 2011, Goldwater 2011). According to the definition of SIDS, there should be no pathological findings from the autopsy (including genetic samples) and cases in which there is a positive genetic finding linked to a higher risk of sudden death should therefore be diagnosed as explained SUDI.

At the same time, it is possible that there could be a genetic predisposition for SIDS, representing a polygenic inheritance pattern leading to sudden death when combined with other risk factors. This predisposition (internal factor) at the vulnerable age and, for example, a prone sleeping position, or bed sharing (external factor), could affect the CNS and reduce the response to a critical event leading to SIDS.

### **1.11.5 Neurotransmitters**

Serotonin is the neurotransmitter that has attracted the most attention in the SIDS research field during the last decade. This substance is localised in the brainstem and is thought to be involved in the regulation of sleep. It is also involved in the control of respiration, blood pressure, body temperature, upper airways and arousability, all of which are factors that are discussed in relation to the background to SIDS (Richerson et al. 2004, Paterson et al. 2006).

Studies have shown low serotonin levels in several nuclei affecting sleep and respiratory control in SIDS deaths, especially among boys (Duncan et al. 2010, Paterson 2013, Rognum et al. 2014). An association with a promoter polymorphism of the serotonin transporter gene has also been seen in a study, but only for Afro-American infants (Weese-Mayer et al. 2003).

Acetylcholine has also been discussed, because it is an important neurotransmitter in the parasympathetic nervous system for communication with the vagus nerve. Acetylcholine affects the infant's ability to be aroused and it can be affected negatively by maternal smoking and nicotine exposure, which has been shown in experimental studies in the rat (Cohen et al. 2005).

### **1.11.6 Infections**

There has been a discussion about whether used mattresses increase the risk of SIDS. Used polyurethane foam cot mattresses were investigated and it was found that bacterial colonisation was greatly increased (Tappin et al. 2002).

*E. coli* was isolated from the dorsal region of the mattresses, significantly greater degree if the infant slept in the prone position (Sherburn et al. 2004).

Another study (Highet et al. 2014) focused on gut microflora in SIDS (n=52) comparing it with faecal samples from age-matched live infants (n=102). The results showed that the gut microbiome of SIDS babies differs from that of control babies. The major finding was that significantly more babies dying prone were colonised by *S. aureus* than babies dying in other positions (supine/side).

It is hypothesised that prone sleeping increases the risk of colonisation by *S. aureus* and *E. coli* or the induction of temperature-dependent toxins, such as the staphylococcal pyrogenic toxin, when the nasal temperature of infants is increased in the prone position (Molony et al. 1999, Harrison et al. 1999). Several studies reported an increased colonisation rate by toxigenic bacteria in the gut of babies who have died of SIDS compared with healthy living babies or babies who died of other causes (Bettelheim et al, 1990, Blackwell et al. 2001). The theory is that bacterial infection plays a role in the events triggering SIDS and leads to bacterial sepsis/toxaemia and hypoxaemia and eventually bradycastole followed by gasping (Poets et al. 1999).

Infection with *Helicobacter pylori* has been discussed as a trigger for sudden infant death. A study investigating *Helicobacter pylori* stool antigen revealed a significantly higher positive association with SIDS and SUDI compared with controls at the age of up to five months (Stray-Pedersen et al. 2008). The authors concluded that it is not possible to rule out whether the higher detection rate of the incidence of *Helicobacter pylori* in SIDS and deaths due to infections reflects lower hygienic standards or whether there is an unknown causal mechanism.

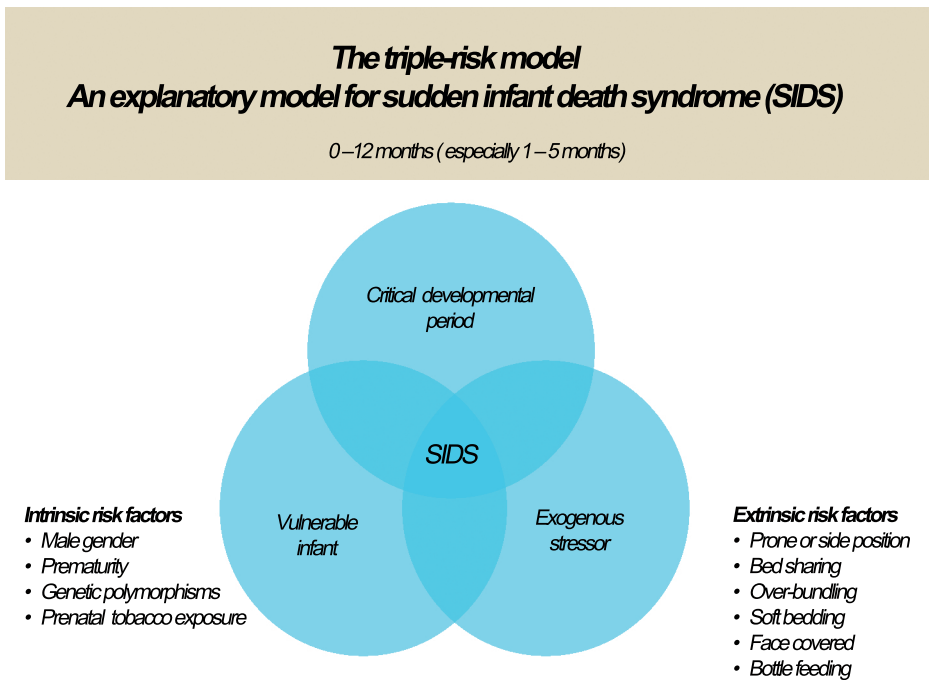
### **1.11.7 Toxic gases**

In the 1990s there was a hypothesis that there could be a link between toxic gases such as phosphorus, antimony or arsenic released from mattresses (Richardsson 1994). Two case-control studies were able to state, both pathologically (Howatson et al. 1995) and epidemiologically (Mitchell et al. 1995), that cot mattresses were not responsible for SIDS.

### **1.11.8 Triple risk model**

Today, the best explanation of SIDS pathogenesis appears to be offered by the triple risk model, originally proposed by Filiano and Kinney (Filiano et al. 1994). This hypothesis has recently been highlighted and developed in

other papers (Tractenberg et al. 2012, Bergman 2015). In this model, findings from epidemiological studies are brought together to form a plausible pathophysiological scenario. According to this model (Figure 4), interaction between different risk factors is needed to result in SIDS. The first issue is a critical developmental period, when there are several physiological changes in respiratory control and arousal. The second issue is a vulnerable child and the third an exogenous stressor (extrinsic risk factor). In a model of this kind, one hypothetical scenario could be a three-month-old boy with a mother that had smoked during pregnancy who is bedsharing and falls over from the side to a prone position with his face towards the mattress. Breathing is obstructed and oxygenation deteriorates, but the expected arousal does not occur, as nicotine exposure has led to a blunted arousal response. A vicious circle with apnoea, bradycardia and asystole is initiated.



**Figure 4. Triple risk model of SIDS pathogenesis. Modified from Filiano and Kinney 1994 and Trachtenberg et al 2012.**

## 1.12 Explained SUDI

When an infant dies suddenly and unexpectedly, we are unable to classify the cause of death before a review of the clinical history, a death scene investigation and an autopsy are performed. We use the term sudden unexpected death in infancy (SUDI), to describe any sudden and unexpected death, whether explained or unexplained, including SIDS, which occurs during the first year of life (AAP 2011). When studying all SUDI in Sweden in 2005-2011, we noted a lack of systematic reviews describing the causes of explained SUDI and comparing the risk factors for SIDS and explained SUDI in Sweden.

In Europe, two case-control studies from the UK and Germany have published data on SIDS and explained SUDI (Leach et al. 1999, Vennemann et al. 2007).

In the UK study, both the SIDS group (n=325) and the explained SUDI group (n=72) were characterised by the same infant, maternal and social factors. Compared with the matched controls (n=1588), the unemployment figures were much higher and 48% of these families received no wage income. In a multivariate analysis, three significant differences could be identified between SIDS and explained SUDI. The first was a different age distribution where explained SUDI peaked in the first two months and was then more uniform compared with SIDS. The second finding was that congenital anomalies (20%) were more common among explained deaths compared with SIDS (8%). This was not surprising given that 10% of explained SUDI were diagnosed due to congenital anomalies. The third result was that smoking was significantly more common in both groups compared with the controls, but that, among SIDS mothers, the proportion of smokers was significantly higher than among mothers of explained SUDI. Infections were the most common diagnosis among explained deaths, representing almost half the cases (46%), but the actual study does not describe cause of death in detail.

The German study analysed all sudden and unexpected deaths over three years (1998-2001) and matched every case (n=455) with three controls. The result showed a similarity in terms of risk factors for SIDS and SUDI, except for sleeping position and breastfeeding. Prone sleeping was a major risk factor for SIDS, aOR 7.16 (95% CI 3.85-13.31) but not for explained SUDI, aOR 1,71 (95% CI 0.25-11.57).

Not being breastfed in the first two weeks of life was a risk factor for SIDS, aOR 2.37 (95% CI 1.46-3.84), but not for explained SUDI, aOR 0,39 (95%



CI 0.08-1.83)). There were no significant differences regarding gender, seasonality or age at death. Maternal smoking did not differ between the two groups but was higher than expected and should be regarded as a risk factor for both SIDS and explained SUDI.

The causes of explained SUDI were classified into groups in the German study and severe bronchopneumonia (35%) and generalised infections (45%) dominated the causes of death. Malformations of the heart are not uncommon (8 %) and some cases of congenital errors of metabolism were found.

Both studies showed a similarity between the risk factors for SIDS and explained SUDI in general, which strengthens the need for an effective preventive approach in general and targeted information for parents at higher risk.

The importance of a death scene examination prior to post-mortem examination, as well as case reviews, is obvious in order accurately to determine cause of death, with 2.5-5% of cases in one study presenting as sudden unexpected death and being diagnosed as non-SIDS based on the death scene examination or reconstruction, and 14 % based on case review (Byard et al 1994, Byard et al 1997).

Abuse and neglect are a diagnostic challenge when it comes to identifying and also understanding possible causes of SUDI, especially for most of us paediatricians. We focus on identifying diseases and other possible explanations when a child has died unexpectedly. Unfortunately, however, child abuse exists as a cause of sudden unexpected death in infancy and must be identified. A death scene investigation, a review of the circumstances and other environmental factors related to the infant make it more possible to identify these cases and this requires effective collaboration between the paediatricians involved and forensic medicine.

A classification of explained SUDI based on data from paper IV is presented in table 2.

