Sudden Infant Death Syndrome in Twins and Singletons

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Twins compared with singletons and monozygous (MZ) compared with dizygous (DZ) twins are at increased risk of fetal and infant death, cerebral palsy and many congenital anomalies. The aim of this study is to investigate whether zygosity is a risk factor for the sudden infant death syndrome (SIDS). Birth registration data and draft infant death certificates for all multiple births in England and Wales 1993 to 2003 were provided by the Office for National Statistics. As a partial proxy for zygosity, same-sex was compared with opposite-sex twins for birthweight-specific mortality and mortality attributed to SIDS. Data on singleton infants were obtained by subtraction of multiple births from routinely published population births and infant deaths. SIDS mortality among low birthweight infants was significantly less in twins than singletons. The twin-singleton relative risk was reversed in infants of normal birthweight. Among infants of normal birthweight, neonatal SIDS was significantly more common in same- compared with opposite-sex pairs. Among infants of low birthweight, postneonatal SIDS was significantly more common in same- compared with opposite-sex pairs. The difference in birthweight distribution of same- compared with opposite-sex twins for neonatal SIDS suggests that zygosity is a risk factor for SIDS. As congenital cerebral anomalies are a feature of many monozygous twin conceptions, a detailed macro- and microscopical examination of the brain in twin SIDS may indicate an otherwise unrecognised pathology.

The association of increased risk of Sudden Infant Death Syndrome (SIDS) with environmental factors such as sleeping position and over-heating from swaddling is well known. Public education about these risks has contributed to a decreasing trend in the incidence of SIDS. Pre-term or low birthweight has an independent effect from sleeping position on the risk of SIDS (Blair et al., 2006; Thompson et al., 2006). The crude relative risk is also greater in twins compared with singletons and adjustment should be made for the confounding effect of low birthweight (Malloy & Freeman, 1999).

We previously reported on the epidemiology of SIDS in twins and singletons in England and Wales 1993 to 1998, confirmed that twins compared with singletons were at significantly increased risk and observed that in both twins and singletons the risk of SIDS increased with decreasing birthweight. The higher crude relative risk in twins was attributable to the higher proportion of twins that were of low birthweight. The hypothesis that some SIDS deaths in twins may have been attributable to unrecognized prenatally acquired cerebral impairment associated with monozygotic monochorionic twinning was tested using, as a partial proxy for zygosity, a comparison of same- and opposite-sex twin SIDS mortality. No significant difference was found and it was concluded that zygosity was not an important factor (Platt & Pharoah, 2003).

The study now reported complements the earlier one by extending the analysis to cover the years 1993 to 2003. The aim of this study is to examine time trends in SIDS mortality in twins and singletons and to determine whether the previous observations in birthweight-specific mortality and same- and opposite-sex twin differences are confirmed.

Methods

The Office for National Statistics (ONS) supplied annual files of multiple births for the years 1993 to 2003. These files provided data on all twins, triplet and higher order multiple births in England and Wales. Data only for twins were used and the variables provided were birthweight, sex and whether the twins were of same- or opposite-sex.

Statistics

The Twin/Singleton relative risk was determined as:

Incidence of SIDS among twins/Incidence of SIDS among singletons.

Mantel-Haenszel weighted relative risks were calculated using EPIinfo.

Received 3 April, 2007; accepted 23 May, 2007.

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Table 1

Trends in Mortality Due to SIDS

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	1993–2003 Total
Singletons												
No.of SIDS	406	394	343	372	354	260	238	208	205	153	159	3092
No. of live births	654,224	646,887	629,948	631,760	624,654	617,754	604,088	586,868	577,281	578,518	603,410	6,755,392
SIDS/1000 live births	0.62	0.61	0.54	0.59	0.57	0.42	0.39	0.35	0.36	0.26	0.26	0.46
Twins												
No. of SIDS	23	23	25	21	15	11	14	12	8	11	7	170
No. of live births	16,268	16,577	17,196	16,931	17,551	17,256	16,987	16,785	16,717	17,097	17,686	187,048
SIDS/1000 live births	1.41	1.39	1.45	1.24	0.85	0.64	0.82	0.71	0.48	0.64	0.40	0.91

χ^2 with Yates' correction and Fisher's exact test were used for two by two tables.

