ETS AND SUDDEN INFANT DEATH SYNDROME

Trends in SIDS

Sudden infant death syndrome (SIDS), defined as the sudden death of an infant that remains unexplained by clinical or necropsy evidence, is the most common single cause of death in the postneonatal period (1-12 months) in most developed countries [1]. Following campaigns discouraging parents from putting babies to sleep in the prone position, SIDS deaths have reduced substantially in several countries, including the UK, Ireland, USA, New Zealand, Australia, Scandinavia, Germany and the Netherlands [2-9]. In the UK the rate of SIDS fell by 70% between 1987 and 1992, from 2.2 to 0.7 per 1000 live births [7]. This decline has continued in recent years, with rates in England and Wales falling between 1995 and 2003 from 0.61 to 0.29. However, interpretation of the recent decline is complicated by the increasing rate (from 0.02 to 0.19 over the same period) of infant deaths classified as "unascertained", a term that is to some extent used interchangeably with SIDS [10].

Factors associated with SIDS

Epidemiological studies have identified a large number of factors that are associated with SIDS [e.g. 1,9,11,12]. Other than prone sleeping position, these factors include the use of soft mattresses, overheating, head covering, season, having had a recent illness (gastro-intestinal as well as respiratory), complications of pregnancy, low birthweight, premature birth, not being immunised, male sex, central nervous system abnormalities, lack of breast-feeding, using a pacifier, sharing a bed with the parents, intrauterine growth retardation, alcohol consumption and illicit drug use by the mother during pregnancy, young age of the mother, no pre-natal care, size of family, race, the mother's education, and socio-economic status. The role of smoking by the parents, with particular relevance to possible effects of ETS exposure, is the main interest of this summary.

Maternal postnatal smoking

Although it has been claimed that exposure of infants to ETS is associated with SIDS, there are difficulties in interpreting the epidemiological data. Studies have compared the incidence of SIDS among infants exposed to ETS by a parent who smokes after the birth with the incidence among infants who have not been so exposed.

Some 28 studies on SIDS and ETS exposure from smoking by the mother after pregnancy have been published [8,13-39]. Of these, 12 studies [8,13,18,19,21,22,24,25,27,30,36,38] reported a statistically significant increased risk of SIDS among exposed infants based on adjusted analyses, four [29,31,32,37] reported a significant increase in unadjusted but not adjusted analyses, and seven [14,16,20,23,26,35,39] reported a significant unadjusted increase but did not report adjusted findings (Table 1). One further study [15] reported a raised unadjusted relative risk per cigarette per day that was of borderline significance. In addition, eight of these studies [13,19,21,24,25,27,31,32] also reported evidence of a dose-response relationship (data not shown).

Maternal smoking in pregnancy

As ETS exposure is the main interest of this review, a detailed presentation of the evidence relating SIDS risk to maternal smoking in pregnancy is not provided. In any case, it is usually difficult to separate out the effects of smoking during pregnancy, as most women who smoke during pregnancy continue to do so after the birth of their child. Indeed the only study identified as presenting results jointly by prenatal and postnatal maternal smoking [31] included only two SIDS cases exposed only prenatally and one exposed only postnatally, as against 25 exposed at both times, the numbers being far too small to estimate the individual effects reliably. Not surprisingly, therefore, many studies [8,19,21,26,27,29,31] report very similar relative risks for maternal smoking during and after pregnancy, though some studies [28,34,37] report rather higher estimates for smoking in pregnancy. A recent large multi centre European case-control study [9] reported results only for maternal smoking in pregnancy as this explained SIDS risk better than did maternal smoking after pregnancy.

Smoking by the father

Nineteen studies on the risk of SIDS and paternal smoking have been published [8,9,13,14,16,17,19,21,24,25,29,31,37,38,40-44] (Table 2). Thirteen of these studies [8,9,14,19,21,24,25,29,37,38,42-44] reported a statistically significant increase in the risk of SIDS among infants whose fathers smoked, although in four of these [14,29,37,38] this was only in unadjusted analyses. In the majority of studies the risk estimates for paternal smoking are less than the corresponding risk estimates for maternal postnatal exposure shown in Table 1. However, there are some exceptions [21,29,38]. (Note that Table 2 excludes some publications considered in Table 1, to avoid duplication with the combined analyses of Carpenter *et al* [9].

