Adult Hemoglobin Levels at Birth and Risk of Sudden Infant Death Syndrome

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Background: During the final weeks of gestation, infants normally begin a transition from the production of fetal to adult hemoglobin. Delayed or faulty transition to the production of adult hemoglobin might play a role in the etiology of sudden infant death syndrome (SIDS).

Objective: To examine the association between adult hemoglobin levels measured at birth and the subsequent risk of SIDS.

Design and Setting: Cohort study of all infants born in California between March 1, 1990, and December 31, 1997, who were enrolled in the state's Newborn Screening Program and followed up during the first year of life to identify deaths attributed to SIDS.

Participants: Population-based sample of 3.2 million infants.

Main Outcome Measure: Risk of death attributed to SIDS.

Results: The study included 2425 infants whose deaths were attributed to SIDS. There was an inverse relationship between adult hemoglobin level, expressed as a percentage of total hemoglobin, and the subsequent incidence of SIDS. After adjustment for infant sex, race/ethnicity, length of gestation, maternal age, maternal education, maternal smoking, intrauterine growth restriction, and preeclampsia/eclampsia, the relative risks of SIDS for infants in the lower 4 quintiles of adult hemoglobin level were, in descending order, 1.12 (95% confidence interval [CI], 0.96-1.32), 1.38 (95% CI, 1.19-1.59), 1.55 (95% CI, 1.34-1.80), and 2.15 (95% CI, 1.87-2.47) compared with infants in the highest quintile.

Conclusions: These findings suggest that infants with low levels of adult hemoglobin in the first hours after birth are at elevated risk of SIDS. Delayed maturation in production of adult hemoglobin may play a role in the etiology of some SIDS cases.

whether hemoglobin levels measured at birth predict risk of SIDS.

In this article we report on the findings of a large population-based cohort study of adult hemoglobin level and the risk of SIDS. In addition to encompassing a large number of SIDS cases, this investigation uses information on hemoglobin levels collected from newborns, rather than information derived from postmortem blood samples.8,11,13-15 The cohort design of this study allows us to clearly establish the temporal relationship between hemoglobin levels and SIDS, something that could not be done in previous autopsy-based case-control studies. A database of hemoglobin measurements for more than 3.2 million live births included in the California Newborn Screening Program was linked with California vital statistics records. These data were used to examine the association between levels of adult hemoglobin and SIDS among infants born in the state of California from 1990 to 1997.

**METHODS**

The level of adult hemoglobin at birth, expressed as a percentage of the total hemoglobin in the blood sample, was determined for 99% of live-born infants in the state of California from March 1, 1990, through December 31, 1997, as part of the California Newborn Screening Program.16,17 Dried blood-spot specimens, collected via a heel stick, were analyzed by means of high-performance liquid chromatography. The screening is mandatory for all live births in the state, regardless of whether the birth occurs in a hospital. In this study, we used information from the Newborn Screening Program for all nontransfused infants who had an adequate blood specimen collected within 6 days of birth.

These Newborn Screening Program records were linked to California’s birth cohort (live birth and infant death) records. All live-born infants with a birth certificate registered in the state of California during the study period were followed up during the first year of life to identify infant deaths; for infant deaths occurring out of state, death certificates were sent to California under the National Infant Death Linkage Project. The percentage of Newborn Screening Program records successfully linked to birth cohort records ranged from 3% in 1990 to 92% in 1997.

Deaths due to SIDS were identified by code 798.0 of the International Classification of Diseases, Ninth Revision. California has a rigorous system of verification of each SIDS case that includes detailed protocols for autopsy and death scene investigation.19

Information from the birth certificate was used to define study covariates. Information on sex and date of birth was complete for all infants. Infant race and Hispanic ethnicity were assigned using maternal and paternal race/ethnicity information.20 Infants of unknown race (<1%) were classified as white; infants of unknown ethnicity (7%) were classified as non-Hispanic. Length of gestation was determined by subtracting the date of last menses from the date of birth. Infants for whom length of gestation could not be calculated owing to missing information on the date of last menses were excluded (Table 1). In regression analyses, we included a continuous term for length of gestation; newborn hemoglobin-SIDS associations were also examined in subgroups defined by length of gestation. Intrauterine growth restriction was defined as any infant whose birth weight was below the 10th percentile for their gestational age based on a standardized tabulation of birth weight for gestational age by race, sex, and parity for US newborns.21 Infants with missing birth weights were excluded from the analyses (Table 1). Maternal age was categorized into 7 groups (<16, 17-19, 20-24, 25-29, 30-