Results

In the 11 years covered by the study, there were 3092 singleton infant SIDS among 6,755,416 live-births and 172 SIDS among 187,048 twin live-births in England and Wales. Fifteen deaths in twins, with the cause of death recorded as 'unascertained', were excluded from the analysis. The mortality rate attributed to SIDS, among both singletons and twins, has declined over the 11 years (Table 1).

For both twins and singletons, there is a negative correlation between birthweight and the risk of SIDS; the lower the birthweight, the higher is the risk of SIDS and the crude relative risk of SIDS in twins is twice that in singletons (0.91 vs. 0.46 per 1000 live-births; $p < .0001$; Table 2). However, this conceals the significant differences observed when birthweight-specific groups are examined (Figure 1).

For infants of birthweight 3000 g or more, twins are at significantly higher risk than singletons. Paradoxically, within each of the low birthweight subgroups, twins are at lower risk than singletons (Table 2). This is because there is a much higher proportion of low birthweight infants in twins than singletons. Allowing for the different birthweight distributions, twins are at lower risk than singletons; the Mantel-Haenszel weighted relative risk is 0.81 (95% confidence interval [CI] 0.69 to 0.95; $p < .01$). Thus there are two components to the crude relative risk of SIDS in twins compared with singletons. Low birthweight infants, whether singletons or twins are at greater risk of SIDS than normal birthweight infants. Therefore one component of the crude relative risk of twins relates to the higher proportion that are of low birthweight. The second component relates to the lower relative risk in twins compared with singletons among the low birthweight groups (Figure 1).

The increased risk of infant mortality and severe neurological morbidity in mono- compared with dizygous conceptions, prompted an examination of the differential effects of zygosity, specifically for SIDS mortality. National birth and death registrations of multiple births do not record zygosity, however, as a partial proxy for zygosity, comparison may be made between same- and opposite-sex twins. Opposite-sex twins are all dizygous but same-sex twins comprise mono- and dizygous twins in approximately equal proportions. Table 3 confirms a previous observation (Platt & Pharoah, 2003) that there were no significant differences between same- and opposite-sex twins in

Table 2

Birthweight-Specific SIDS Mortality Rates in Singletons and Twins 1993–2003

	Twins			Singletons		
Birthweight	No. of SIDS	No. of live-births (%)	SIDS rate per 1000	No. of SIDS	No. of live-births (%)	SIDS rate per 1000
< 1500 g	26	17,472	1.43	112	63,578	1.76
1500–1999 g	34	26,039	1.31	154	74,569	2.07
1500–2499 g	53	55,564	0.95	379	266,591	1.42
2500–2999 g	35	61,428	0.59	777	1,099,794	0.71
≥ 3000 g	22	25,550	0.86	1636	5,202,404	0.31
Not stated	0	995	0	34	48,480	0.70
All birthweights	170	187,048	0.91	3092	6,755,416	0.46

Note: Crude relative risk, comparing twins with singletons, is 1.99 (95% CI 1.70 to 2.32; $p < .0000001$)
Mantel-Haenszel weighted relative risk, comparing twins with singletons, is 0.81 (95% CI 0.69 to 0.95; $p < .01$)

https://doi.org/10.1375/twin.10.4.644 Published online by Cambridge University Press