**Table 2. Causes of explained sudden unexpected death in infancy (SUDI)**

<b>Cause of death</b>	n (125)	%
<b>Lung/respiratory disease</b>		
Bronchopneumonia	14	
Pneumonia, bacterial	10	
Pneumonia, viral	7	
Malformations (lung fibrosis, tracheal)	2	
Bronchial obstruction (aspiration)	1	
Pneumonia UNS	1	
	<b>35</b>	<b>28.0</b>
<b>Heart disease</b>		
Congenital heart defect (VOC, cardiomyopathy)	17	
Ischaemic causes	3	
Infection (pericarditis, myocarditis)	2	
Cardiac insufficiency	1	
	<b>23</b>	<b>18.4</b>
<b>CNS</b>		
Anoxia	5	
Malformations	3	
Cerebral oedema	3	
Infection	2	
Unspecified brain disease	2	
Epilepsy	1	
Bleeding, intracerebral	1	
	<b>18</b>	<b>14.4</b>
<b>Miscellaneous</b>		
Perinatal complications	15	
Sepsis	9	
Perinatal anoxia	6	
Metabolic disorders	6	
Accidental suffocation	3	
Intestinal infections	3	
Trauma, violence	3	
Viral, generalised infection	2	
Unclear	2	
	<b>49</b>	<b>39.2</b>

### 1.12.1 Accidental suffocation

The question of whether some SIDS cases should be classified as accidental suffocation, which could lead to a diagnostic shift towards explained SUDI, has been discussed. A recent study from New Zealand has shown that accidental suffocation is not an uncommon cause of sudden unexpected infant death, particularly in a bed sharing situation (Hayman et al. 2015). A diagnosis of accidental suffocation appears to be more common when the examination includes a death scene investigation and clinical documentation and observations of the infant's environment, especially sleeping conditions and bedding arrangements (Arnestad et al. 2002, Scheers et al. 2015).

In Sweden, seven cases of early sudden unexpected death in infancy (ESUDI), defined as death occurring in newborns during the first hours of life, were first reported and analysed as much as three decades ago (Polberger et al. 1985). A recent review of the literature found 132 cases of ESUDI reported in the literature from 1985-2012 (Gnigler et al. 2013). The result was that first parity and unobserved early skin-to-skin contact appeared to be prime predictors of ESUDI. Other previously discussed risk factors, such as mode of delivery, birth weight, mother's age and body mass index were not regarded as significant in this study.

The mechanism explaining why this skin-to-skin situation is dangerous for some babies is not totally understood, but we know is that the ventilator response to hypoxic stressors changes within the first hours and days of life and a newborn's answer to hypoxia can be apnoea (Bissonnette 2000). This could explain why an obstruction can quickly lead to a death without other underlying risk factors.

Deaths due to this skin-to-skin situation are described in our material and in this case as in many other case reports, the prone position is described as a risk factor (paper IV. 2015). We believe and argue, in terms of safety and potential outcome, that there should be supervision from the other parent or health professionals during the first hours, especially during early skin-to-skin contact.

Two studies have reported the hypothesis that infants who die in a shared sleeping situation are different from those who die alone. One retrospective study demonstrated that the gender ratio of infants sleeping alone was 2:1 (males to females), which was quite different from the ratio of 1:1 of those sleeping with another person (Byard et al. 2012). The authors supported a theory that this disparity could be explained by some of the fatalities in

shared sleeping situations being due to suffocation and not to SIDS. In the other paper, two studies (performed in Denmark and Australia respectively) were undertaken and studied the B-amyloid precursor protein (B-APP) staining in the brain (Jensen et al. 2014). In both cohorts, from geographically quite separate areas, there was a significant increase in the amount of cerebral B-APP staining in those sleeping alone. As B-APP takes time to accumulate, this may mean that deaths while bed sharing occur at a faster rate than when an infant sleeps alone.

In the United States accidental suffocation and strangulation in bed mortality rates remained unchanged until the late 1990s. The rates started to increase, beginning in 1998, and reached the highest rate at 2.08 deaths per 10000 live births in 2013. These statistics from 2013 represent about 24% of all sudden unexpected death in the United States and SIDS represents about 45% (CDC 2013).

The mechanism of accidental suffocation is discussed in the chapters on head covering, swaddling, bed sharing and bedding (1.8.4-1.8.7), but violence and child abuse as a cause of suffocation must be mentioned. It is a diagnostic challenge for forensic examiners to identify suffocation by intentionally closing the mouth and nose. Findings, such as blood from the nose or mouth and intra-alveolar haemorrhages, are reported to be indicative of suffocation but are not specific and may also be found in SIDS and other causes of death (Meadow 1999, Hanzlick 2001).

As mentioned above, a careful death scene investigation and case review enhance the opportunity to identify crimes and neglect. A Norwegian study showed that cases determined as neglects and abuse had an age peak similar to that of pure SIDS and borderline SIDS cases (Arnestad et al. 2002).

## **1.13 Communication**

Really succeeding with communication is an art in itself it is crucial for the implementation of advice to prevent SIDS. It is also a huge challenge to meet parents who have lost their child in SIDS, both in the acute phase and when some time has passed.

### **1.13.1 Communicate preventive advices**

“Said but not listened, listened but not heard, heard but not understood, understood but not put in practice”. This quote from an unknown source describes the problem of compliance and the number of “layers” we have to

overcome before what we can say what has really happened. The Swedish health organisation, with free access for all pregnant women to maternal health care and for the parents and children to child health-care centres is a huge advantage. The confidence and adherence to visiting maternal health and child health facilities is very high and more than 99% of the targeted population attend the health programme. The children are monitored up to the age of six when they begin school when the school health system continues the health surveillance.

When describing the optimal communication on the prevention of SIDS in Sweden, the first step is the information directed at the pregnant woman and her partner about the risk factors for SIDS at the maternal health visits. In particular, the risk of smoking and the use of other nicotine drugs that increase the risk of SIDS should be emphasised and the information should be given both orally and in writing.

The second step is at the maternity ward where the national advice on how to reduce the risk of SIDS is presented and discussed before the parents and baby leave the hospital.

When the nurse from the child health-care centre offers a home visit in the first week after delivery, the parents are given information again in their home, together with a pamphlet from the National Board of Health and Welfare (Socialstyrelsen) with the six pieces of advice. The pamphlet is translated into 16 different languages (October 2015). Since infants are given regular check-ups at the child health-care centre, there are normally plenty of opportunities to discuss and give feedback about sleeping position, bed sharing, breastfeeding, smoking, the use of a pacifier and other sleeping environment arrangements.

During the last few years a comprehensive booklet, in which the parents can fill in different data about their child and which also contains the preventive advice has been available. In conclusion, the parents are informed orally at least three times by professional health workers and are also offered written information free of charge.

It is essential to have an open dialogue with the parents, meet them with respect and be humble when they have another opinion. One way to create more participation is to ask the parents what they know about SIDS and then add the information that is necessary. Sometimes, it is an advantage to divide information and discussions to achieve improved compliance. The language should be easy to understand, intelligible and adjusted to the receiver and an

interpreter is sometimes needed. Different cultures can have different ways of taking care of their children in terms of bed sharing and swaddling and it is important that all conversation is characterised by respect and that we have to accept other opinions and not exaggerate the risk when not all advice is accepted.

To encourage and educate the professionals and give the scientific background relating to the preventive advice the Swedish National Board of Health and Welfare published guidelines in 2014 (Socialstyrelsen 2014).

### **1.13.2 Communicating with bereaved parents**

In the acute phase when an infant has unexpectedly died, the parents are naturally shocked in every respect. Some react by distancing themselves and are unable to understand the tragedy, others may panic and feel guilty and some experience injustice and anger. There is no right or wrong in these different ways of tackling a tragedy, but the most important thing for health professionals is to show empathy, listen and stay close. Being there and having the time to listen and be present without beepers and other disturbing things is important.

After the acute phase, there is a need for all the questions that arise in the parents' mind to be addressed and it is important that a meeting with the doctor involved is planned as quickly as possible. It can be beneficial if other professionals involved also meet the parents and are prepared to consult psychological or psychiatric expertise if needed. The time for grief is not limited and the parents should have the opportunity to contact addressed people as long as they want. If this is not taken care of with compassion and an effective structure, there is a considerable risk of secondary stress disorders.

If the parents try to have a baby again, there can be a great deal of fear and anxiety both during pregnancy and after the baby is born. The demand for advice can be huge and it is a strength if they can meet a colleague with special knowledge in this field.

## **1.14 Routines when an infant dies unexpectedly in Sweden**

In Sweden during the last decade, about 35-40 infants have died unexpectedly every year. In approximately every second case, the diagnosis of SIDS is made and in the other cases a cause is found that can explain the

death (Paper IV). The legal system in Sweden states that, when a child dies unexpectedly, the police authority should be contacted urgently. It is the doctor involved at the emergency department who should contact the police (Swedish healths regulation, HSLF-FS 2015:15) and also issue a death certificate (Swedish law 1990:1144, 4 kap. 4 § BL).

The police should visit the place where the child was found and make an inspection. In the event of a suspected crime, a police investigation should be opened and a crime scene investigation should be performed with police specialised in forensics.

The police authority should always contact the forensic department (police law 1984:387) when a child has died unexpectedly and an extensive autopsy is the standard procedure.

The National Swedish Board of Forensic Medicine is an independent state department and is not a part of the Swedish health-care system. It works on behalf of the legal systems, primarily the police authority, but also for the prosecutors and judges.

At the emergency department a body investigation is made after resuscitation efforts had been performed at home, in the ambulance or in the emergency room. Blood, urine and tissue samples are collected, photographs are taken, and a medical history is documented. The child's sleeping position should be described, as well as other environmental factors such as if the infant was bed sharing, breastfed, swaddled, used a pacifier or if any special bed arrangements were made. Smoking and nicotine use in the family is documented and whether alcohol, medication or other drugs were consumed. All these important factors are difficult to ask questions about and it may be easier and more psychological to put these questions after the most acute phase.

The infant is transported to one of the six forensic departments that are located at the university hospitals and, before the autopsy, a computer tomography examination is usually performed.

After the extensive investigation of blood, bacteria, virology, genetics, radiology and the results of the autopsy, a classification is made. If there is no evidence of a reasonable cause that explains the death, the SIDS diagnosis is a fact. The documentation and clinical history are always an important tool for the forensic examiner, as if there is a death scene investigation.

After the forensic examiner has completed the investigation and classification of the death, the police and the paediatrician involved are contacted and receive the diagnosis and death report. The standard procedure is that the paediatrician meets the parents and informs them of the findings and diagnosis, but it is also possible for the parents to talk to and in rare cases also meet the forensic examiner.

