

ORIGINAL ARTICLE

## Second-Trimester Maternal Serum Levels of Alpha-Fetoprotein and the Subsequent Risk of Sudden Infant Death Syndrome

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ABSTRACT

**BACKGROUND**

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Unexplained stillbirth and the sudden infant death syndrome (SIDS) share some features. A raised maternal serum level of alpha-fetoprotein during the second trimester of pregnancy is a marker of placental dysfunction and a strong predictor of the risk of unexplained stillbirth. It is unknown whether alpha-fetoprotein levels also predict the risk of SIDS.

**METHODS**

We linked a prenatal-screening database for women in western Scotland with databases of maternity, perinatal death, and birth and death certifications to assess the association between second-trimester levels of maternal serum alpha-fetoprotein and the subsequent risk of SIDS.

**RESULTS**

Among 214,532 women with singleton births, there were 114 cases of SIDS (incidence, 2.7 per 10,000 births among women with alpha-fetoprotein levels in the lowest quintile and 7.5 per 10,000 births among those with levels in the highest quintile). When the lowest quintile was used as a referent, the unadjusted odds ratios for SIDS for the second through fifth quintiles were 1.7 (95 percent confidence interval, 0.8 to 3.5), 1.8 (95 percent confidence interval, 0.9 to 3.7), 2.5 (95 percent confidence interval, 1.3 to 4.8), and 2.8 (95 percent confidence interval, 1.4 to 5.4), respectively (P for trend=0.001). The risk of SIDS varied inversely with the birth-weight percentile and the gestational age at delivery; after adjustment for these factors, the odds ratios for SIDS were 1.7 (95 percent confidence interval, 0.8 to 3.5), 1.7 (95 percent confidence interval, 0.8 to 3.5), 2.2 (95 percent confidence interval, 1.1 to 4.4), and 2.2 (95 percent confidence interval, 1.1 to 4.3), respectively (P for trend=0.01).

**CONCLUSIONS**

There is a direct association between second-trimester maternal serum alpha-fetoprotein levels and the risk of SIDS, which may be mediated in part through impaired fetal growth and preterm birth.

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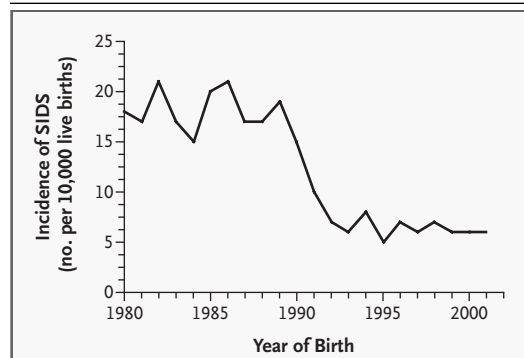
**T**HE SUDDEN INFANT DEATH SYNDROME (SIDS) is defined as the death of an infant during the first year of life in cases in which all identifiable causes of death can be ruled out by appropriate assessment. Observational studies have highlighted the prone sleeping position and environmental tobacco smoke in the infant's bedroom as factors that are associated with SIDS.<sup>1</sup> Widespread public health campaigns directed at modifying these behaviors have been followed by a sharp reduction in the incidence of SIDS. However, SIDS remains the most important single cause of infant death in the industrialized world.<sup>1,2</sup> A number of studies have identified obstetrical factors that are associated with an increased risk of SIDS, such as poor intrauterine growth and premature birth.<sup>1</sup> Moreover, as programs designed to address environmental risk factors have become widespread, the relative importance of obstetrical determinants has increased.<sup>3</sup>

The mechanisms linking complications of pregnancy and the risk of SIDS remain obscure. Previous studies have suggested similarities between unexplained stillbirth and SIDS with respect to clinical and pathological findings, suggesting that the two conditions may be related.<sup>4,5</sup> A raised maternal serum level of alpha-fetoprotein during the second trimester of pregnancy is one of the best biochemical predictors of the risk of unexplained stillbirth.<sup>6</sup> If SIDS and unexplained stillbirth have common pathophysiological determinants, there might be a direct association between maternal serum alpha-fetoprotein levels and the risk of SIDS. We designed this study to test the hypothesis that the risk of SIDS would increase with increasing maternal serum levels of alpha-fetoprotein in a large Scottish database linking biochemical, pregnancy, birth, and death records for 214,532 live-born singleton infants.