Smoking by other household members

In addition, six studies investigated the relationship between ETS and smoking by other members of the household (data not shown). Two of these reported a significant unadjusted relative risk that became non-significant after adjustment [19,27], one reported a significant adjusted association in whites but not blacks [18], two reported significant adjusted associations using various indices [8,21], and one reported no significant association [22].

Interpretation of the results

Recently, there have been a number of reviews of the association between SIDS and parental smoking [1,11,25,45-47]. When attempting to interpret the results relating to ETS exposure, various points should be borne in mind.

Limited attention to potential confounding factors

Twelve of the studies [14-17,20,23,26,34,35,39-41] reporting an association between SIDS and ETS exposure have not adjusted for any other risk factors, while many others [8,13,18,21,22,27,28,30-32,37,38,42,43] have only taken a few of them into account. Only eight studies [9,19,24,25,29,33,36,44] have taken a fairly extensive list of potential confounders into account in at least some of their analyses.

Effect of adjustment for multiple risk factors

Five publications [9,19,24,25,44] based on large studies (of at least 200 SIDS cases) have reported both unadjusted risk estimates and risk estimates adjusted for a large number of potential confounding variables. All have found that a major part of the unadjusted association can be explained by confounding. Thus, for example, the Mitchell I study [19] found that adjustment reduced the relative risk for maternal smoking after pregnancy from 4.24 to 1.70, i.e. explained 78.4% of the excess risk.[1] Other studies of maternal smoking after pregnancy found that the percentage of the excess risk explained was 75.5% or 84.9%, depending on the index used [25], and 38.7% [24]. For paternal smoking, corresponding estimates were 73.8% [19], 39.3% [24], 66.9% [9] and 66.2% [44]. Since such adjustments will inevitably be incomplete, partly because not all relevant factors will have been

[1] If RR_U, RR_A are the unadjusted and adjusted relative risks, the ratio of excess risks given by $S = (RR_A-1)/(RR_U-1)$ and the percentage of the excess risk explained by adjustment is $100(1-S)$.

considered and partly because data errors or the use of surrogate variables limit the ability to control for confounding, it is not implausible that all of the claimed SIDS/ETS association could, in fact, be explained by confounding.

Relevance of the QT interval

In a study involving over 30,000 infants in which electrocardiograph measurements were made shortly after birth [48], prolongation of the QT interval was associated with a more than 40-fold increased risk of SIDS. This abnormality, seen in 50% of the infants dying of SIDS, is a major risk factor that could not have been caused by postnatal ETS exposure and which has not been taken into account in any of the epidemiological studies of ETS and SIDS.

Disentangling effects of ETS exposure and of maternal smoking in pregnancy

Even if the association between parental smoking and SIDS cannot be fully explained by uncontrolled confounding by other risk factors, it may result not from ETS exposure but from an effect of maternal smoking during pregnancy. Most studies [8,19,21,25,27,31,44], though not all [18], have found that the association of SIDS with postnatal maternal smoking or paternal smoking is reduced if adjustment is made for maternal smoking in pregnancy, or if attention is restricted to non-smoking mothers. Also, as noted above, some recent studies have reported higher relative risks for maternal smoking during pregnancy than for postnatal parental smoking.

Conclusion

Little is known about the cause or causes of SIDS, or the mechanisms by which such causes may act. Furthermore, the epidemiological data are difficult to interpret. It is concluded that the scientific evidence, considered as a whole, does not adequately demonstrate that exposure to ETS is a cause of SIDS.

ETS AND SIDS

THE DATA

The tables that follow summarize the key evidence on SIDS and parental smoking, as indexed by maternal smoking after pregnancy (Table 1) and paternal smoking (Table 2). The tables show, for each successive study providing data, relative risks (RRs) and 95% confidence intervals (CIs), unadjusted, and adjusted for the factors listed. The tables are adapted and extended from tables presented by Thornton and Lee [11] and include all the relevant studies considered in recent reviews [1,25,45-47].