When working with the Swedish National Board of Health and Welfare to revise the guidelines for preventing SIDS in 2012-2014, we became aware of some weaknesses in the above mentioned logistics when an infant died unexpectedly. Firstly, we found that a death scene inspection by the police is rarely made and documented. Secondly, the communication between the police authority and the paediatrician involved is often weak in both directions.

In our studies of sudden unexpected deaths in infancy in 2005-2011 (Paper IV), we also found that the documentation in the medical journals was very poor when it came to environmental factors and that important information on sleeping position, smoking, bed sharing, breastfeeding or pacifier use was frequently lacking.

Another area of improvement is the need for more dialogue and collaboration between the paediatrician involved and the responsible forensic examiner in order to find factors that could have interacted in the death of the infant. We argue that the forensic examiner should have all the medical history and environmental factors described before a diagnosis is made, but this is not always the case.

The Swedish National Board of Health and Welfare has initiated a project to create guidelines for better and more uniform routines when an infant dies suddenly and unexpected and to deal with the weaknesses mentioned above. The work is under way and includes collaboration with the National Board of Forensic Medicine and the Swedish Police Authority and it is planned to be finished in 2016.

When a child dies unexpectedly, the input of the bereaved parents is essential and there must be routines not just for the medical history and examinations but also for the way parents are treated. The way parents are included and their communication with the health-care system has been studied and the authors emphasise the importance of effective routines and empathy (Rudd et al. 2013, Garstang et al. 2014).



The parents need as much information as possible in the acute phase and they need to see and hold their dead child. For this reason, a calm and dignified place should be offered after the care in the emergency room is over. The parents should also be informed about what the eventual first findings or theories about why the infant died might be and that an autopsy is mandatory by law.

All practical issues relating to the death must be reported to the parents and psychological support should be offered before they return home. New appointments and/or homevisits should be agreed on. It is also very important to offer a long-term follow-up to check the well-being of the parents and they should know from whom and how they can get help if they need it.

The information that it usually takes quite a long time before a diagnosis is made should be given to the parents, together with the fact that this is due to the time needed to obtain all the results. They should have the opportunity to put questions to the paediatrician involved in between and he or she can have a dialogue with the forensic examiner and tell the parents about test results, even if the final diagnosis has not been determined. If the parents have another baby, it may also be advantageous to have contact with some professional who is familiar with the trauma of having lost a child and who can support the family.

## 2 AIMS

The overall aim of this thesis was to study environmental factors that could affect the risk of SIDS and with this knowledge, try still further to prevent SIDS deaths in Sweden in the future.

The specific aims of the thesis were:

To compare the current prevalence of risk factors for SIDS in Sweden with the situation a decade earlier and assess factors associated with prone sleeping (Paper I)

To examine how accepted the advice to prevent SIDS is among parents (Paper I)

To identify changes in the epidemiology of SIDS since 1995 (Paper II)

To examine bed sharing at six months of age and the factors that are associated with bed sharing (Paper III)

To investigate the environmental circumstances associated with SIDS by analysing data from all sudden unexpected deaths in infancy in Sweden from 2005 to 2011 (Paper IV)

To describe the cause of death in explained sudden unexpected deaths in infancy in Sweden 2005-2011 (Paper IV)

## **3 METHODS**

### **3.1 Paper I: SIDS risk factors and factors associated with prone sleeping in Sweden**

#### **Study design**

##### **Infants of Western Sweden**

Data were obtained from a prospective, longitudinal cohort study of children born in the region of western Sweden in 2003. The region has 1.5 million inhabitants, which is equal to one sixth of the Swedish population. It encompasses urban, rural and coastal areas and the largest city is Gothenburg, with 500,000 inhabitants. Of the total birth cohort of 16,682 infants, the families of half (8176 families) were randomly selected. An invitation to participate, together with a questionnaire to be filled in, was sent when the infant had reached the age of six months. The questionnaire was filled in by 5600 parents, i.e. the response rate was 68,5%.

##### **The Nordic Epidemiological SIDS Study**

Conducted between 1992 and 1995, this study (NordSIDS) aimed to update the epidemiology of SIDS in Scandinavia during this period. The study recruited 244 cases and 869 matched controls in Norway, Sweden and Denmark, of which 117 cases and 430 controls came from Sweden. The response rate was 83% among cases and 72% among controls. The mean age of the infants used as controls was 19 weeks.

##### **SIDS incidence**

Information on SIDS incidence was obtained from data from the National Board of Health and Welfare and forensic departments. In Sweden, all infants who die outside hospital undergo a forensic autopsy, due to legal regulations.

##### **Statistics**

Comparisons were carried out using the Epi Table option in Epi Info v. 6.0.4. Binary logistic regression was used to calculate odds ratios for factors associated with a prone sleeping position using the SPSS statistical package. The percentage of missing answers was 0.0-4.4% in the Nordic Study, and

0.4-4.0% in the Western Sweden Study, with the exception of when breastfeeding was stopped, where 12.3% of answers were missing. This is probably due to the fact that many mothers continue to breastfeed after the age of one year and were thus unable to state when breastfeeding stopped.

## **Ethical approval**

Ethics committees approved both studies. The Nordic study was approved in all participating countries. Infants of Western Sweden was approved by the Ethics Committee at the University of Gothenburg.

## **3.2 Paper II: Sudden infant death syndrome during low incidence in Sweden in 1997-2005**

### **Study design**

Between 1997-2005, 247 infants died with R95 as the assigned cause of death (according to ICD 10), i.e. sudden infant death. Diagnoses were obtained from the National Board of Health and Welfare and forensic departments in Sweden. Of these, 201 had no other underlying cause of death (underlying cause of death and first contributory cause R95), whereas 46 had other contributory causes or an underlying or first contributory cause which was not R95. The diagnosis of these 46 infants were re-examined by a paediatrician with long experience of SIDS research. After this evaluation, six of them were labelled as “probable non-SIDS” and 11 as “probable SIDS”. As the “probable non-SIDS” cases had conditions that were able to explain the death, and the “the probable SIDS” cases had a higher age of death and an overweight of female infants, both groups were excluded from the analysis. According to the definition of SIDS (Beckwith et al. 1970, Krous et al. 2004), six cases with an age of more than 365 days were excluded. As SIDS is rare in the perinatal period and other causes are more frequent, we also excluded the infants with an age below seven days at deaths (17 infants) to ensure that the remaining material consisted of as many true SIDS as possible. This resulted in a data set comprising 207 cases.

We randomly selected 11000 infants from the Swedish Medical Birth Register to serve as controls. Medical Birth Register data were collected up to 2005, as long as it was completed at the time of the study. Smoking has been registered in the MBR since 1983. The smoking habits of women during pregnancy are asked about at three different visits to prenatal health-care. The

validity of data on smoking was studied by the National Board of Health and Welfare in 2002 and, from 1993-1998, the smoking status was known in about 91-96% of woman in early pregnancy (Swedish National Board of Health and Welfare; Evaluation of the Swedish Medical Birth Register, 2002).

## **Statistics**

Odds ratios (ORs) were calculated by binary logistic regression, using the SPSS statistical software package. For the assessment of time trends in ORs for risk factors, linear regression and Pearson's R were used.

Comparisons of proportions were made using the chi-square test in the EpiInfo package, version 6.04 b. Pearson's R was calculated in Microsoft Excel 2008.

For the analysis of seasonality, we used the test designed by Freedman (any deviation from a uniform incidence) and Edwards (test for a simple harmonic curve with a trough six months after the peak) in the PEPI package (Gahlinger et al. 1995).

Small for gestational age (SGA) was defined as a birth weight below -2 standard deviations from the mean expected for the gestational age, as determined according to the current Swedish gestational age-growth curves (Marsal et al. 1996). This resulted in 2.9% of the controls being classified as SGA.

## **Ethical approval**

The study was approved by the Regional Board of Ethics in Gothenburg in 2008.

# **3.3 Paper III: Bed-sharing among six-month-old infants in western Sweden**

## **Study design**

Infants of Western Sweden is an ongoing study in the western Sweden region, which is described in Section 3.1.1. The purpose of the study was to collect early data on infant care and nutrition, medical history and socio-economic background to analyse the prevalence of risk factors for sudden infant death syndrome and asthma and allergic diseases. The age of six months was chosen as a convenient time to collect early exposure data and

socio-economic characteristics. The questionnaire was completed by 5654 parents, i.e. a response rate of 68,5%. The question asked on bed sharing was “Where does your baby usually sleep at night?”

## Statistics

In the statistical analysis, 2x2 tables with the chi-square test and binary logistic regression were used and statistical effects were estimated using odds ratios (OR) with 95% confidence intervals (CI). To avoid problems with mass significance, we only included variables that were significant with a p-value of <0.01 in the univariate analysis in the multivariate model. We conducted analyses of breastfeeding in the first week and at six months, separately and with models containing both variables. The differences were minor and did not make any difference to the outcome of the models. We therefore decided to keep both variables in the model. Maternal smoking, a known risk factor for SIDS and interacting with bed sharing, although significant (p=0.039), did not reach the cut-off level of 0.01 but was included in the model anyway.

Parental education did not show significance in the univariate analysis, but parental cohabitation did and was thus included as a marker of socio-economic status. When analysing correlations, we found significant correlations between parental cohabitation at birth and at six months, more than three nightly awakenings and other sleeping problems, as well as sleeping position at birth and at six months. We therefore decided to reduce the model and keep cohabitation at six months, nightly awakenings at six months and sleeping position at six months.

The final multivariate model therefore contained the following variables: parental cohabitation, housing, maternal alcohol after pregnancy, any formula in the first week, maternal smoking during pregnancy, usual position placed to sleep at six months, sucking problems first week, 3+ nightly awakenings at six months, pacifier use, vegetarian diet in family, AD vitamin supplementation, adherence to vaccination programme and breast-feeding at six months.

The SPSS v.17 statistical package was used for statistical calculations.

## Ethical approval

The study was approved by the Ethics Committee at the University of Gothenburg.

## **3.4 Paper IV: Bed sharing is more common in sudden infant death syndrome than in explained sudden unexpected deaths in infancy**

### **Study design**

According to Swedish law, all cases involving young people who die suddenly and unexpectedly must be reported to the police. A forensic autopsy is then performed at the Departments of the National Board of Forensic Medicine (Umeå, Uppsala, Stockholm, Linköping, Gothenburg, Lund). Although the diagnosis of SIDS requires a death scene investigation (Krous HF et al, Pediatrics 2004), this is very seldom carried out in Sweden, unless a crime is suspected. All infants in Sweden, aged 0-365 days, who underwent a forensic autopsy in 2005-2011 were included (n=261). The autopsies included histological examinations and toxicological analyses. Bacteriological and virological analyses were performed in most of the cases. The classification made by the forensic examiner was used as the diagnosis. Classification codes 798 A, C and X (ICD-9) and R95 (ICD-10) were defined as SIDS cases. In the explained SUDI cases, the cause of death was classified according to ICD-9.