## METHODS

### SOURCES OF DATA

The Scottish Morbidity Record is a registry in which information on clinical and demographic characteristics and outcomes is collected for all women discharged from Scottish maternity hospitals. The registry is subjected to regular quality-assurance checks and has been more than 99 percent complete since the late 1970s.<sup>7</sup> The Scottish Stillbirth and Infant Death Enquiry is a national registry that routinely classifies all perinatal deaths



**Figure 1. Incidence of SIDS According to the Year of Birth among 1,321,646 Live Singleton Births in Scotland, 1980 to 2001.**

The range in the annual number of births was 48,740 to 65,688, and the range in the annual number of deaths attributed to SIDS was 29 to 131.

in Scotland.<sup>2</sup> All women attending prenatal care in western Scotland are offered biochemical screening, with their serum levels of alpha-fetoprotein and human chorionic gonadotropin used to assess their risk of having a fetus affected by Down's syndrome or a structural abnormality.<sup>8</sup> The laboratory information management system for the prenatal screening program of the West of Scotland Regional Genetics Service of the Institute of Medical Genetics, in Glasgow, contains a database of maternal information and biochemical-screening results. Electronic storage of these data in their current form was started in September 1991. Although serum alpha-fetoprotein was measured during screening before this date, the data were not archived in a format that allowed weight-adjusted multiples of the median to be calculated. The General Register Office, Scotland, maintains electronic birth and death records.

We used a probability-based, matching approach<sup>9</sup> with maternal identifiers to link the Scottish Morbidity Record, the Scottish Stillbirth and Infant Death Enquiry database, the Institute of Medical Genetics prenatal screening database, and the General Register Office database of birth certificates. The birth certificates contained offspring identifiers that were then used to link biochemical data, pregnancy data, and data on perinatal deaths to the death-certificate registry to identify deaths among the offspring. We excluded multiple births, stillbirths, and births before or after 24 to 43 weeks of gestation. Approval of the study was obtained

**Table 1. Demographic and Obstetrical Characteristics of the Cohort.\***

| Characteristic                                 | SIDS (N=114) | No SIDS (N=214,418) | P Value† |
|--|--------------|---------------------|----------|
| <b>Mother‡</b>                                 |              |                     |          |
| Age — yr                                       |              |                     | <0.001   |
| Median   | 25           | 28                  |          |
| Interquartile range                            | 20–31        | 24–32               |          |
| Height — cm                                    |              |                     | 0.002    |
| Median   | 160          | 162                 |          |
| Interquartile range                            | 157–165      | 158–167             |          |
| Body-mass index§                               |              |                     | 0.008    |
| Median   | 23.2         | 23.9                |          |
| Interquartile range                            | 20.9–25.5    | 21.7–27.0           |          |
| Parity — no. (%)                               |              |                     | 0.005    |
| Nulliparous                                    | 42 (36.8)    | 96,234 (44.9)       |          |
| 1 or 2   | 57 (50.0)    | 106,175 (49.5)      |          |
| 3 or 4   | 14 (12.3)    | 10,862 (5.1)        |          |
| ≥5   | 1 (0.9)      | 1,123 (0.5)         |          |
| Carstairs deprivation category — no. (%)       |              |                     | <0.001   |
| 1 (least deprived)                             | 2 (1.8)      | 8,909 (4.2)         |          |
| 2  | 6 (5.3)      | 22,571 (10.5)       |          |
| 3  | 14 (12.3)    | 41,147 (19.2)       |          |
| 4  | 18 (15.8)    | 52,748 (24.6)       |          |
| 5  | 20 (17.5)    | 34,412 (16.1)       |          |
| 6  | 19 (16.7)    | 31,383 (14.7)       |          |
| 7 (most deprived)                              | 35 (30.7)    | 22,893 (10.7)       |          |
| Smoking status — no. (%)                       |              |                     | <0.001   |
| Never smoked                                   | 29 (27.1)    | 124,261 (61.9)      |          |
| Former smoker                                  | 4 (3.7)      | 15,302 (7.6)        |          |
| Current smoker                                 | 74 (69.1)    | 61,264 (30.5)       |          |
| Serum alpha-fetoprotein multiple of the median |              |                     | 0.002    |
| Median   | 1.11         | 1.01                |          |
| Interquartile range                            | 0.91–1.39    | 0.81–1.27           |          |