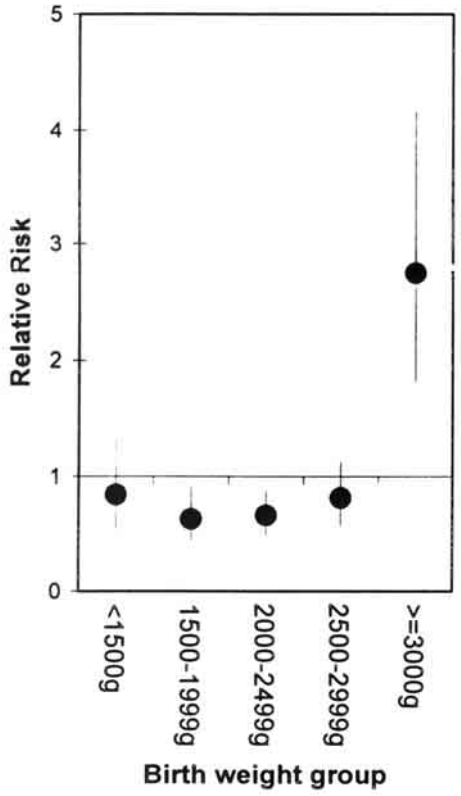

Figure 1

Birthweight specific twin–singleton relative risk.

birthweight specific, crude or weighted relative risks. An initial conclusion is that zygosity is not an important determinant of SIDS.

Deaths ascribed to SIDS are known to peak at about 3 months of age. Failure to observe birthweight-specific SIDS mortality difference in same- and opposite-sex twins, therefore, prompted a comparison of birthweight-specific neonatal and postneonatal deaths. Neonatal deaths with cause certified as SIDS are significantly more common among the normal birthweight same-sex twins. In contrast, postneonatal deaths certified as SIDS are significantly more common among low birthweight twins of same-sex (Table 4).

Comparing same-sex with opposite-sex twins, in infants of birthweight 2500 g or more, all eight neonatal SIDS deaths were from same-sex pairs ($p < .02$). In contrast, same-sex postneonatal SIDS deaths were significantly in excess in the less than 2500 g birthweight group ($p < .03$). The initial conclusion that zygosity was not a determinant in some cases of SIDS had to be revised. The conclusion now is that zygosity may predispose to SIDS in specific birthweight subgroups.

Discussion

The diagnosis of SIDS is made after other causes are excluded and this gives rise to problems interpreting time trends. Following the recognition of 'cot' death as a diagnosis in 1971 and its later renaming as SIDS, the increase in incidence observed was largely a diagnostic artefact due to the transfer of unspecified respiratory and other illnesses to SIDS (Pharoah & Morris, 1979).

The decreasing annual SIDS rate reported here has been noted previously and trends need to be interpreted with caution. Much of the decline in SIDS is clearly due to the change in sleeping position although the precise mechanism is not known. We are unable to adjust for this as a confounding variable but there is no reason to believe that this factor has differentially affected twins and singletons.

Changes in SIDS certification have also influenced the trend. The diagnostic transfer between SIDS and 'unascertained' deaths, differences in the number of cases referred to the coroner and improvements in specialist post-mortem examinations in identifying other causes of death, have all been considered to contribute to the recent downward trend in mortality attributed to SIDS (Corbin, 2005; Dattani, 2001; Dattani & Cooper, 2000). A stigma may be attached to the cause of an infant death being labeled as 'unascertained' and a recent report has recommended that, subject to certain provisos, the term SIDS be retained for all cases (The Royal College of Pathologists and The Royal College of Paediatrics and Child Health, 2004).

Table 3

Birthweight-Specific SIDS Mortality Rates in Like and Unlike Sex Pairs 1993–2003

	Same-sex			Opposite-sex			
Birthweight group	No. SIDS	No. of live-births	SIDS mortality rate	No. SIDS	No. of live-births	SIDS mortality rate	Relative risk same-/ opposite-sex (95% CI)
< 1500 g	22	12,382	1.70	4	5077	0.79	2.26 (0.74 to 7.72) *ns*
1500–1999 g	26	18,156	1.43	8	7877	1.01	1.41 (0.64 to 3.11) *ns*
2000–2499 g	31	37,519	0.83	23	18,016	1.28	0.71 (0.41 to 1.23) *ns*
2500–2999	22	39,734	0.55	13	21,648	0.60	0.92 (0.46 to 1.82) *ns*
≥ 3000 g	12	15,685	0.76	10	9786	1.02	0.75 (0.32 to 1.73) *ns*
All	113	123,476	0.91	57	62,404	0.93	1.02 (0.74 to 1.40) *ns*