Supplementary data were obtained from the Swedish Medical Birth Register and medical records were obtained from the hospitals for all cases. Three pediatricians reviewed the medical records and analysed the data.

SIDS cases and cases of explained SUDI were compared in terms of age at death, maternal age and parity, seasonality, sleeping position, breastfeeding, smoking, Apgar score, birthweight, prematurity, bed sharing and social factors, such as parental education and employment status. Due to sparse data in the medical records, especially relating to environmental factors, such as the use of pacifiers, maternal alcohol use and social factors, correct statistical comparisons between SIDS and explained deaths were not possible when it came to these factors.

### **Statistics**

In the statistical analysis, 2x2 tables with the chi-square test and binary logistic regression were used. Effects were estimated using odds ratios (OR) with 95% confidence intervals (CI). For comparisons of continuous variables, we used Student's t-test. Seasonal variations in SIDS and explained deaths

were evaluated with the Edwards' and Freedman's test (Gahlinger et al. 1995). All other statistical calculations were carried out with the SPSS version 22 package.

## **Ethical approval**

The study was approved by the Ethics Committee at the University of Gothenburg.



## 4 RESULTS AND DISCUSSION

### 4.1 Paper I

In this study, we compared the prevalence of risk factors for SIDS in a cohort (Children of Western Sweden) comprising 5600 healthy six-month-old Swedish infants born in 2003 compared with 430 healthy Swedish infants born between 1991-1995.

The most important risk factor for SIDS, prone sleeping, decreased from 31.8% to 5.6% during this period. Supine sleeping as the preferred sleeping position increased from 35.3% to 47.3%. Side or side/supine sleeping increased from 25.2% a decade earlier to 43.8%. There was a significant decrease in maternal smoking during pregnancy from 23.5% to 9.5%.

In a multivariate analysis, we found that the risk of prone sleeping increased if the mother was unemployed, OR 2.4, (95% CI 1.5-4.0), if she was a heavy smoker in the third trimester, OR 44.1, (95% CI 1.6-1199.6), and if the child was irritable OR 2.5 (95% CI 1.3-5.1). Prone sleeping was also more common if the child shared a bedroom with siblings, OR 2.6 (95% CI 1.0-6.6), or never used a pacifier, OR 3.2 (95% CI 1.9-5.4).

### Discussion

It is important to evaluate how advice is accepted among the targeted population, in this case the infants' parents. Successful prevention should include an important goal, which is very obvious and measurable according to SIDS incidence, such as outcome. It should also be cost effective and Sweden has a major advantage in that more than 99% of future parents visit the maternity health-care centres during the pregnancy. This is the place where they receive the first information and advice to reduce the risk of SIDS, which is also followed up on the maternity ward before going home.

The guidelines for Swedish child health-care centres, recommended that the nurse makes a home visit in the first week after birth. Generally, both parents are at home because the national social security system allows two weeks of leave after birth for the partner who does not have parental leave. This enhances the potential for compliance. On this visit, the parents are given information about SIDS and advice on how to reduce the risk. Parents also have the opportunity to ask questions in their own home, which can be more comfortable than at the outpatient clinic. The parents also receive a pamphlet

with the written recommendations from the Swedish National Board of Health and Welfare (Socialstyrelsen 2013).

During the infant's first six months, the parents and baby visit the child health-care centre several times for regular check-ups, immunisation and at the age of one-two months and at six months of age there is also physical examination. Attendance at the health programme is very high and more than 98% of the parents and infants visit the child health-care centres. The continuity of the nurse is generally good and this enhances the trust. However, communication is also in the mind of the receiver and it cannot be taken for granted that parents follow the advice and recommendations given, which is a reason for examining compliance in real life.

In this study, we can see that parents have complied with advice to prevent SIDS, especially not placing the infant in a prone position. Only one in twenty parents placed their baby in a supine position compared with a third 10 years earlier. Side or side/supine sleeping has increased, which is not in line with the recommendation. One explanation could be that the message to parents focused on "not prone" and that all other variants were perceived as acceptable. The risk of the side position is that it can be unstable and enable the child to fall over into a prone sleeping position, thereby increasing the risk of SIDS. The risk also increases if the infant is not a general "prone sleeper", according to several studies (Carpenter et al. 2004).

The finding, that the use of a prone sleeping position was associated with socio-economic proxies such as smoking and unemployment is interesting and offers an opportunity for the child health-care centres to target the information especially at parents in this situation. The fact that an irritable child is more frequently placed in a prone position can be explained by that prone sleeping, as well as the use of a pacifier, has advantages when it comes to sleep patterns.

Using a pacifier is not a risk factor for SIDS. On the contrary, it has been shown to be slightly protective (Hauck et al. 2006, Mitchell et al. 2006). The association between never using a pacifier and prone sleeping may be explained by the use of prone sleeping as another way to make the baby calm.

Sharing a bedroom with siblings can be a socio-economic variable, but it also indicates that the baby can be disturbed more easily and is therefore placed prone to sleep better. Another explanation could be that the change in preferred sleeping position is not as important if the parents have had several

children before who slept prone without complications and this lowers the motivation and adherence to the new advice.

The massive fall in smoking during pregnancy in a decade has made a major contribution to enhancing both mothers' and children's overall health. The figures are in line with the national statistics and among the lowest in the world. The risk reduction for SIDS is considerable when smoking decreases and the goal should therefore be that infants should not be exposed to smoking and nicotine *in utero* (Mitchell et al, 2006).

One strength of the study is the large cohort of infants where parents answered (n=5605), born in 2003 and the high response rate (68.5%). One limitation is the number of infants (n=430) born between 1991-1995 and selected from the NordSIDS study. This study also included children from Norway and Denmark, but they were excluded because of different national programmes for child health-care systems and guidelines for preventing SIDS. 1991 was the year in Sweden with the highest SIDS incidence (1.2 SIDS/1000 living births), but it was also the year after the discussion about a shift from prone to supine sleeping began and the behaviour started to change before the national guidelines were established in 1994. Back in 1992, the National Board of Health and Welfare in Sweden had commented on the findings from New Zealand that prone sleeping should be abandoned and this influenced the habits in some way. There is therefore a difference in the statistics on sleeping position in 1991-1995, with a higher percentage of prone sleeping in infants born in 1991, when no advice was published, compared with 1995, when the national campaign had begun.

## 4.2 Paper II

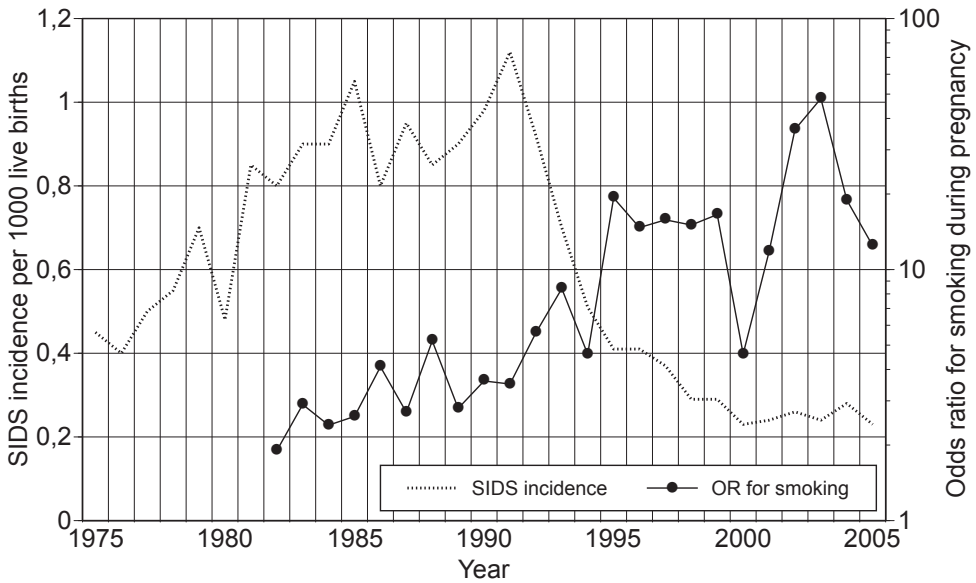
In this study, we attempted to identify changes in the epidemiology of SIDS from the NordSIDS study that ended in 1995 and the low incidence period in Sweden between 1997 and 2005.

The trend for the incidence of SIDS and post-neonatal mortality has decreased significantly after the advice on how to prevent SIDS was established in 1992-1995 and this was followed by a less steep decrease until 2000. Since then, during the studied period until 2007, the incidence curve was almost flat, with an incidence of approximately 0.23-0.28/1000 live births.

As shown before in the NordSIDS study, we found that SIDS cases are still more common at the weekend (Saturday and Sunday). The percentage of cases was 34.8% compared with the expected 28%.

Earlier studies, when SIDS was more common, have shown that there was seasonality, with more SIDS cases during the autumn-winter months compared with spring-summer, but we were unable to demonstrate any seasonality in the 207 cases studied in 1997-2005.

Smoking during pregnancy, a well-studied and accepted risk factor for SIDS, has decreased continuously in the study period. Smoking fewer than 10 cigarettes/day has decreased from 14.5% to 6.2% and smoking more than 10 cigarettes a day from 5.5% to 2.1%. The OR for SIDS when smoking >10 cigarettes/day continued to increase from about 2 in 1982-1991 to more than 15 in 1995 and 1996, reaching still higher values, and was inversely associated with SIDS incidence ( $p=0.0003$ ).



**Figure 5. Odds ratio for smoking more than 10 cigarettes a day in early pregnancy (continuous line) and incidence of SIDS (dotted line) in Sweden in 1974-2005. Data on smoking from the Medical Birth Register of Sweden. (Paper II)**

The median age at death showed a significant decrease ( $p=0.0047$ ). Before the campaign and advice to put the baby in a supine position to sleep (1975-1991), the median age at death was 80 days and, in the period after the campaign (1992-2005), the median was 64 days.

In a multivariate model containing all the variables that were significant in the univariate model, we found that male gender, multiple birth and small for gestational age (SGA) were no longer significant risk factors. The variables that were still significant after multivariate analysis were smoking one to nine cigarettes a day during early pregnancy, OR 4.98 (95% CI 3.46-7.20), and this was even more significant if the mother smoked 10 or more cigarettes a day, OR 7.82 (95% CI 5.23,-11.69).

Parents not living together, OR 1.69 (95% CI 1.08-2.64), as well as low maternal age defined as 19 years or less, OR 5.64 (95% CI 2.79-11.40) and age 20-24 OR 2.12 (95% CI 1.37-3.27) were also significant.