from the Privacy Advisory Committee of the Information and Statistics Division, National Health Service, Scotland.

#### DEFINITIONS

For purposes of this study, SIDS was defined as the death of an infant during the first year of life with this diagnosis listed as the principal cause of death on the death certificate (code 798.0 in the *International Classification of Diseases, 9th Revision* [ICD-9] or code R95 in the *International Classification of Diseases, 10th Revision* [ICD-10]). During the period studied, a diagnosis of SIDS could be written on a death certificate in Scotland only after thorough investiga-

tion of the circumstances of the death. The minimal requirements are described by the Crown Office<sup>10</sup> (the government body that oversees the Procurator Fiscal, whose duties include the investigation of sudden deaths), and an autopsy is mandatory. In practice, the investigation of these deaths was frequently much more involved.<sup>11</sup> A previous, detailed study in which Scottish death certificates between 1992 and 1995 showed 201 deaths attributed to SIDS found that standard diagnostic criteria were fulfilled in all cases.<sup>12</sup> SIDS is a diagnosis of exclusion and is not made in the presence of a major congenital abnormality. The death certificate could contain up to three ICD-9 or ICD-10 di-

| Table 1. (Continued.)                                     |              |                     |           |
|---|--------------|---------------------|-----------|
| Characteristic  | SIDS (N=114) | No SIDS (N=214,418) | P Value†‡ |
| Serum alpha-fetoprotein quintiles — no. (%)               |              |                     | 0.001     |
| 1   | 12 (10.5)    | 43,912 (20.5)       |           |
| 2   | 20 (17.5)    | 42,185 (19.7)       |           |
| 3   | 21 (18.4)    | 42,660 (19.9)       |           |
| 4   | 29 (25.4)    | 43,193 (20.1)       |           |
| 5   | 32 (28.1)    | 42,468 (19.8)       |           |
| Serum human chorionic gonadotropin multiple of the median |              |                     | 0.20      |
| Median  | 0.95         | 1.00                |           |
| Interquartile range                                       | 0.60–1.44    | 0.71–1.40           |           |
| <b>Infant</b>   |              |                     |           |
| Male sex — no. (%)  | 72 (63.2)    | 109,883 (51.2)      | 0.01      |
| Birth-weight percentile                                   |              |                     | <0.001    |
| Median  | 28           | 50                  |           |
| Interquartile range                                       | 12–56        | 25–75               |           |
| Birth weight — g  |              |                     | <0.001    |
| Median  | 3000         | 3410                |           |
| Interquartile range                                       | 2530–3310    | 3060–3750           |           |
| Gestational age — wk                                      |              |                     | <0.001    |
| Median  | 39           | 40                  |           |
| Interquartile range                                       | 37–40        | 39–41               |           |

\* Of the 114 cases of death attributed to SIDS, data were missing on the mother's height in 2 (1.8 percent), body-mass index in 9 (7.9 percent), and smoking status in 7 (6.1 percent). Of the remaining 214,418 records, data were missing on the mother's height in 2510 (1.2 percent), body-mass index in 15,877 (7.4 percent), parity in 24 (<0.1 percent), deprivation category in 355 (0.2 percent), and smoking status in 13,591 (6.3 percent) and were missing on the infant's sex in 9 (<0.1 percent), birth-weight percentile in 61 (<0.1 percent), and birth weight in 53 (<0.1 percent).