TABLE 1 Maternal smoking after pregnancy and SIDS

Study Ref	Author	Year	Location	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjustment factors
13	Bergman	1976	USA, Washington State	2.42(1.22-4.82)[a]	2.38(1.17-4.83) 2.05(1.00-4.24)	MA ED
14	Cameron	1986	Australia, Victoria	4.04(2.63-6.20)[a,b]	-	-
15	Victora	1987	Brazil	1.06(1.00-1.11)[c]	-	-
16	McGlashan	1989	Australia, Tasmania	1.92(1.26-2.92)[a]	-	-
17	Engelberts	1991	Netherlands	1.47(0.97-2.23)[a]	-	-
18	Schoendorf	1992	USA, National			
	(i) after or during pregnancy					
	- Black			2.77(2.08-3.70)[a,d]	2.78(2.12-3.64)	ED,MA,MS,MSA,MSP
	- White			3.65(2.27-4.81)	2.66(2.04-3.48)	As above
	(ii) only after pregnancy					
	- Black			2.40(1.49-3.83)[d]	2.33(1.48-3.67)	As above
	- White			2.22(1.29-3.78)	1.75(1.04-2.93)	As above
19	Mitchell I	1993	New Zealand			
	- any			4.24(3.39-5.31)[e]	1.70(1.21-2.37)	A,AN,BF,BS,BW,CAN, GA,MA,MAP,MS,P,R, REG,S,SA,SE,SES,SL,TD
	- in house			2.20(1.38-3.51)[f]	-	-
	- never in house			5.07(1.50-15.41)	-	-
20	Jorch	1994	Germany	3.30 (2.30-4.80)[g]	-	-
21	Klonoff-Cohen	1995	USA, California			
	- any			3.13(1.75-5.60)	2.28(1.04-4.98)	AN,BF,BW,MC,MSP,SL
	- same room			6.17(2.60-14.61)	4.62(1.82-11.77)	As above
22	Ponsonby	1995	Australia, Tasmania	3.96(1.91-8.24)	3.82(1.43-10.2) 2.39(1.01-6.00)	BH,FAS,MA,SL,VHC EMP,FAS,MA,SL
23	Wigfield	1995	England, Avon			
	- study 1			2.90(1.60-5.40)	-	-
	- study 2			4.60(1.90-11.40)	-	-
24	Brooke	1997	Scotland	5.91(3.61-9.68)	4.01(2.19-7.33)[a]	BF,BW,CBP,DEP,DRG, ED,GA,MA,MS,MTO, OID,P,S,SES,SL,SPR,SS, SWD,SYM,TOG
25	Mitchell II	1997	New Zealand			
	- after birth			6.56(4.32-9.95)[a]	6.26(4.07-9.63)[a] 2.36(1.27-4.37)[a]	BS BF,BS,BW,MA,MS,P,R,S, SA,SL
	- 2 months after birth			5.85(3.37-10.20)[a]	5.42(3.10-9.47)[a] 1.73(0.75-3.95)[a]	BS BF,BS,BW,MA,MS,P,R,S, SA,SL
26	Schellscheidt	1997	Germany	5.90(2.60-13.90)[g]	-	-
27	Alm	1998	Norway, Sweden, Denmark	3.80(2.80-5.30)	3.70(2.50-5.50)	A,ED,MA
28	Kohlendorfer	1998	Austria			
	- early SIDS			1.90(0.90-4.00)	Not significant	AN,BW,FID,GA,MA,NS, RAE,SL
	- late SIDS			1.00(0.50-1.80)	Not significant	As above
29	L'Hoir	1998	Netherlands	2.80(1.51-5.18)[a]	3.53(0.73-16.99)[a,g]	A,AL,BF,BW,CR,D,DU, MA,MB,SES,SL,SSU
30	Blair	1999	England, 3 areas	5.91(4.30-8.12)[a,g]	6.05(4.23-8.66)[a]	A,BS
31	Dwyer	1999	Australia, Tasmania	3.38(1.58-7.23)	2.20(0.67-7.23)[a]	MSP