Parity was shown to be significant for more than one child and the OR increased for every child and was seven times higher if parity was four or more, OR 7.12 (95% CI 4.13-12.29). Short gestational age defined as < 31 weeks was significant, OR 4.34 (95% CI 1.61-11.71) as well as defined as 32-37 weeks, OR 2.69 (95% CI 1.71-4.23).

## Discussion

We believe that the most important explanation for the initial steep decrease in the incidence of SIDS is the change in preferred sleeping position from prone to supine.

Another important risk factor is smoking among pregnant woman and during the studied period, an almost linear decrease in smoking during pregnancy was seen, which may have contributed to the reduction in SIDS. The break in the curve seen in 2000 is not correlated to the prevalence of smoking during pregnancy that shows a decrease during the whole studied period, but there could be other changes in epidemiology that play a role together with smoking.

A diagnostic shift or diagnostic transfer, in terms of the reduction in SIDS incidence being due to cases previously diagnosed as SIDS now being classified as explained deaths, could be one explanation. However, as can be seen from Fig. 2, the SIDS incidence and the post-neonatal mortality incidence are almost parallel. This speaks in favour of the notion that the decrease in SIDS is not correlated to another diagnostic classification. This

has been demonstrated in an earlier study in the Nordic countries in 1976-1994 (Wennergren et al. 1997)

Seasonal variation has been a frequently described characteristic of SIDS (Wakley et al. 1998, Chang et al. 2008) but we were unable to find it in this material. When the change in the preferred sleeping position to supine is established and the incidence is much lower, the seasonality appears to disappear (Alm et al. 2001). One explanation could be that the statistical power is too low in low incidence periods. We feel it is more likely that, regardless of the cause of the seasonal variation (infections, overheating by clothing, and so on), it can be modified by the supine sleeping position.

Socio-economic factors are known to exert a considerable influence on SIDS. In the material in this study, we lack data on educational level, income and unemployment, but we have information on smoking during pregnancy, age of the mother and if parents are living together. We found a significant effect of parents not living together with  $p=0.022$  in the multivariate analysis.

The higher percentage of SIDS cases at weekends is well documented (Mitchell et al. 1988, Alm et al. 2001) but has not been explained, even if a relationship with alcohol is suspected. In this material, we found that there were 25% more cases than expected on Saturdays and Sundays, which is about the same as in the previous Swedish study (Alm et al. 2001). This has also been reported in US material between 1995 and 1999 (Malloy et al. 2004), as well as in the Nordic countries such as Finland (Rintahaka et al. 1986) and Norway (Kaada et al. 1990). However, in a study from California that studied epidemiological changes in 1989-2004 it was found that SIDS was more frequent on weekdays than at weekends (Chang et al. 2008). An interaction with maternal education has been suggested (Spiers et al. 1999), but, as maternal education is not present in the MBR (Medical Birth Register), we were not able to test this hypothesis. However, after splitting the file on whether or not parents lived together at birth, we were not able to demonstrate any significant difference in the weekend/weekday ratio.

Smoking during pregnancy has decreased considerably during the studied period but the reduction of prone sleeping has decreased even more, which makes smoking a relatively more important risk factor. Approximately 6% of infants were still sleeping prone in 2003 in western Sweden and 9,5% of mothers smoked during pregnancy (Paper I).

The median age of death in SIDS has decreased compared with our earlier study including cases between 1973-1996 (Alm et al. 2001) from 80 days

before the campaign to a reduction in the risk to 64 days between 1992-2005. This finding speaks in favour of the hypothesis that infants under three to four months of age would benefit more from the change to a supine sleeping position than older infants, as they are unable to turn over spontaneously.

For preterm birth, the OR was 4,34 (1.61-11.71) for a gestational age below 31 weeks and 2,69 (1.71-4.23) for a gestational age between 32 and 37 weeks. This can be compared with the earlier finding of 3,5 (2.1-5.9) suggesting that the interaction with time has disappeared following the constant low incidence.

Male gender is still overrepresented in the univariate analysis with an odds ratio of 1.39 (95% CI 1.05-1.84) and males represent 59,4% of the cases. When comparing with other Swedish studies in terms of male/female ratio, this is in line with their figures and most of these studies present the univariate analysis and not the multivariate one (Norvenius 1987, Wennergren et al. 1987, Rammer 1991).

One limitation of the study is that the prone sleeping position is missing in all models, because official statistics do not contain this information. This could definitely affect the outcome of the models, but we have no reason to believe that there has been any substantial change in the prevalence of sleeping position. From the study describing a western Sweden population born in 2003, we can estimate the percentage of infants sleeping prone as about 6%.

## 4.3 Paper III

In this paper we examined bed sharing at six months of age and associated factors.

The study showed that as many as 19.8% of six-month-old infants slept in the parental bed. Only 12.4% slept alone in a separate bedroom, while 2.1% slept in a bedroom with other infants. A separate bed in the parental bedroom was used by two-thirds of the infants.

In the multivariate model, variables significantly associated with bed sharing at six months were parents not living together at six months, OR 2.04 (95% CI 1.19-3.51), any formula first week, OR 0.70 (95% CI 0.54-0.90), prone sleeping position, OR 0.43 (95% CI 0.24-0.76), varying side/back, OR 1.58 (95 % CI 1.29-1.94), and varying side/prone sleeping, OR 1.72 (95% CI 1.03-2.85). Other significant variables in this multivariate model were three or more awakenings per night at six months, OR 2.70 (95% CI 2.20-3.32),

never pacifier, OR 1.40 (95% CI 1.14-1.73), and breastfeeding at six months, OR 1.94 (95% CI 1.56-2.41).

## Discussion

The main finding in this study is that as many as 20 % of Swedish six-month-old infants sleep in the same bed as their parents, but at the same time, two-thirds sleep in a separate bed in the parents' bedroom. Factors independently associated with bed sharing at six months were parents not living together, formula-feeding first week, breastfeeding at six months, prone sleeping position, nightly awakenings and non-use of a pacifier.

The risk of SIDS associated with bed sharing is mainly confined to very young infants (Carpenter et al. 2004, Stray Pedersen et al. 2005, Tappin et al. 2005). It is possible that the practice may change as other factors (infant's sleeping or feeding patterns or changes in health and well-being) change. In an Irish study, the frequency of bed sharing among controls was unchanged between 10 and 52 weeks (McGarvey et al. 2006). However, in a Dutch study, the prevalence of bed sharing in a cohort was highest during the first two months (Ruys et al. 2007). This study speaks in favour of the hypothesis that bed sharing in the first months of life is probably no less than our finding of 19.8% at six months of age. The figure is also comparable to the NordSIDS study in 1992-1995 where 17.7% of the controls slept in the parental bed. In a US setting, 20.5% reported bed sharing always and 14.7% almost, which is fairly close to our data (Lahr et al. 2007). However, bed sharing and infant sleeping behaviour are complex and include different cultural traditions (Nelson et al. 2001).

Sleeping in the same bedroom as the parents in a separate bed has been shown to have a protective effect on SIDS (Carpenter et al. 2004, Scragg et al. 1996, Schluter et al. 2007). In this study, we confirm that this behaviour is common in Sweden with 65,7 % of six-month-old infants sleeping in a separate bed in the parents' bedroom.

The direction of the association between breastfeeding and bed sharing, OR 1.94 (95% CI 1.56-2.41) cannot be determined by epidemiological methods alone. Our interpretation, however, is that there is interplay between breastfeeding and bed sharing, and that in reality, breastfeeding promotes bed sharing, while bed sharing facilitates breastfeeding.



We found that prone sleeping was significantly less common when sharing a bed, which has also been found in some other studies (Richard et al. 1996) but not in others (Vennemann et al. 2009). One explanation of this could be that both bed sharing and prone sleeping can be used to soothe the baby and, if one is used, the other will not be necessary. As a result, fussy babies sleeping non-prone can, in some instances, be taken to bed to be soothed.

The finding that varying side/supine and side/prone was associated with bed sharing can be explained by the fact that changes in body position are more frequent while bed sharing. Another possibility is that parents are more aware of changes in the baby's body position when they sleep on the same surface. These findings suggest that risks associated with various sleep positions and changing sleep position may be different for bed sharers compared with non-bed sharers.

Several studies have shown that pacifier use has a protective effect on SIDS (Carpenter et al. 2004, Vennemann et al. 2009, Mitchell et al. 1993, Fleming et al. 1999, Hauck et al. 2005, Li et al. 2006). In this study, we found that 40.1% of the infants that shared the parentel bed used a pacifier every day, compared with 51.3% among non-bed sharers, OR 0.54 (95% CI 0.46-0.62). We hypothesise that both bed sharing and a pacifier can calm the infant, which could explain the inverse relationship between the two practices. It may also be that mothers who breastfeed and bed share tend to be more negative about using a pacifier.

We found that any bottle-feeding during the first week of life was negatively associated with bed sharing OR 0.70 (95% CI 0.54-0.90). It is well known that this association exists (Mosko et al. 1997, McKenna et al. 1997). The question of whether bed sharing promotes breastfeeding or early feeding difficulties result in bottle-feeding and thus reduce the need for bed sharing is the subject of debate. However, we believe that early bottle-feeding is rarely imposed on the baby without prior signals from it. On the contrary, it is mostly a practice that is introduced because there have been early feeding difficulties, regardless of whether they in turn are caused by maternal or infant related factors.

Infants that have several nightly awakenings, three times or more, bed shared significantly more often than others. The cause of this is unknown, but one explanation could be that they have a lowered arousal threshold, which has been suggested by other authors (Hunsley et al. 2002, McKenna et al. 2005). It is also possible that an infant with several nightly awakenings tend to be more often taken to the parental bed.

Bed sharing was more common if the parent was single when the infant was six months old. It seems natural that a single parent would take the infant to the parental bed more frequently than cohabitating parents if the infant wakes up several times.

The main strengths of the study are the large numbers of infants and the good response rate. We have compared the prevalence of smoking during pregnancy in our study (9.5%) with statistics from the National Swedish Board of Health and Welfare that show that 10% of all pregnant women in western Sweden and in Sweden as a whole smoked in 2003 (Smoking habits among pregnant women and parents of small infants, SoS 2004). Because smoking is associated with several disadvantageous factors, the consistency between national data on smoking percentage and the percentage that we have found indicates that the data from western Sweden are representative of the population.

One weakness of the study is that, because the primary goal of the study was to map a wide range of living conditions, we did not ask about bed sharing in detail. The question we asked was “Where does your baby usually sleep at night”. Furthermore, as the questionnaire was distributed at six months of age, we do not have data on infants aged one to three months, when the SIDS incidence is highest.