† P values were calculated by the Mann-Whitney U test, the chi-square test, or the chi-square test for trend, as appropriate.

‡ The mother's age is the age at the time of delivery, and the body-mass index and smoking status are those documented at her first visit for prenatal care. The Carstairs deprivation category is estimated on the basis of socioeconomic indicators in the area of residence; the method of calculation has been described in detail elsewhere.<sup>13</sup> The multiple of the median is the ratio of an individual value to the median value for the given week of gestation, corrected for maternal weight.<sup>17</sup>

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

agnostic codes. We ruled out coexisting congenital abnormalities by searching the second and third diagnostic codes (for ICD-9 codes 740.0 to 759.9 or ICD-10 codes beginning with "Q"); none of the cases in which death had been attributed to SIDS on the certificate also had these codes.

The mother's age and parity, the postal code of her residence, and all outcome data were obtained solely from the Scottish Morbidity Record. The mother's weight was obtained solely from the biochemical database. Her height and smoking status were obtained from the Scottish Morbidity Record or, in cases in which they were missing from the Scottish Morbidity Record, from the biochemical database. The smoking status (current, former, or never) was determined on the basis of information

gathered at the time of the first prenatal visit or at the time of prenatal screening if this information was obtained from the biochemical database. The mother's age was defined as the age of the mother at the time of delivery. Her body-mass index was calculated as the weight in kilograms recorded at the time of sampling for the alpha-fetoprotein assay divided by the square of the height in meters. Socioeconomic status was estimated on the basis of the postal code of the mother's residence, according to Carstairs socioeconomic-deprivation categories<sup>13</sup> (based on 1991 Census data on car ownership, employment status, number of occupants per household room, and social class within postal-code sectors of residence that contain, on average, about 1600 residents).

The gestational age at birth was defined as the number of weeks of gestation completed, on the basis of the estimated date of delivery in each woman's clinical record; standard national criteria exist for estimation of the date of delivery with the use of menstrual and ultrasonographic data.<sup>14</sup> Since the early 1990s, the estimated gestational age has been confirmed by ultrasonography during the first half of pregnancy in more than 95 percent of pregnancies in the United Kingdom.<sup>15</sup> The birth weight was categorized into sex-specific and gestational-age-specific percentiles, as previously described in detail.<sup>16</sup> Maternal serum levels of alpha-fetoprotein and human chorionic gonadotropin were quantified as multiples of the median (the ratio of the individual value to the median value) for the given week of gestation, after correction for the mother's weight.<sup>17</sup>

#### STATISTICAL ANALYSIS

Univariate comparisons were performed with the Mann-Whitney U test, the chi-square test, and the chi-square test for trend, as appropriate. The P values for all hypothesis tests were two-sided. Crude and adjusted odds ratios for SIDS were obtained by means of logistic-regression analysis.<sup>18</sup> Biochemical data were categorized into deciles or quintiles. The mother's age, height, body-mass index, and parity were treated continuously in logistic-regression models, as were the birth-weight percentile and the gestational age (in weeks) at delivery. Non-linearity of continuous variables in the logistic regression was tested and modeled with the use of fractional polynomials. The regression techniques involved the use of robust standard errors, as well as unique maternal identifiers, to account for dependence between births to the same mother.

The statistical significance of interaction terms was assessed by means of the Wald test, and results were considered significant when the P value was less than 0.01. Observations for which values were missing for variables that were more than 99.8 percent complete in the linked database were dropped from the multivariate analysis. For variables that were 99.8 percent or less complete in the linked database, missing values were estimated by multiple multivariate imputation.<sup>19</sup> The goodness of fit of the models was assessed with a Hosmer-Lemeshow test based on deciles of probability. All statistical analyses were performed with use of Stata software, version 8.2.