Note: ns = nonsignificant
Mantel-Haenszel weighted relative risk 0.99 (0.71 to 1.38)

https://doi.org/10.1375/twin.10.4.644 Published online by Cambridge University Press

Table 4

Birthweight-Specific Neonatal and Postneonatal Deaths in Same- and Opposite-Sex Twins

Birthweight	Same-sex	Opposite-sex	Total
Neonatal deaths			
< 2500 g	5	6	11
≥ 2500 g	8	0	8
Total	13	6	19
Postneonatal deaths			
< 2500 g	74	28	101
≥ 2500 g	26	23	49
Total	100	51	151

Note: Neonatal deaths: 2-tailed Fisher's exact test, $p < .02$
Postneonatal deaths: χ^2 (2 *df*) with Yates' correction = 4.8, $p < .03$

Changes in definitional criteria for SIDS may continue to affect the trend but it is unlikely that the criteria have been differentially applied to twins and singletons.

Recent studies have confirmed that being preterm or of low birthweight are at increased risk of SIDS compared with term or normal birthweight births (Blair et al., 2006; Thompson & Mitchell, 2006). Within the subgrouping according to birthweight, the extended data set used here shows that twins differ in their risk of SIDS compared with singletons. This confirms the previous observation that low birthweight twins are less prone to SIDS than singletons of the same birthweight groups. A proposed explanation is that, for a given birthweight, twins are more advanced gestationally and may be more competent immunologically than singletons owing to the maternal transfer of immunoglobulins occurring late in gestation (Platt & Pharoah, 2003).

The previous observation that same- and opposite-sex are at equal risk of SIDS is also confirmed. It was concluded then that zygosity was not a determinant of SIDS. However, the significant difference between same- and opposite-sex twins when neonatal and postneonatal mortality are separately examined, suggests that the role of zygosity in some subsets of twin SIDS should be reassessed. Monozygous twins are always same-sex and are at significantly increased risk of infant mortality and severe morbidity, particularly neurological impairment, in those who survive (Pharoah, 2005). The neurological abnormalities include holoprosencephaly, schizencephaly, hydranencephaly, porencephaly and multicystic encephalomalacia (Scheller & Nelson, 1992). While most of these pathological abnormalities are easily recognized on routine postmortem examination, others may require a more detailed histological examination. We propose that some twin SIDS, particularly the heavier infants who die in the neonatal period, should have a thorough histological examination of the brain. As neuronal migration abnormalities have been described in the surviving twin whose co-twin suffered fetal demise in the first (Baker et al., 1996) and second (Van Bogaert et al., 1996) trimesters, detailed histological examination of the brain of apparently singletons infants of normal birthweight should also be considered. This is in line with the recommended autopsy protocol for sudden unexpected deaths in infancy in the joint report by The Royal College of Pathologists and The Royal College of Paediatrics and Child Health (2004). The importance of neuropathological autopsy needs to be stressed to counteract the recent uncertainty over indiscriminate organ retention that has had such an adverse effect on post-mortem examination rates (Esiri & Ansorge, 2006).

If some SIDS are attributable to unrecognized cerebral impairment sustained in utero, prevention is unlikely with current medical practice. However, if cause can be ascribed to a case, it may assuage the guilt feeling parents experience over an unrecognized act of omission or commission.

Acknowledgments

We thank Nirupa Dattani and Tania Corbin of the Office for National Statistics for providing birth and death registration data.

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https://doi.org/10.1375/twin.10.4.644 Published online by Cambridge University Press