Furthermore, we compared statistics on gestational age, birth weight, maternal age and percentage of caesarean deliveries between the full birth cohort in Sweden 2003 and our study material. There were no significant differences, which suggests that our subjects are representative of the national Swedish cohort in 2003.

## 4.4 Paper IV

In this study we investigated the environmental circumstances associated with SIDS, by analysing data from all sudden unexpected deaths in infancy (SUDI) in Sweden from 2005 to 2011. The study also provides new information on the causes of explained infant deaths in Sweden.

Of the 261 infants that died unexpectedly during the studied period, 136 were defined as SIDS and 125 as explained SUDI. Age at death in SIDS cases was a median of 64 days compared with 79 days in explained deaths ( $p=0.79$ ).

The most prominent finding was a higher prevalence of bed sharing in SIDS than in explained deaths. In the medical records, where place of sleeping was

stated, 93,5% of SIDS cases involved bed sharing, compared with 65.1% of explained SUDI. This gave an OR of 7.77 (95% CI 2.36-25.57) for bed sharing.

Where data were available, 67% of SIDS cases were found prone. Ten SIDS cases were placed to sleep in the side position but were found dead in the prone position. No infant was placed in the side position and found dead on its back.

Maternal smoking was considerably higher in SIDS (35.7%) than in explained SUDI (23.6%). Breastfeeding was more common among the mothers of SIDS cases than among explained SUDI (78.9% versus 60.2%) and this gave an OR of 2.48 (95% CI 1.29-4.76). Preterm birth was more common among explained SUDI cases.

In a multivariate model containing the univariate significant variables of breastfeeding and preterm birth, bed sharing was still significant, OR 14.89, (95% CI 1.11-199.82), albeit with a wide confidence interval, due to small numbers.

We found no significant seasonal variations in SIDS and no significant difference between SIDS versus explained SUDI in terms of caesarean section, parity or maternal age.

## **Causes of explained SUDI**

Due to sparse documentation in medical records, there were not enough data to analyse the use of pacifiers, the use of alcohol and social background. The records did show that 14 infants with SIDS and 11 infants with explained SUDI were found dead in places such as sofas, armchairs and child car seats during the studied period.

To describe the causes of explained SUDI, we studied all the forensic reports and diagnoses made by the forensic examiner. Most cases were classified by ICD-9, but in nine cases ICD-10 was used and recoded by us as ICD-9. The most common cause of death in explained SUDI was infectious diseases affecting the respiratory system (27.2%), mostly bronchopneumonia or bacterial pneumonia. The second most common cause (16%) was other infectious diseases including septicaemia, bacterial meningitis and severe viral disease. Congenital anomalies were not uncommon as a cause of death (14.4%) and cardiac malformations, such as atrial septal defect, ventricular septal defects or transposition of the great vessels, dominated. Four cases of congenital anomalies of the nervous systems were also found. Conditions

originating in the perinatal period (8.8%), diseases of the nervous systems (8.8%) and diseases of the circulatory system (8.0%) represented other common causes of death in explained SUDI. Three deaths were due to accidental suffocation and strangulation in bed (E 913 in ICD-9 and W 75 in ICD-10).

As a complement to the classification of explained SUDI by ICD-9 codes in paper IV, Table 2 shows a classification based on pathology.

## Discussion

The main finding in this study was the high incidence of bed sharing in SIDS compared with explained SUDI. In medical records, where place of sleeping was mentioned, more than 90% of SIDS cases involved bed sharing compared with two-thirds of explained SUDI. This strengthens the notion that bed sharing is a significant risk factor for SIDS (Carpenter et al. 2013) and supports the Swedish guidelines from 2014 (Socialstyrelsen 2014). The guidelines state that the safest place for an infant of up to three months of age to sleep is in his or her own bed, in the same room as the parents.

Bed sharing should be avoided, regardless of the infant's age, if the mother is a smoker, has taken drugs or alcohol, or if the baby sleeps in a place other than the crib, usually a sofa (Blair et al. 2014, Carpenter et al. 2013, Blair et al. 2009, Tappin et al. 2005, Blair et al. 1996).

The reason why bed sharing increases the risk of SIDS is not totally understood, but it is possible that the infant's breathing is obstructed by the parent's body or that the head becomes covered by a blanket or a pillow (Carpenter et al. 2013, Schlaud et al. 2010, Blair et al. 2008). Several studies have also shown that bed sharing leads to a higher infant body temperature and thereby increases the risk of thermal stress (Williams et al. 1996, Vennemann et al. 2009).

Another possibility is that the small jaw of the infant can be pushed backwards so that the tongue closes the upper airway (McIntosh et al. 2009). Moreover, if there is a connection between a change in sleep patterns and bed sharing, this could act as an external trigger and increase the risk of SIDS (Kahn et al. 2000). In a study comparing sleep characteristics in two-month-old infants, where the infants in one group slept on their own and the infants in the other group were bed sharing, there were more reports of disturbed sleep among the infants that were bed sharing (Kelmanson et al. 2010).

Prone sleeping is still common in SIDS, despite the recommendation that the supine sleeping position is the safest. Where data were available, two-thirds of SIDS cases were found prone. This can be compared with a Swedish study that showed that 5.6% of the population of six-month-old infants slept prone in 2004 (Paper I). Assuming that all infants with missing data on sleep position were sleeping supine, the prone sleepers would still represent a third of infants with a SIDS diagnosis.

If the infant is placed in the side position, there is a risk that it can roll over into a prone position, which increases the risk of SIDS, especially if the baby is not used to sleeping prone (Carpenter et al. 2004). We found some SIDS cases (n=10) were placed on the side but were found dead in the prone position, while no infant was placed on its side and found dead on its back. This emphasises the fact that the side position is not stable (Skadberg et al. 1998) and that the risk of SIDS is greatly increased when a child who is not used to the prone position rolls over (Carpenter et al. 2004).

Maternal smoking is a well-known environmental factor that makes it more difficult for the vulnerable child to respond when oxygen saturation falls (Kato et al. 2003). Both SIDS and explained deaths showed higher frequencies of maternal smoking than the comparable national Swedish figures (10%). The fact that maternal smoking is more common in SIDS than in SUDI has been reported before in two major case-control studies (Leach et al. 1999, Vennemann et al. 2007). The present data show that maternal smoking is a risk factor not only for SIDS but also for explained SUDI.

When it was documented, breastfeeding was less common in explained SUDI than in SIDS. This may reflect the fact that the infants with explained deaths had more frequently been ill, preterm or both and that the mother had therefore had difficulties initiating breastfeeding. However, breastfeeding in the general population was more frequent than in both SIDS and explained SUDI.

The median age at death in the SIDS cases in this study was the same as in our earlier Swedish study in 1997-2005, which was 64 days (Paper II). There was no statistically significant difference between SIDS cases and explained SUDI cases regarding age at death.

From the present study, we conclude that there are three highly important measures that need to be taken to further reduce the incidence of SIDS in Sweden. Firstly, avoid bed sharing until three months of age as matter of routine and extend this period if the parents have risk factors such as maternal

smoking. Secondly, always place infants to sleep supine and, thirdly, reduce maternal smoking still further. This provides an opportunity for targeted information in prenatal care and at child health-care centres.

This study also provides new information about the causes of explained infant deaths in Sweden, which has not been studied earlier. Infectious diseases, such as sepsis or localised infections in the lungs, brain and heart were the most common causes of explained SUDI. This is in line with case-control studies from the UK (Leach et al. 1999) and Germany (Vennemann et al. 2007). Malformations in the heart and the central nervous system, as well as perinatal events leading to asphyxia, are other important causes. Metabolic disorders involving lipid synthesis and trauma or violence, for example, are fairly uncommon and together represent less than every tenth death. Trauma and violence are preventable in most circumstances and there is a need for further, more detailed studies of this.

We found three infant deaths diagnosed as accidental suffocation or strangulation in bed (E913 in ICD-9 and W75 in ICD-10). One of the deaths occurred on the maternity ward shortly after birth and demonstrates that, when placed skin-to-skin, the newly born baby can have problems keeping its airway free. This may not be noticed by a mother who is exhausted by the delivery. It should therefore be stressed that, when a newly born baby is placed skin-to-skin, to initiate breastfeeding for example, checks must be made to ensure that breathing is free. The other two deaths illustrate the importance of a safe bedding environment.

A recent study from New Zealand (Hayman et al. 2015) has shown that accidental suffocation is not an uncommon cause of sudden unexpected infant death, particularly in a bed sharing situation. During sleep, accidental suffocation may occur due to the overlaying or wedging of the infant. The risk is most prominent during the first months of life. The reason why Sweden has so few diagnosed cases of accidental suffocation is probably the lack of routine death scene investigations in Sweden. We strongly believe that death scene investigation would improve the validity of the final diagnoses in cases of SUDI. Moreover, it would add to our knowledge of unsafe sleeping conditions and hopefully make it possible to prevent these deaths.

Finally, this study shows that Swedish paediatric medical records must be improved in SUDI cases. The authors, together with the Swedish National Board of Health and Welfare and the Swedish National Board of Forensic Medicine have initiated a project to promote this. In the future, we hope to be

able to study environmental factors on a yearly basis, which will give us the opportunity to notice changes and communicate this to the public, with the goal of reducing the incidence of SIDS still further.

## 5 GENERAL DISCUSSION

There have been few studies in Sweden during the last decade relating to changes in SIDS epidemiology. The question of infants' sleeping environment has not been well studied and, in the new era of the internet and social media, new ideas travel fast. New trends may change habits among parents when it comes to putting their baby to sleep, attitudes to breastfeeding, bed sharing, the use of a pacifier and other sleeping arrangements. This thesis attempts to contribute, add knowledge and inspire the more continuous surveillance of environmental factors, with the aim of discovering and identifying changes with the goal of further preventing SIDS in the future.

### 5.1 Methodological aspects

There are always limitations when it comes to find data to describing a large population. In this research field, the routines for the way a baby is placed to sleep, if the parents and infant share the same bed and other sleep arrangements are mostly unknown. The Swedish Medical Birth Register contains reliable data on smoking during pregnancy, Apgar score, gestational age, birth weight and birth height among other things.

Breastfeeding, vaccinations, maternal or paternal smoking during the first year of life can also be found in national data, albeit only aggregated. However, sleeping arrangements are not registered. In the National Board of Health and Welfare's Cause of Death Register, it is possible to study weekday incidence and seasonality, as well as geographical differences in terms of deaths in infancy.

To collect information about sleeping conditions, such as bed sharing, the use of a pacifier and sleeping position we have to approach the parents with questionnaires and it is important that both the response rate and the validity of the answers are good and that the questionnaire is representative of the population.