### Table 1. Enumeration of Study Cohort

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of infants in the Newborn Screening Program</td>
<td>3,488,982</td>
</tr>
<tr>
<td>1990-1997</td>
<td>4,541,765</td>
</tr>
<tr>
<td>No. with an adequate specimen†</td>
<td>3,931,490</td>
</tr>
<tr>
<td>No. with an adequate specimen and successfully linked to California birth cohort records</td>
<td>3,488,982</td>
</tr>
<tr>
<td>Exclusions, No. of infants</td>
<td>2,242,606</td>
</tr>
<tr>
<td>Missing high-performance liquid chromatography results</td>
<td>113,043</td>
</tr>
<tr>
<td>Unknown length of gestation</td>
<td>104,942</td>
</tr>
<tr>
<td>Unknown birth weight</td>
<td>28,385</td>
</tr>
<tr>
<td>Unknown maternal age</td>
<td>6</td>
</tr>
<tr>
<td>Study cohort, No. of infants</td>
<td>1,242,606</td>
</tr>
</tbody>
</table>

†Includes an adequate blood specimen collected before any blood transfusion and within 6 days of birth.

**RESULTS**

Enumeration of the study cohort is summarized in Table 1. The study included 3,242,606 infants among whom 2,425 deaths were attributed to SIDS; the overall risk of SIDS was below the 10th percentile for their gestational age based on information derived from postmortem blood samples.8,11,13-15 Hemoglobin levels measured at birth were categorized into 7 groups (<16, 17-19, 20-24, 25-29, 30-

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SIDS was 74.8 per 100,000 infants. Similar to observations from previous research, the risk of SIDS was higher among male than female infants, higher among non-Hispanic black infants than other infants, and higher among those born prematurely and with intrauterine growth restriction (Table 2). The risk of SIDS was higher among infants whose mothers were young and educated at a high school level or less. The risk of SIDS was higher among infants whose mothers smoked during the pregnancy and had experienced preeclampsia or eclampsia. It was also lower among Asian and non-Hispanic black infants than other infants. The average level of adult hemoglobin was higher among infants whose mothers were young, were educated at less than a high school level, had smoked, or had experienced preeclampsia or eclampsia during pregnancy (Table 2).

Table 3 shows the distribution of SIDS deaths and the crude (unadjusted) risk of SIDS by adult hemoglobin level. Categories were defined by quintiles of the adult hemoglobin distribution, so each group included 20% of the infants in the study cohort. The 20th, 40th, 60th, and 80th percentiles of the distribution (which define the quintiles) were 7.5%, 9.4%, 11.4%, and 14.0%, respectively; the 50th and 95th percentiles were 5.2% and 18.5%, respectively. The risk of SIDS was greater for infants who had relatively low levels of adult hemoglobin at birth than for infants who had higher levels of adult hemoglobin. After adjusting for sex, race/ethnicity, maternal age, maternal education, maternal smoking, preeclampsia/eclampsia, intrauterine growth restriction, and length of gestation, the risk of SIDS was estimated to be 2.15-fold greater for infants in the lowest quintile of the adult hemoglobin distribution compared with infants in the top quintile of the adult hemoglobin distribution (Table 3).

We developed a regression model for the association between adult hemoglobin level and SIDS risk. A model with linear, quadratic, and cubic polynomial terms for adult hemoglobin level fit the data significantly better than a simple linear model (likelihood ratio test, 40.9 [2 df]); inclusion of higher-order polynomial terms led to no significant improvement in model fit compared with the linear-quadratic-cubic model (Figure). The regression coefficients for this model are used in the following predicative equation for the natural logarithm (ln) of the relative risk (RR) of SIDS when comparing 2 groups of infants with different adult hemoglobin levels, denoted as a and b:

\[ \ln(\text{RR}) = -0.178(a - b) + 0.005(a^2 - b^2) - 0.00004(a^3 - b^3). \]

Restriction of the cohort to the 3,196,863 infants with the normal hemoglobin pattern, Hb FA, led to nearly identical estimates of association between adult hemoglobin level and SIDS for each of the categories plotted in the Figure with the exception of the lowest category of adult hemoglobin, for which the adjusted risk estimate was 7% higher in the restricted cohort (338 SIDS cases per 100,000) than in the full cohort (311 SIDS cases per 100,000).