## RESULTS

A total of 1,321,646 live singleton births at 24 to 43 weeks of gestation were recorded in the Scottish Morbidity Record between 1980 and 2001, and 1673 of the infants died from SIDS (12.7 per 10,000). Figure 1 shows the incidence of SIDS according to year of birth and indicates a sharp decline around 1990 and 1991, coincident with the public appreciation of the effects of a prone sleeping position and environmental tobacco smoke on the risk of SIDS. There were 216,563 linked records for singleton births for which the maternal serum alpha-fetoprotein level had been recorded. Of these, we excluded 867 (0.40 percent) with extreme levels of alpha-fetoprotein (defined as values at or below the 0.2nd percentile or at or above the 99.8th percentile), 1060 stillbirths (0.49 percent), and 131 births at a gestational age of less than 24 weeks or more than 43 weeks (0.06 percent); 2031 records listed one or more of these reasons for exclusion. Thus, the study cohort comprised 214,532 live births between November 15, 1991, and December 31, 2001.

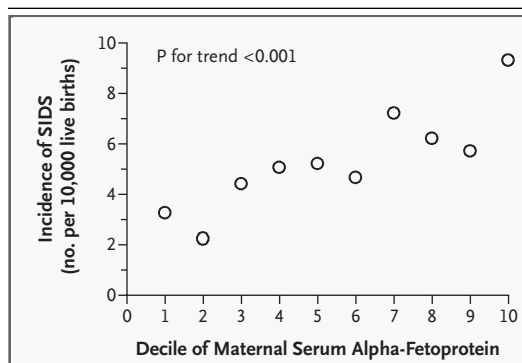
There were 114 deaths attributed to SIDS in the cohort, yielding an incidence of 5.3 (95 percent confidence interval, 4.4 to 6.4) per 10,000 live births. The incidence in the whole of Scotland over the same period was 6.5 (95 percent confidence interval, 5.8 to 7.2) per 10,000 live births. There were 880 deaths during the first year of life in the cohort. In 311 of these deaths (35.3 percent), one or more of the three diagnostic codes included on the death certificate was the code for a congenital abnormality. There were no congenital abnormalities listed among the three diagnostic codes on the death certificate in the 114 cases of SIDS.

The assays for alpha-fetoprotein were performed between 15 and 21 weeks of gestation. The range of the maternal serum level of alpha-fetoprotein, expressed as multiples of the median, was 0.35 to 3.75; the 5th percentile was 0.59 and the 95th percentile 1.82. The quintiles of the maternal serum level of alpha-fetoprotein, expressed as multiples of the median for gestational age, were less than or equal to 0.77; greater than 0.77 but less than or equal to 0.93; greater than 0.93 but less than or equal to 1.10; greater than 1.10 but less than or equal to 1.35; and greater than 1.35. The demographic and obstetrical characteristics of the study cohort are shown in Table 1. Women whose infants

ultimately died of SIDS were younger, shorter, had a lower body-mass index, were of higher parity, were more likely to live in a very socioeconomically deprived area, were more likely to smoke, had higher second-trimester levels of alpha-fetoprotein, were more likely to have delivered a male infant, had offspring with lower birth-weight percentiles, and had delivered earlier than women whose infants did not die of SIDS (Table 1).

The risk of SIDS increased with increasing second-trimester maternal serum levels of alpha-fetoprotein (Fig. 2). The incidence of SIDS was 2.7 per 10,000 births among women with alpha-fetoprotein levels in the lowest quintile and 7.5 per 10,000 births among those with levels in the highest quintile, and there was a linear trend across the quintiles (Table 2). The risk of SIDS was inversely related to the birth-weight decile and the gestational age at birth (Fig. 3). Adjusting for these factors attenuated the strength of the association between alpha-fetoprotein levels and the risk of SIDS, but a significant relationship persisted: adjusted odds ratios for the second through fifth quintiles were 1.7 (95 percent confidence interval, 0.8 to 3.5), 1.7 (95 percent confidence interval, 0.8 to 3.5), 2.2 (95 percent confidence interval, 1.1 to 4.4), and 2.2 (95 percent confidence interval, 1.1 to 4.3), respectively (P for trend=0.01). In multivariate analysis, the risk of SIDS also varied according to the sex of the infant and the mother's age, parity, and smoking status (Table 2). Further adjustment for these factors did not materially affect the association between the alpha-fetoprotein level and the risk of SIDS (Table 2).