Study Ref	Author	Year	Location	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjustment factors
32	Jonville-Bera	2001	France	1.72(1.09-2.72)[a]	1.72(0.95-3.11)	BF,BW,PI,S,SL,TM,V
33	Toro	2001	Hungary	0.85(0.27-2.67)[a]	0.90(0.20-3.00)	AL,AP,BOF,BW,DEP,GA, IP,MA,MC,MI,P,PI,SL
34	Iyasu	2002	USA, 3 states	1.20(0.50-2.40)	-	-
8	McDonnell	2002	Ireland	7.52(4.78-11.81)	4.16(2.48-6.97)	AL,DEP,ED,MA,MSP
35	McMartin	2002	USA, Maryland	4.36(1.60-11.88)[a,g]	-	-
36	Sanderson	2002	England, Sheffield	-	7.24(2.76-19.01)	BF,BW,DEP,DP,GA,HV, MA,MB,MPH,MSF,P,S, SB,YB
37	Nelson	2005	Hong Kong	4.90(1.20-20.10)	4.60(0.90-22.70)	S,SES
38	Stray-Pederson	2005	Norway	11.63(3.92-34.49)[a]	6.60(1.10-37.50)	BF,BS
39	Tappin	2005	Scotland	5.81(3.01-11.23)[a]	-	-

[a] Estimated from data given
[b] Women smoking 20 or more cigarettes per day
[c] Relative risk per cigarette per day, but not clear whether data refers to maternal smoking during or after pregnancy
[d] Relative risk compared to mothers smoking neither during pregnancy nor after infant's birth
[e] Data came from reference 49. An alternative reference 50 gave an unadjusted estimate of 4.24(3.33-5.40) and an estimate of 1.79(1.30-2.48), adjusted for a similar list of factors but including INT and MP and excluding CAN
[f] Data came from reference 51
[g] Postnatal ETS exposure of child

Key to adjustment factors:
A = Postnatal age; AL = Alcohol consumption by mother; AN = Antenatal classes; AP = Apgar score <7; BF = Breast feeding; BH = Bedroom heating; BOF = Bottle feeding; BS = Bed sharing; BW = Birthweight; CAN = Cannabis use by mother since birth; CBP = Cot bumper used; CR = Change in routine; D = Dummy use; DEP = Deprivation; DP = Depression; DRG = Drug treatment; DU = Duvet use; ED = Education; EMP = Employment status; FAS = Family history of asthma; FID = Family history of infant death; GA = Gestational age; HV = Number of visits by health visitor; IP = Interval between pregnancies; MA = Maternal age; MAP = Mother's age at first pregnancy; MB = Multiple birth; MC = Medical conditions at birth; MI = Maternal illness; MPH = Maternal psychiatric history; MS = Marital status; MSA = Maternal postnatal smoking; MSF = Maternal satisfaction with infant feeding; MSP = Maternal smoking in pregnancy; MTO = Old mattress used; NS = Night sweating; OID = Other infant death; P = Parity; PI = Previous illness; R = Race; RAE = Repeated apnoea episodes; REG = Region; S = Sex; SA = School leaving age; SB = Season of birth; SE = Season; SES = Socio-economic status; SL = Sleep position; SPR = Sleeps with parents; SS = Sweating during sleep; SSU = Use of sleep sack; SWD = Usually swaddled; SYM = Symptoms; TD = Time of day; TM = Type of mattress used; TOG = Tog value; V = Vaccinations; VHC = Visits to health clinic; YB = Year of birth within study