We examined the association between adult hemoglobin level and SIDS within subgroups defined by length of gestation (Table 4). Exposure categories were defined by quintiles of the adult hemoglobin distribution within each subgroup. There was evidence of an inverse association between adult hemoglobin level and SIDS, adjusting for all other study covariates (including gestational age to control residual confounding within gestational age categories), within each subgroup; trends were not monotonic in the subgroups for infants with the shortest lengths of gestation (<34 and 34–35 weeks).

An inverse association between adult hemoglobin level and SIDS was observed in nearly all strata defined by maternal age, education, preeclampsia/eclampsia dur-
Be associated with hemoglobin levels measured at birth. These analyses, because any potential confounder must reflect the effects of other factors associated with both adult hemoglobin levels and SIDS risk. Pre-natal characteristics are a priori more plausible than post-natal characteristics as potential confounding factors in these analyses, because any potential confounder must be associated with hemoglobin levels measured at birth.

During the study period, the risk of SIDS declined from 106.8 deaths per 100,000 infants in 1990 to 52.7 deaths per 100,000 infants in 1997. Despite the decline in SIDS risk during the study period, evidence of an adult hemoglobin–SIDS association was observed for infants in each of the birth cohorts (Table 4).

In this cohort, there was an inverse association between adult hemoglobin levels measured in the first days of life and the subsequent risk of SIDS (Figure). High-performance liquid chromatography was used to quantitate adult hemoglobin levels, with results expressed as a percentage of total hemoglobin. A low adult hemoglobin level, therefore, is evidence that an infant has experienced a delayed or faulty transition to production of adult hemoglobin; it is not necessarily evidence that the infant has a low total hemoglobin level (ie, anemia). In fact, newborns with significantly low total hemoglobin levels were excluded from analyses because their blood samples were considered inadequate for determination of hemoglobin levels (Table 1). It is possible that a deficit in adult hemoglobin level at birth (and corresponding elevation in fetal hemoglobin level) is a marker of an underlying chronic pathologic condition or developmental impairment (eg, in cardiorespiratory control) or that elevated fetal hemoglobin level is itself involved in the etiology of some deaths due to SIDS.

An alternative possibility is that the observed association between adult hemoglobin level and SIDS reflects the effects of other factors associated with both adult hemoglobin level measured at birth and SIDS risk. Prenatal characteristics are a priori more plausible than post-natal characteristics as potential confounding factors in these analyses, because any potential confounder must be associated with hemoglobin levels measured at birth.

Prenatal maternal smoking, for example, appears to be associated with adult hemoglobin levels at birth and subsequent SIDS risk (Table 1), and therefore could be a confounder of the association under study. Although we adjusted our regression analyses for maternal smoking during pregnancy, the information that we used was self-reported and permitted only adjustment for a dichotomous indicator of prenatal maternal smoking status; therefore, control for potential confounding by this factor is incomplete. We also adjusted our analyses for several sociodemographic factors, including race/ethnicity and maternal education. Adjustment for these factors may also help to control for the effects of some potential confounding environmental or behavioral factors. Nonetheless, potential bias due to uncontrolled confounding remains an important consideration in the interpretation of these findings.

Although there was an inverse association between adult hemoglobin levels and SIDS risk among non-Hispanic white and black infants, Hispanic infants, and infants of other race, there was no evidence of an association between adult hemoglobin level and SIDS among Asian infants (Table 4). Asian infants had the lowest risk of SIDS and the lowest average adult hemoglobin levels in this cohort (Table 2). It is unclear why the predictive value of adult hemoglobin level as a risk factor for SIDS is poorer for Asian infants than for other infants.