There were no significant interactions between the maternal serum alpha-fetoprotein level and any of the maternal or obstetrical characteristics in any of the models. The goodness of fit of all the models appeared to be adequate, as assessed by global tests of goodness of fit, which showed no significant difference between the observed and expected numbers of deaths attributed to SIDS when women were categorized according to the decile of probability predicted by the multivariate model. When maternal serum alpha-fetoprotein was treated as a continuous variable in logistic-regression models, the unadjusted odds ratio for SIDS associated with an increase of 1 in the multiple of the median was 2.0 (95 percent confidence interval, 1.4 to 3.0;  $P < 0.001$ ). The odds ratio adjusted for birth-weight percentile and gestational age was 1.6 (95 percent confidence interval, 1.1 to 2.3;  $P = 0.02$ ); the odds



**Figure 2.** Incidence of SIDS, According to the Decile of Maternal Serum Alpha-Fetoprotein Level.

ratio adjusted for birth-weight percentile, gestational age, and all maternal characteristics was 1.5 (95 percent confidence interval, 1.0 to 2.2;  $P = 0.03$ ); and the odds ratio adjusted for birth weight as a continuous variable was 1.6 (95 percent confidence interval, 1.1 to 2.3;  $P = 0.02$ ). When all other continuous variables were categorized and missing values treated with the use of indicator variables, the adjusted odds ratio for an increase of 1 in the multiple of the median of maternal serum alpha-fetoprotein was 1.6 (95 percent confidence interval, 1.1 to 2.3;  $P = 0.02$ ).

There was no significant association between the risk of SIDS and maternal serum levels of human chorionic gonadotropin, either expressed as a continuous variable (odds ratio for an increase of 1 in the multiple of the median for gestational age, 0.92; 95 percent confidence interval, 0.67 to 1.24;  $P = 0.57$ ) or categorized into quintiles ( $P$  for trend=0.19).

## DISCUSSION

The present study shows that the risk of an infant's death from SIDS increased with increasing serum levels of alpha-fetoprotein in the mother during the second trimester of pregnancy. The risk of SIDS among the infants of women with alpha-fetoprotein levels in the highest quintile was 2.8 times that among infants whose mothers' levels was in the lowest quintile, although the absolute risk of SIDS remained low, even in the highest quintile (7.5 per 10,000 live births). We observed no significant association between serum levels of human chorionic gonadotropin and the risk of SIDS.

Both preterm birth and intrauterine growth re-

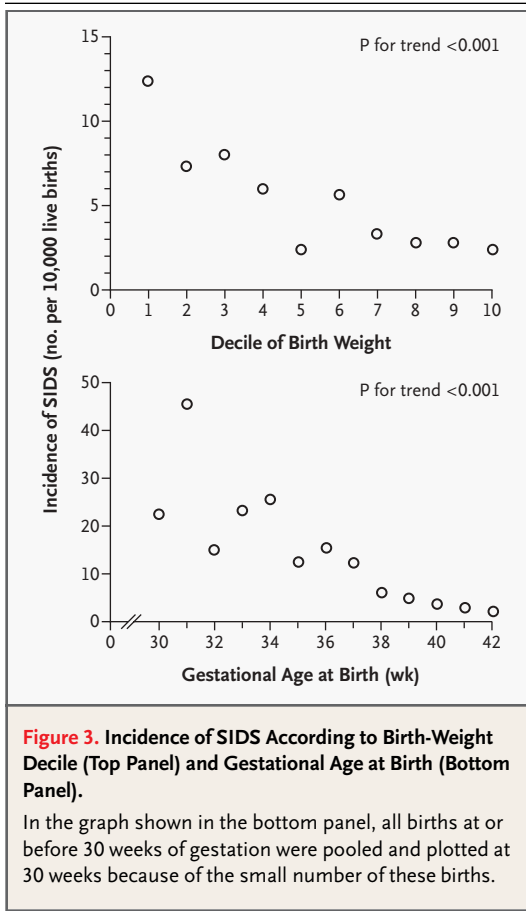
**Table 2. Unadjusted and Adjusted Odds Ratios for SIDS in Relation to Characteristics of the Mother and Infant.\***