In our "Infants of western Sweden study" (Papers I, III) we obtained a response rate of 68.5% (approximately 6000 answers). We compared the answers relating to smoking with the national figures as a proxy for representativeness. We concluded that the differences were small, although there were slightly fewer smokers in the study. This indicates that there might



be an over-representation of families with higher education, as we know that there is an association between less smoking and higher educational level.

In Paper III, we made a comparison between the incidence of SIDS between 1997-2005 and an earlier Scandinavian study (NordSIDS). We used 11000 randomly selected controls from the MBR as controls for the 207 defined SIDS cases during the studied period. As mentioned earlier there are no data on sleeping position or bed sharing in the MBR. The NordSIDS study comprised 244 SIDS cases from 1992-1995 and 869 matched controls. We excluded SIDS cases from the other Nordic countries to make it possible to compare the Swedish material. The remaining 117 cases were included, together with 430 matched controls, with a response rate of 83% of cases and 72% of controls.

There was no analysis of non-responders in the Swedish material, but in Norway they studied non-responders among both cases and controls in terms of marital status, maternal age, and birth order. They found that the proportions of single mothers, young mothers and first births were lower in the case-control data than in the Medical Birth Registry of Norway, but that they were similar in cases and controls. It is concluded that the control material probably contains more healthy infants and infants with a more favourable social situation. Nevertheless, statistical analyses of the crude odds ratios, from the Medical Birth Register of Sweden in 1993-1996 including birth weight of < 2500 g, gestational age of < 37 weeks, smoking 10 cigarettes a day in early pregnancy, young maternal age and single mother, do not differ when comparing them with the NordSIDS study.

It is not possible to perform randomly controlled prospective studies in the area of SIDS because of ethical issues. The retrospective study (Paper IV) with manually collected paediatric medical records from all the different hospitals and death certificates from forensic medicine is both time consuming and expensive.

Our vision is to change this system to be more accurate, updated and easy to follow on a yearly basis. If the medical documentation after a death in infancy has occurred includes environmental factors in a structured and complete way, according to planned national guidelines, it can be communicated to the forensic examiner. The clinical information we argue for includes environmental factors that need to be present for the forensic examiner and adds important information when it comes to understanding the scenario. Moreover, in some cases, it might be of importance for the diagnosis. This will also enable the rapid and accurate surveillance of

environmental factors that can interact in SIDS and SUDI cases as well as changes over time.

## 5.2 Incidence of SIDS

The incidence of SIDS in Sweden today is about 0,2/1000 live births and it has been stable at this level for the last decade. It is a low incidence compared to other countries and we have shown in paper I that the adherence to advice given is good. The main reason for the decreasing incidence of SIDS is the change in sleeping position from prone to supine and that the prevalence of smoking during pregnancy has decreased as well.

When the incidence has decreased considerably in the space of a few years, the impact of environmental risk factors also changes (Figure 5). In Paper II we have shown that the OR for smoking > 10 cigarettes/day during pregnancy was inversely associated with SIDS incidence, which means that smoking is an even greater risk factor for SIDS when the total incidence of SIDS is declining.

The mean and median age at which SIDS occurs are of great interest in the work of prevention. When SIDS was much more common (1975-1991), the median age at death was 80 days compared with 64 days in the period 1992-2005 after the prevention campaign was established. In Paper IV (Study period 2005-2011), we compare the findings from this earlier study and conclude that there were no differences in median age; it was still 64 days, during this low incidence period.

Seasonality, with a higher incidence during the winter months, has previously been shown when SIDS was more common, but we were unable to confirm this (Paper II). We used Freedman's and Edwards' test and found no significance. We also aggregated the material collected between 1993-2005 (n=372) and were unable to demonstrate any seasonality here either. This suggests that, when the most prominent risks, such as prone sleeping and smoking, decrease, the interplay in the vulnerable period also changes. In the absence of these risk factors, the impact of temperature and more upper tract infections in winter, does not appear to interact differently than during other seasons.

The percentage of cases at weekends defined as Saturdays and Sundays is still over-represented in our study (Paper II). The percentage of cases at weekends was 34.8% compared with the expected 28% in the period 1997-2005. The reason why SIDS is more common at weekends is not clearly

understood, but there could be an association with more alcohol consumption at weekends and less arousal among parents especially if bedsharing. Families also travel more at weekends and it is possible that babies are more often placed in less safe sleeping environments.

### 5.3 Adherence to advice

Looking retrospectively, primary preventive advice has been the key to success in preventing SIDS. When the finding that supine sleeping was the safest sleeping position was made at the beginning of the 1990s, some early adopters changed their behaviour, but it was not until a national campaign was initiated a couple of years later that the incidence curve rapidly declined.

Advice has to be evidence based and also accepted by the target population. It is also necessary that it is communicated effectively and systematically, where we in Sweden have the great advantage of the system of free attendance and almost universal acceptance of maternal and child health care.

We conclude that compliance is good with the advice that is given to prevent SIDS in Paper I. However, the finding that the number one risk factor, prone sleeping, is over-represented among unemployed mothers, irritable children, smoking mothers, infants sharing bedroom with siblings and infants never using a pacifier offers an opportunity to target information at the child health-care centres.

In Paper IV, we discuss the importance of being able to follow changes in the epidemiology of environmental factors over time and also the importance of death scene investigations. This may contribute to a more up-to-date knowledge about important changes in baby-care routines that could interplay with SIDS and also prevent accidental suffocations and other hazardous sleeping arrangements. This work has begun together with the Swedish National Board of Health and Welfare and the National Board of Forensic Medicine.

We also argue in favour of the importance of a continuous revision of the national advice for preventing SIDS to keep the guidelines as updated as possible, follow new research and keep up the interest and knowledge communicated to both parents and health professionals.

## 5.4 Bed sharing

In the national Swedish guidelines for preventing SIDS published in 2006 bedsharing was mentioned for the first time as a riskfactor. The context was that bedsharing should be avoided in the first three months if the mother had been smoking during pregnancy, had been drinking alcohol or was very tired, or had medication that affected her arousability. The advice was based on several international studies but was not totally accepted among all health professionals due to a suspected disadvantageous effect on breastfeeding

In December 2013, the new guidelines were presented by the Swedish National Board of Health and Science, where the advice was expanded in relation to bed sharing. The new advice emphasised the fact that the safest sleeping place for a baby up to three month of age was to sleep supine in his/her own bed. There has been a discussion about whether this advice might reduce breastfeeding, as in Paper III we conclude that there is a positive correlation between bed sharing and breastfeeding. Our interpretation is that it is not possible to know whether mothers who bed share, are more positive about breastfeeding from the beginning or if bed sharing facilitates breastfeeding. The scientific background is convincing; bed sharing is a considerable risk factor up to three months of age, even in the absence of other risk factors, and it is a major risk factor if combined with smoking and/or drinking alcohol. We see no problems with breastfeeding a baby in the parental bed, but the safest place for the infant to sleep is in its own bed during the first months and the bed should be placed in the parents' bedroom.

After the new guidelines were published there has been no reduction in the national figures for breastfeeding (2014). Instead, a small increase was seen after a decade of decrease.

In Paper III we also describe an association between bed sharing and the parent being single, the infant never using a pacifier or if the baby had several awakenings at night. A lower percentage of bed sharing was seen if the infant was bottle-fed in the first week.

In the study, we only asked about bed sharing at the age of six months. The explanation is that the goal of the study was to map a wide range of living conditions. It would have been interesting also to know the figures for bed sharing also during the previous months when the SIDS incidence is higher. Other studies performed outside Sweden have shown that bed sharing does not increase over time and the figure for bed sharing at the age of one to five months might therefore be even higher. We have a questionnaire with data

from 700 Swedish infants about their sleeping environment which was performed in 2013 and preliminary hitherto unpublished data show a higher figure in relation to bed sharing than in Paper III.

In Paper IV, one of the main results is that bed sharing is significantly over-represented among SIDS cases compared with SUDI cases.

## 5.5 Sleeping position

A supine sleeping position has been the recommended sleeping position since the risk-reducing campaign began in 1992 in Sweden. In paper I, we conclude that the prone position is unusual (5,6%) and that the supine position dominates (47.3%) but that it is still common for the baby to be placed on its side or side/supine. Compared with a decade earlier, side or side/supine has increased from 25.2% to 43.8%. We do not know why so many infants are placed on their side, but we have found that it is not unusual for the advice especially from the maternity wards to be “not prone, but supine or side is fine”. The side position in itself is not regarded as a risk, but it is an unstable position and can lead to the infant rolling into a prone position.

In Paper IV, we describe ten cases that have been placed on their side and found dead in the prone position, but we found no SIDS cases placed on their side that were found dead in the supine position. Other studies have shown that there is a major increase in risk if an infant that is not used to sleeping prone is placed prone or rolls over to this position compared with an infant that always sleeps prone.

In the same Paper IV, we conclude that the prone position is still significantly over-represented among SIDS cases. Even if all the infants for whom the sleeping position was not mentioned slept supine, at least one third of the SIDS cases slept prone or were found prone.

There is still potential to reduce SIDS if the supine position is the recommended position instead of the side position and if the fraction of five per cent of infants that still use the prone position can be reduced. Paper I concludes that special attention and targeted information should be considered due to the association between the prone position and maternal smoking, the temperament of the child, pacifier use, maternal employment status and sharing a bedroom with siblings.

## 5.6 SUDI

In the retrospective study, Paper IV, when examining all diagnoses of sudden unexpected death in infancy in 2005-2011, we were surprised by how few studies and papers had been published in this area. SIDS has been the major interest for our research group, but we believe that there is potential to prevent some of explained SUDI cases as well.

The most common diagnoses are infections, especially pneumonia and sepsis, which can be detected and treated in many cases if the symptoms are discovered at an early stage and the child is admitted to medical care. If health professionals meeting children are more educated, especially about the fact that symptoms are far more subtle in sick infants, especially in the first months, we believe that there is the potential to reduce the number of deaths. The knowledge that fever is not always present and, if it is, it is often not very high and that respiratory symptoms can be mild but suddenly become very severe should also be emphasised in the routines and guidelines for phone counselling (in Sweden, number 1177). A liberal attitude to recommending parents to seek medical aid during the first months when their infant has symptoms should be adopted.

Other causes of SUDI that are in the area of possible prevention are trauma, intoxication and violence. This does not involve many deaths, but the ambition must be that there should be none and, with competent and detailed death scene investigations, we can add knowledge that can be used for prevention. Dangerous sleeping arrangements can be discovered, the signs of child abuse will be more visible and other circumstances will be revealed and open the door to prevention.