The Back to Sleep campaign and other efforts to reduce exposure to environmental risk factors for SIDS have coincided with a significant reduction in deaths due to SIDS²; during the study period, the risk of SIDS in California decreased by approximately 50%. Despite this decline, the association between adult hemoglobin level at

**COMMENT**

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Adult Hemoglobin Level, %a</th>
<th>No. of Deaths</th>
<th>Unadjusted SIDS Mortality Risk†</th>
<th>Adjusted RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>≥14.0</td>
<td>295</td>
<td>44.6</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>11.4 to &lt;14.0</td>
<td>334</td>
<td>52.2</td>
<td>1.12 (0.96-1.32)</td>
</tr>
<tr>
<td>3</td>
<td>9.4 to &lt;11.4</td>
<td>442</td>
<td>66.5</td>
<td>1.38 (1.19-1.59)</td>
</tr>
<tr>
<td>2</td>
<td>7.5 to &lt;9.4</td>
<td>505</td>
<td>79.7</td>
<td>1.55 (1.34-1.80)</td>
</tr>
<tr>
<td>1</td>
<td>&lt;7.5</td>
<td>849</td>
<td>131.8</td>
<td>2.15 (1.87-2.47)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; SIDS, sudden infant death syndrome.

*Expressed as a percentage of total hemoglobin level.
†Calculated as the number of SIDS deaths divided by number of infants at risk (per 100,000).
‡Indicates estimated RR, adjusted for infant sex, race/ethnicity, maternal age, maternal education, maternal smoking, preeclampsia/eclampsia, intrauterine growth restriction, and length of gestation.

Table 3. SIDS Cases, Mortality Risk, and Adjusted RR Estimates According to Level of Adult Hemoglobin Measured at Birth

Prenatal maternal smoking, for example, appears to be associated with adult hemoglobin levels at birth and subsequent SIDS risk (Table 1), and therefore could be a confounder of the association under study. Although we adjusted our regression analyses for maternal smoking during pregnancy, the information that we used was self-reported and permitted only adjustment for a dichotomous indicator of prenatal maternal smoking status; therefore, control for potential confounding by this factor is incomplete. We also adjusted our analyses for several sociodemographic factors, including race/ethnicity and maternal education. Adjustment for these factors may also help to control for the effects of some potential confounding environmental or behavioral factors. Nonetheless, potential bias due to uncontrolled confounding remains an important consideration in the interpretation of these findings.

Although there was an inverse association between adult hemoglobin levels and SIDS risk among non-Hispanic white and black infants, Hispanic infants, and infants of other race, there was no evidence of an association between adult hemoglobin level and SIDS among Asian infants (Table 4). Asian infants had the lowest risk of SIDS and the lowest average adult hemoglobin levels in this cohort (Table 2). It is unclear why the predictive value of adult hemoglobin level as a risk factor for SIDS is poorer for Asian infants than for other infants.

The Back to Sleep campaign and other efforts to reduce exposure to environmental risk factors for SIDS have coincided with a significant reduction in deaths due to SIDS²; during the study period, the risk of SIDS in California decreased by approximately 50%. Despite this decline, the association between adult hemoglobin level at
A number of studies have examined postmortem measurements from birth to 6 weeks and have noted that low adult hemoglobin levels at birth are inversely correlated with SIDS risk (results not shown). Despite this limitation, fetal hemoglobin levels were inversely correlated with adult hemoglobin levels and, consequently, positively correlated with SIDS risk (results not shown).

We suspect that low adult hemoglobin levels at birth (and corresponding elevations in fetal hemoglobin) are correlated with low adult hemoglobin levels later in infancy when SIDS deaths tend to occur. Such a correlation was observed in a small pilot study that examined repeated hemoglobin measurements from birth to 6 weeks of age.\(^\text{13}\) A number of studies have examined postmortem levels of fetal hemoglobin in SIDS cases. Many\(^\text{6,11,13}\) but not all\(^\text{14,15}\) of these investigations support the conclusion that fetal hemoglobin levels are abnormally elevated in postmortem blood samples from SIDS cases. A useful direction for future research might be to obtain follow-up hemoglobin measures several weeks (eg, 4-8 weeks) after the newborn screening to investigate whether the latter measure is also a predictor of SIDS risk.

Stewart\(^\text{24-26}\) suggested that infants with difficulty switching from fetal to adult hemoglobin may also have difficulty switching from passive to active immunity. She postulated that high levels of fetal hemoglobin (and low levels of adult hemoglobin) may be associated with risk of death due to SIDS and death due to respiratory infection. Similarly, Fagan and Walker\(^\text{9}\) suggested that elevated fetal hemoglobin levels might be a marker of a predisposition to sudden death in response to a variety of insults, rather than a unique marker of predisposition to SIDS.