| Variable   | Unadjusted Analysis |                 | Analysis Adjusted for Characteristics of Mother and Infant† |                |
|--|---------------------|-----------------|---|----------------|
|  | Odds Ratio (95% CI) | P Value         | Odds Ratio (95% CI)   | P Value        |
| <b>Mother</b>  |                     |                 |   |                |
| Serum alpha-fetoprotein quintile                     |                     |                 |   |                |
| 1 (referent)   | 1.0                 |                 | 1.0   |                |
| 2  | 1.7 (0.8–3.5)       | 0.13            | 1.7 (0.8–3.6)   | 0.13           |
| 3  | 1.8 (0.9–3.7)       | 0.10            | 1.8 (0.9–3.6)   | 0.12           |
| 4  | 2.5 (1.3–4.8)       | 0.009           | 2.2 (1.1–4.4)   | 0.02           |
| 5  | 2.8 (1.4–5.4)       | 0.003           | 2.2 (1.1–4.2)   | 0.02           |
|  |                     | 0.001 for trend |   | 0.01 for trend |
| Age (yr)‡  |                     |                 |   |                |
| 20 (referent)  | 1.0                 |                 | 1.0   |                |
| 25   | 0.5 (0.4–0.6)       | <0.001          | 0.5 (0.4–0.6)   | <0.001         |
| 30   | 0.3 (0.2–0.5)       | <0.001          | 0.3 (0.2–0.5)   | <0.001         |
| 35   | 0.4 (0.2–0.6)       | <0.001          | 0.3 (0.2–0.55)  | <0.001         |
| 40   | 0.7 (0.4–1.3)       | 0.26            | 0.5 (0.2–1.1)   | 0.10           |
| Height (per 10-cm increase)                          | 0.6 (0.5–0.8)       | 0.001           | 0.8 (0.6–1.1)   | 0.24           |
| Body-mass index (per 5-unit increase)                | 0.8 (0.6–1.0)       | 0.07            | 0.9 (0.7–1.2)   | 0.62           |
| Parity (per one-birth increase)                      | 1.4 (1.2–1.6)       | <0.001          | 1.5 (1.3–1.7)   | <0.001         |
| Carstairs deprivation category                       |                     |                 |   |                |
| 1 (least deprived; referent)                         | 1.0                 |                 | 1.0   |                |
| 2  | 1.2 (0.2–5.9)       | 0.84            | 1.0 (0.2–4.8)   | 0.97           |
| 3  | 1.5 (0.3–6.7)       | 0.58            | 1.0 (0.2–4.4)   | 0.98           |
| 4  | 1.5 (0.4–6.6)       | 0.57            | 0.8 (0.2–3.7)   | 0.79           |
| 5  | 2.6 (0.6–11.1)      | 0.20            | 1.2 (0.3–5.1)   | 0.83           |
| 6  | 2.7 (0.6–11.6)      | 0.18            | 1.2 (0.3–5.2)   | 0.83           |
| 7 (most deprived)                                    | 6.8 (1.6–28.3)      | 0.008           | 2.2 (0.5–9.6)   | 0.28           |
| Smoking status                                       |                     |                 |   |                |
| Never smoked (referent)                              | 1.0                 |                 | 1.0   |                |
| Former smoker  | 1.3 (0.4–3.5)       | 0.67            | 1.1 (0.4–3.1)   | 0.90           |
| Current smoker                                       | 4.9 (3.1–7.6)       | <0.001          | 2.5 (1.5–4.1)   | <0.001         |
| <b>Infant</b>  |                     |                 |   |                |
| Male sex   | 1.6 (1.1–2.4)       | 0.01            | 1.6 (1.1–2.3)   | 0.02           |
| Birth-weight percentile (per 10-percentile increase) | 0.8 (0.8–0.9)       | <0.001          | 0.9 (0.8–1.0)   | 0.003          |
| Gestational age (per 1-wk increase)                  | 0.8 (0.8–0.9)       | <0.001          | 0.8 (0.8–0.9)   | <0.001         |

\* All data were treated as continuous except the quintile of serum alpha-fetoprotein, the Carstairs deprivation category, smoking status, and the infant's sex. CI denotes confidence interval.