Accidental suffocation is a reality but the diagnosis is rare in Sweden compared with other countries. We believe that, if we have better documented clinical information and a better description of the environmental factors presented to the forensic examiner, a death scene investigation and dialogue between the paediatrician and the forensic examiner, more deaths will have a SUDI diagnosis instead of SIDS. This will enable more preventive advice to avoid accidental suffocation.

In our analyses of SIDS and SUDI, we found that both showed higher frequencies of maternal smoking, which has previously been described in other countries. We know that the reason why smoking is a major risk factor for SIDS is due to less arousability and it is possible to speculate whether an

infection in the respiratory system, in combination with intrauterine exposure to nicotine, increases the risk of a fatal outcome.

## 5.7 Documentation and medical routines

Sleeping position and bed sharing are not documented in the child health records and this is something we claim should be of interest. We have excellent data from the Medical Birth Register and breastfeeding, smoking and vaccinations are well documented in the child health records. If we were able to receive this information on a yearly basis, it would be easy to follow changes and also enable comparisons between SIDS and SUDI deaths.

When studying the 261 medical records representing all unexpected sudden infant deaths in Sweden in 2005-2011, we were both disappointed and surprised to see how little information was documented about environmental factors. We feel that it should be mandatory to ask and document latest sleeping position, bed sharing, maternal or paternal smoking, breastfeeding, parental alcohol intake, bed arrangements and hopefully also whether a pacifier was used. Social factors are also very important to document, even if they are more difficult to assess.

Our explanation of why documentation is poor is that this is a dramatic situation which focuses on the medical scenario, possibly a resuscitation situation, and that it is difficult to remember and even to put the questions to the parents. We believe that the on-going work with the Swedish National Board of Health and Welfare will give the paediatric emergency wards guidelines to handle both the psychological support to manage the situation and also make the documentation good with regard to describing the environmental factors mentioned above.

Another task for the on-going national work is to have guidelines on the blood samples, medical examinations and other tests that are desirable in the emergency department. This task is discussed both from the paediatric viewpoint and with experts from the National Board of Forensic Medicine. It is important that there are no quality differences when it comes to the way an unexpected death in infancy is taken care of by the health system, regardless of geography.

## 6 CONCLUSION

The specific aims of the thesis were as follows:

**To compare the current prevalence of risk factors for SIDS in Sweden with a decade earlier, and assess factors associated with prone sleeping (Paper I)**

The major preventable risk factors for SIDS, prone sleeping and maternal smoking during pregnancy, decreased significantly during the study period. Breastfeeding rates remained largely unchanged. Furthermore, there were no differences regarding admissions to neonatal care, the use of a pacifier, colicky pains, prevalence of bed sharing, or the prevalence of sleeping indoors with outdoor clothes on. Alcohol use during and after pregnancy is unusual and decreased during the studied period compared with a decade earlier. Fewer infants slept in a separate bedroom. The strongest association with prone sleeping at six months was how the infant was placed to sleep in the first week. Other factors associated with prone sleeping were whether the mother was unemployed, the infant was irritable during the first week, whether the mother smoked, the infant shared a bedroom with siblings or never used a pacifier.

**To examine how accepted the advice to SIDS is among parents (Paper I).**

The compliance among parents with the advice they are given is generally good. More efforts and information are needed to bring about a change to an exclusively supine sleeping position, as many infants are still placed in side or side/supine positions. The goal to reduce smoking among pregnant woman has been realised, but there is still potential to lower it still further, which may have a beneficial effect on SIDS incidence. Knowledge of factors associated with prone sleeping offers an opportunity to target information at child health-care centres.

**To identify the changes that have occurred in the epidemiology of SIDS since 1995 (Paper II)**

The incidence has remained low in Sweden and there was no evidence of a change in the effect of known risk factors for SIDS in the studied period. Independent risk factors were smoking during pregnancy, parents not living together, low maternal age, high parity and a short gestational age. Maternal



smoking decreased considerably during the studied period, but the odds ratio for smoking has continued to increase as a risk factor for SIDS.

Age at death continued to decrease during this low incidence period from 80 days to 64 days. Seasonality was no longer significant, but there are still about 25% more SIDS cases than expected at weekends. The absence of data on sleeping position and some other important environmental risk factors in the Swedish Medical Birth Register is a limitation.

### **To examine bed sharing at six months of age and the factors that are associated with bed sharing (Paper III)**

We found that every fifth infant bed shared at the age of six months. This figure is comparable to that in a similar study a decade earlier. Breastfeeding was more common if the infant shared a bed with the mother and the reason for this could be both that the mother had decided to bed share to facilitate breastfeeding or that bed sharing facilitates breastfeeding. Sharing a bed was significantly more common if the baby had several nightly awakenings or the mother was single. We suggest that one explanation could be that the infant has a lower arousal threshold when bed sharing or that a baby that wakes up frequently is taken to the parental bed more often. We believe that the reason a single parent shares a bed more frequently is that it may be easier to calm the baby and have it in the same bed for breastfeeding.

If the baby was formula fed, bed sharing was not as common and this has been shown in other studies. The question of whether sharing a bed promotes breastfeeding or early feeding difficulties result in bottlefeeding, thus reducing the need for bed sharing is the subject of debate.

If the infant never used a pacifier, it was more common for the baby to bed share. Our suggested explanation is that both bed sharing and pacifier use can calm the infant, and one of these behaviours is enough. Another hypothesis is that a mother who chooses to bed share has a more positive attitude to breastfeeding and a more negative attitude to the use of a pacifier.

### **To investigate the environmental circumstances associated with SIDS, by analysing data from all sudden unexpected deaths in infancy in Sweden from 2005 to 2011 (Paper IV)**

The latest national preventive advice in Sweden states that the safest place for a baby, less than three months of age is to sleep in his/her own bed in a supine position. When studying SIDS cases and explained SUDI cases, we

found that bed sharing was significantly more common in the SIDS group. Prone sleeping was also over-represented in SIDS cases and was the sleeping position reported in at least a third of all deaths. Ten cases with a SIDS diagnosis were reported to have been placed in a side position and found dead in a prone position. No SIDS cases were placed on their side and found supine.

The median age at death in SIDS was the same as in the previously studied period (Paper II), i.e. 64 days, and there was no statistical difference in age when it came to explained deaths.

We found no significant seasonal variations in SIDS incidence and this confirms our previous study result that seasonality is not present in a low incidence environment.

Our conclusion after this study is to emphasise the advice always to place the infant supine, to avoid bed sharing until three months of age as a matter of routine, to extend this period if the parents have risk factors as maternal smoking and to reduce maternal smoking still further.

The poor documentation in medical records on circumstances and environmental facts is a problem, which needs to be resolved. We have initiated a project together with the National Board of Health and Welfare to promote better routines for documentation, medical examinations and approach to support parents in crisis. This work is on-going and will hopefully also provide better opportunities to follow changes in epidemiology in the future.

#### **To describe the cause of sudden unexpected death of infancy in Sweden in 2005-2011 where the forensic examiner found an explanation (Paper IV)**

Infectious diseases are the most common cause of explained SUDI in Sweden. The respiratory system is the site of infection in every fourth case and pneumonia is the dominant diagnosis. Sepsis is found in several of these respiratory tract infections but also in the central nervous system (CNS) and heart.

Malformations in the heart and CNS are not uncommon as a cause of explained SUDI and perinatal events leading to asphyxia are described, but the question of whether this represents unexpected deaths in every case or

should be classified as a complication during or after delivery can be discussed.

Congenital errors of metabolism, especially involving lipid synthesis, are rare but still represent SUDI cases and can have a late and sudden and severe onset in infancy. Trauma and violence are uncommon in Sweden but could be prevented in most cases and more studies are needed to identify babies at risk.

Accidental suffocation is very rare in the studied material compared with other countries and we believe this is because we do not routinely perform death scene investigations. A certain and important risk on the maternity ward that we would like to stress is when a newborn is placed skin-to-skin with the mother. The infant can have problems keeping its airway free and this can pass unnoticed if the mother is exhausted after delivery. Deaths are described in our material in this situation and several reports of serious events have been documented and published in recent years.

## 7 FUTURE PERSPECTIVES

Mediarelease 1 in March 2020:

“The Swedish National Board of Health and Welfare has today published new figures on the incidence of sudden infant death syndrome (SIDS) in 2019. This is the first time ever that we are able to announce that no SIDS diagnosis was reported during a year. Since the first national advice to prevent SIDS was published in 1992, the SIDS incidence has declined dramatically. After a plateau of around 20 deaths/1000 live births until 2014, the new preventive advice directed at parents, together with new national guidelines and routines, has succeeded in bringing about a one-digit incidence of SIDS during the last few years. This year is, however, the first time ever that a zero vision has been accomplished in relation to SIDS.

“The head of the National Board of Health and Welfare declares that the collaboration between the hospitals, forensic departments and the police authority has been the key to achieving this zero vision. A death scene investigation is always conducted jointly by specially educated professionals from the police and health-care system in order to find factors that could have interplayed and been preventable. This new routine has been accepted by parents and the new structured plan to support parents psychologically has been appreciated.

“The expert group connected to the National Board of Health and Welfare concludes that there were 13 sudden unexpected deaths in infancy (SUDI) in Sweden in 2019. This is a reduction with almost 50% comparing with figures before the “zero vision” was postulated. The decline represents mostly preventable infections relating to the respiratory system and sepsis and one explanation could be the educational programme initiated to find early signs of disease in infants. Trauma and violence are extremely rare and is not a cause of death every year.

“The diagnoses that still exist as causes of unexpected deaths are congenital errors of metabolism, congenital anomalies especially in the heart and CNS and some sudden and severe infections. The expert group concludes that it is difficult to find and treat these congenital diseases but emphasises that the intensive work on the zero vision for SIDS in Sweden has also had a beneficial effect on reducing explained SUDI due to less maternal smoking and good compliance with the recommended safer sleeping environment. Special attention has been paid to the discussed accidental suffocation as a

cause of preventable death and better routines and documentation related to environmental factors and a dialogue between the paediatrician involved and the forensic examiner has resulted in accidental suffocation becoming a rare diagnosis, even if it exists in other countries.”

This Utopian press release may never be published, but I believe that it is a realisable goal and that the way to reach it will save lives in any case. Looking back to times when the sleeping position gradually changed from supine to prone without evidence that it was a safer position is tragic but also informative. After the preventive advice was successfully communicated to parents, thousands of lives have been saved and we have an important task for the future to follow the change in epidemiology and trends to minimise the numbers of infants that are exposed to risk factors that are preventable.

Our vision for the future is collaboration between all the authorities that are involved when an infant unexpectedly dies, an easy way to collect the data year by year to follow the epidemiology and trend in the fast-moving society in which we live. Most of all, we hope that the general conditions for our children are as equal and favourable as possible, which is essential in every aspect of child health, including the incidence of SIDS.

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