### CONCLUSIONS

The findings of this study support the conclusion that the etiology of some SIDS cases begins before birth. In this large cohort, the level of adult hemoglobin, measured in the first days of life, was associated with subsequent risk of SIDS. The relative risk of SIDS was more than 2-fold higher in the upper quintile of the adult hemoglobin distribution, and more than one third of SIDS cases occur among infants in the upper quintile of the adult hemoglobin distribution. Given the rarity of SIDS, however, the current findings suggest that information on newborn hemoglobin levels would not have the nec-

<table>
<thead>
<tr>
<th>Length of gestation, wk</th>
<th>Quintile of Adult Hemoglobin RR (95% CI)†</th>
<th>Quintile of Adult Hemoglobin RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highest‡</td>
<td>Second</td>
</tr>
<tr>
<td>&lt;34</td>
<td>1.00</td>
<td>1.48 (0.84-2.61)</td>
</tr>
<tr>
<td>34-35</td>
<td>1.00</td>
<td>1.32 (0.72-2.39)</td>
</tr>
<tr>
<td>36-37</td>
<td>1.00</td>
<td>1.05 (0.71-1.56)</td>
</tr>
<tr>
<td>38-39</td>
<td>1.00</td>
<td>1.14 (0.89-1.46)</td>
</tr>
<tr>
<td>40-41</td>
<td>1.00</td>
<td>1.13 (0.85-1.50)</td>
</tr>
<tr>
<td>≥42</td>
<td>1.00</td>
<td>1.06 (0.67-1.67)</td>
</tr>
</tbody>
</table>

†Adult hemoglobin level is expressed as a percentage of the total hemoglobin level. The 20th, 40th, 60th, and 80th percentiles of the adult hemoglobin level are 3.7%, 4.9%, 7.0%, and 10.3%, respectively, for less than 34 weeks’ gestation; 5.2%, 6.6%, 8.4%, and 11.2%, respectively, for 34-35 weeks’ gestation; 6.1%, 7.6%, 9.2%, and 11.5%, respectively, for 36 to 37 weeks’ gestation; 7.5%, 9.2%, 10.9%, and 13.2%, respectively, for 38-39 weeks’ gestation; 8.6%, 10.5%, 12.5%, and 15.2%, respectively, for 40 to 41 weeks’ gestation; and 8.4%, 10.5%, 12.6%, and 15.4%, respectively, for greater than or equal to 42 weeks’ gestation. The 20th, 40th, 60th, and 80th percentiles of adult hemoglobin level are 7.3%, 9.2%, 11.0%, and 13.5%, respectively, for non-Hispanic white infants; 7.6%, 9.2%, and 11.5%, respectively, for 36 to 37 weeks’ gestation; 7.5%, 9.2%, 10.9%, and 13.2%, respectively, for 38-39 weeks’ gestation; 8.6%, 10.5%, 12.5%, and 15.2%, respectively, for 40 to 41 weeks’ gestation; and 8.4%, 10.5%, 12.6%, and 15.4%, respectively, for greater than or equal to 42 weeks’ gestation.

‡Indicates referent category.

**Abbreviations:** CI, confidence interval; RR, relative risk; SIDS, sudden infant death syndrome.
Infants normally begin a transition from the production of fetal to adult hemoglobin during the final weeks of gestation. It has been suggested that delayed or faulty transition to the production of adult hemoglobin plays a role in the etiology of SIDS. We conducted a large population-based cohort study of the association between adult hemoglobin level measured at birth and subsequent risk of SIDS. The study's findings suggest that newborns with low adult hemoglobin levels are at elevated risk of SIDS.

Accepted for publication December 23, 2003.

This study was supported by a Research Council Grant from the University of North Carolina at Chapel Hill.

We thank Jim Sutocky, Center for Health Statistics, Office of Health Information and Research, California Department of Health Services, Sacramento, for his work in conducting the linkage of California birth cohort and Newborn Screening Program data, and Alice Stewart, MD, for conducting the linkage of California birth cohort and New-SIDS data, and for her important contribution to the conception of this project.

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REFERENCES