† P=0.37 by the global test of goodness of fit (evaluated separately for each imputed data set and the lowest P value reported).

‡ The relationship between the mother's age (in years) and the risk of SIDS was nonlinear and was fitted with use of the following polynomials: the square of the age and the square of the age multiplied by the log of the age. Point estimates of the odds ratios and 95 percent confidence intervals (with reference to an age of 20 years) are given to illustrate the pattern of association. All other continuous variables were linear in the log odds scale.



striction are associated with an elevated maternal serum level of alpha-fetoprotein.<sup>6</sup> The association between the maternal serum alpha-fetoprotein level and the risk of SIDS appeared to be mediated in part by these factors. However, even after adjusting for gestational age at birth and birth-weight percentile, we found that the infants of mothers with alpha-fetoprotein levels in the upper two quintiles had a risk of SIDS that was more than twice the risk among infants of mothers with values in the lowest quintile.

Alpha-fetoprotein is the main protein contributing to oncotic pressure in the fetal circulation and is comparable to albumin in adults.<sup>20</sup> Elevated maternal serum levels of alpha-fetoprotein in the absence of fetal abnormality are thought to indicate increased placental permeability and therefore a defect in placental function.<sup>6</sup> Associations between elevated maternal serum levels of alpha-fetoprotein and both poor fetal growth and pre-

term birth<sup>21</sup> are believed to reflect the role of defective early placental function in these outcomes. Adjusting for gestational age and birth weight may thus result in an underestimation of the association between maternal serum alpha-fetoprotein levels and the risk of SIDS, since an adverse early intrauterine environment may mediate the subsequent risk of SIDS in part by its consequences on fetal growth and the timing of birth. In this study, a significant association remained after adjustment for these factors, however, suggesting that the intrauterine environment may influence the probability that a given postnatal environment will lead to SIDS. Experimental studies have shown that fetal hypoxemia induces a chemoreceptor-mediated redistribution of cardiac output, increasing flow to the cardiac and cerebral circulations.<sup>22</sup> Chronic, mild fetal hypoxemia leads to premature maturation of fetal cardiovascular control, manifested as a lower heart rate and a higher blood pressure early during gestation.<sup>23</sup> We speculate that a suboptimal intrauterine environment may lead to altered cardiorespiratory control, which could in turn predispose an infant toward SIDS, although this hypothesis requires further study.

The strengths of the present study include its large size, the availability of detailed information on the characteristics of the mothers, and the fact that all exposure data were collected independently of the ascertainment of events. Whereas previous studies have shown that the risk of SIDS varies according to both preterm birth and intrauterine growth restriction,<sup>1</sup> many studies have dichotomized gestational age at birth as term or preterm and have dichotomized birth weight as above or below a given percentile for gestational age. We found continuous relationships between gestational age at birth and the risk of SIDS as well as between birth-weight percentile and the risk of SIDS; this approach reduces the likelihood of residual confounding due to categorization of continuous variables. Nevertheless, some misclassification is possible. We relied on women's postal codes to classify their socioeconomic status, and for women who reported smoking, we did not have data on the number of cigarettes they smoked. However, after adjustment for gestational age and birth-weight percentile, further adjustment for characteristics of the mothers based on the available data had no material effect.

The sharp decline in the incidence of SIDS after the inception of public health programs aimed at improving infants' sleeping conditions has led to a search for factors that might explain the remaining cases. The observed association between elevated maternal serum alpha-fetoprotein levels during the second trimester and the incidence of SIDS

suggests that an adverse intrauterine environment during the first half of pregnancy may be another important determinant of the risk of SIDS.

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