TABLE 2 Paternal smoking and SIDS

Study Ref	Author	Location	Year	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjustment factors
13	Bergman	USA, Washington State	1976	1.53(0.78-3.01)[a]	-	-
40	Lewak	USA, California	1979	No association	-	-
14	Cameron	Australia, Victoria	1986	1.85(1.32-2.60)[a]	-	-
41	Lee	Hong Kong	1989	3.57(0.98-13.0)	-	-
16	McGlashan	Australia, Tasmania	1989	1.73 [p=0.05]	-	-
17	Engelberts	Netherlands	1991			
	- during pregnancy			1.02(0.68-1.55)[a]	-	-
	- after birth			0.96(0.63-1.45)[a]	-	-
42	Nicholl	UK, 8 centres	1992	1.99(1.38-2.86)	1.63(1.11-2.40)	BW,MA,P,SRA
43	Gilbert	UK, Bristol	1993	2.78(1.59-4.87)[a]	2.43(1.32-4.48)[a]	SES
19	Mitchell I	New Zealand	1993	2.41(1.92-3.02)	1.37(1.02-1.84)	A,BF,BS,BW,MA,MS,MSP,R, REG,S,SE,SES,SL,TD
21	Klonoff-Cohen	USA, California	1995			
	- during pregnancy (around mother)			3.56(2.11-6.00)	-	-
	- after birth			3.53(1.99-6.27)	3.46(1.91-6.28)	AN,BF,BW,MC,MSP,SL
	- after birth, in same room			9.20(3.66-23.15)	8.49(3.33-21.63)	As above
24	Brooke	Scotland	1997	2.40(1.57-3.65)[a]	1.85(1.08-3.18)[a]	BF,BW,CBP,DEP,DRG,ED, GA,MA,MS,MTO,OID,P,S, SES,SL,SPR,SS,SWD,SYM, TOG
25	Mitchell II	New Zealand	1997			
	- after birth			3.84(2.54-5.80)[a]	-	
	- 2 months after birth			3.21(1.87-5.52)[a]	-	
	- time not stated			-	2.1(1.3-3.40)[a]	MSA
29	L'Hoir[b]	Netherlands	1998	3.76(2.08-6.82)[a]	-	-
31	Dwyer	Australia, Tasmania	1999	1.10(0.56-2.16)[c]	-	-
8	McDonnell[d]	Ireland	2002			
	- father during pregnancy			4.60(3.04-6.92)	2.65(1.49-4.72)	AL,DEP,ED,MA,MSP
	- father after birth			4.40(2.92-6.63)	2.64(1.49-4.67)	As above
44	Fleming[e]	UK, 5 centres	2003			
	- all controls			3.60(2.68-4.83)	1.88(1.26-2.81)	AL,BF,BW,DU,GA,LBP,MA, MB,MC,MS,MSP,OID,P,PAL, PDU,PSB,RD,S,SCBU
	- post-matched controls			2.25(1.60-3.16)	1.89(1.23-2.90)	AL,BW,DU,GA,LBP,MB,MC, MSP,P,PAL,PDU,RD,S,SCBU
9	Carpenter	Europe, 20 regions	2004	2.69(2.24-3.23)[a,c]	1.56(1.24-1.97)[a,c]	A,ALTE,BW,D,EMP,MA,MB, MS,MSP,P,S,SC,SCBU,SL,UP
37	Nelson	Hong Kong	2005			
	- before pregnancy			3.40(1.20-9.80)	2.90(0.96-8.80)	S,SES
	- 2nd trimester			3.40(1.20-9.80)	2.90(0.96-8.80)	As above
	- since birth			3.50(1.20-10.00)	3.00(0.99-9.10)	As above
38	Stray-Pedersen	Norway	2005	3.48(1.29-9.43)[a]	6.90(1.00-47.00)	BF,BS

[a] Estimated from data given
[b] Based on 73 cases and 146 controls, 31 cases and 61 controls appear to have been included in study by reference 9
[c] Smoking postnatally by any household resident other than the mother

[d] Based on 203 cases and 608 controls, 92 cases and 322 controls appear to have been included in study by reference 9
[e] All 195 cases and 780 controls included in study by reference 9
[f] Interaction with bed-sharing

Key to adjustment factors:
A = Postnatal age; AL = Maternal alcohol consumption; ALTE = Apparent life-threatening events; AN = Antenatal classes; BF = Breast feeding; BS = Bed sharing; BW = Birthweight; CBP = Cot bumper used; D = Dummy use; DEP = Deprivation; DRG = Drug treatment; DU = Use of illegal drugs; ED = Education; EMP = Employment status; GA = Gestational age; LBP = Late booking of pregnancy; MA = Maternal age; MB = Multiple birth; MC = Medical conditions at birth; MS = Marital status; MSA = Maternal postnatal smoking; MSP = Maternal smoking in pregnancy; MTO = Old mattress used; OID = Other infant death; P = Parity; PAL = Paternal alcohol consumption; PDU = Paternal use of illegal drugs; PSB = Previous stillbirth; R = Race; RD = Resuscitation at delivery; REG = Region; S = Sex; SC = Study centre; SCBU = Admission to special care baby unit; SE = Season; SES = Socio-economic status; SL = Sleep position; SPR = Sleeps with parents; SRA = State of major accommodation; SS = Sweating during sleep; SWD = Usually swaddled; SYM = Symptoms; TD = Time of day; TOG = Tog value; UP = Urinary tract infection in pregnancy.

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