Outdoor carbon monoxide, nitrogen dioxide, and sudden infant death syndrome

H Klonoff-Cohen, P K Lam, A Lewis

Aims: To investigate whether infants who died of SIDS were more likely to have higher acute and lifetime average exposures to outdoor carbon monoxide (CO) and nitrogen dioxide (NO2) than comparison healthy infants.

Methods: A total of 169 case and 169 matched control infants born between 1988 and 1992, were studied. CO and NO2 concentrations, averaged for all days within the infant’s lifespan, and the last 30 days, 7 days, and 3 days, and 1 day of life were obtained from air pollutant data provided by the California Air Resources Board.

Results: Based on monthly aggregated data, average CO and particularly NO2 were associated with SIDS count, even after adjustment for seasonal trends. SIDS outcome was not significantly associated with high average outdoor CO levels for any time period. However, high average outdoor NO2 levels on the last day of the infant’s exposure period were significantly associated with SIDS; the adjusted odds ratio was 2.34 (95% CI 1.13 to 4.87).

Conclusions: SIDS may be related to high levels of acute outdoor NO2 exposure during the last day of life. Further studies are needed to replicate this finding.

Sudden infant death syndrome (SIDS), is the sudden and unexpected death of an infant under 1 year of age, whose death remains unexplained after a postmortem examination, including a death scene investigation and a review of the case history. SIDS mysteriously claims the lives of 2705 babies each year in the United States. To date, five studies have evaluated the relation of SIDS and outdoor air pollution, while only two studies have addressed the effects of gaseous air pollution. Hoppenbrouwers et al reported that levels of carbon monoxide (CO), sulphur dioxide (SO2), nitrogen dioxide (NO2), and hydrocarbons and SIDS deaths peaked in winter, and the average age of SIDS victims was younger in areas of higher pollution, while Greenberg et al reported no effect of SO2 on SIDS deaths.

To our knowledge, this is the first case-control study to examine whether infants who succumbed to SIDS were more likely to have higher acute and lifetime exposure to outdoor CO and NO2 than healthy comparison infants.

METHODS

This manuscript was based on a secondary analysis of passive tobacco smoke and SIDS, and a description of the methodology appears elsewhere.

Study sample

SIDS cases, confirmed by postmortem examination, were identified from death certificates located in five health departments in Southern California. The lifespan of all infants was between 1988 and 1992, before the Back to Sleep campaign. Infants with evidence of underlying respiratory disease, fetal distress, metabolic disturbances, dysmorphic features, or genetic abnormalities were excluded from the study. Multiple births, infants over 1 year, and adopted infants were also excluded.

Controls were randomly selected from a pool of all eligible live infants born in the same 110 hospitals as the case infants. Each control was matched to a case on date of birth, sex, race, and birth hospital. This study was based on a sub-sample of the original 200 cases and 200 controls in the passive smoking and SIDS analysis.

Ethics committee approval for interview and data collection

This study was approved by the Human Subjects Committee at UCSD and participating institutions. Parents of all eligible case babies were contacted by mail following a grief period of minimum of 3–6 months as required by the Committee. Written informed consent was obtained from parents for the telephone interview and access to medical records.

Outdoor air quality data

Outdoor air pollutant levels, measured from >200 air monitoring stations in California from 1980 to 1999, were obtained from the California Air Resources Board (ARB). Maximum daily one hour averages for CO and NO2 were extracted from the monitoring station closest to the infant’s street address/zip code for this analysis.

Lifetime and acute periods of pollutant exposure were assessed. The exposure period was defined as the time from birth to death for cases and the comparable period for matched controls. Lifespan exposure was calculated by averaging daily concentrations of CO and NO2 for all days within each infant’s exposure period. Concentrations were also averaged for the last 30, 7, and 3 days, and last day of exposure period.

Statistical analysis

Comparisons between cases and controls were made using Fisher’s exact test for: (1) infants’ county of residence; (2) distance in kilometres between air pollution monitoring stations and infants’ home addresses; (3) season of last exposure day; and (4) weekend of last exposure day.

In preliminary analyses, monthly aggregated data were used to examine correlations between SIDS count and average CO and NO2 levels, while removing dominant seasonal trends. Robust non-linear smoother was used to smooth the month-to-month variability in each data series. Smoothed values were subtracted from observed values, and autoregressive integrated moving average models were used.

Abbreviations: SIDS, sudden infant death syndrome; CO, carbon monoxide; NO2, nitrogen dioxide; SO2, sulphur dioxide; ARB, Air Resources Board
to remove remaining autocorrelation within the residual data.

Because associations observed on the aggregate level may be subject to ecologic fallacy, further analyses were carried out at the individual level. Conditional logistic regression was used to investigate the association of CO and NO2 with SIDS in univariate and multivariate analyses. CO and NO2 data were analysed as continuous as well as dichotomous variables, to determine whether the relation between the pollutants and risk of SIDS is linear or has a threshold.

Maternal smoking during pregnancy, postnatal tobacco smoke exposure, low birth weight, infant medical conditions at birth, infant sleep position, highest parent education level, and season and day of week of last exposure were considered as potential confounders, particularly if they changed the odds ratio of CO or NO2 more than 10% when removed from multivariate models.

With two independent hypotheses (CO and NO2 versus SIDS) and five time points for each pollutant, there was no good method for adjusting the 10 resulting p values; therefore, p values are presented as is. All analyses were performed with Stata software.12

RESULTS
A total of 400 eligible cases were initially identified from death certificates located in health departments of Southern California. One hundred case parents were untraceable despite tremendous efforts to locate this transient population,13 and therefore had no matching control parents.

In this secondary analysis, an additional 62 infants (31 pairs) of infants were excluded, 40 due to missing questionnaire or ARB (n = 8) information, and 11 due to residing outside of California. The resulting study sample consisted of 338 infants (169 cases, 169 matched controls).

Cases and controls did not differ by county of residence, distance from air pollution monitoring stations to infants’ home addresses, or season or day of week of last exposure day (table 1). The majority of infants (62%) lived in Los Angeles county, within 5 km of a station (72%), and had their last exposure day in the winter or spring (64%), on a non-weekend day (64%).

On an aggregate level, SIDS occurrences and CO and NO2 seemed to follow seasonal distributions (fig 1). Generally, peaks in SIDS counts seemed to correspond to peaks in pollution levels during the colder months, especially in the latter half of the study. After removing the dominant seasonal trend, a positive correlation remained between SIDS count and average CO and NO2 (p = 0.07 and p = 0.01, respectively).

Univariate and multivariate analyses of CO and NO2 as continuous variables did not yield any statistically significant association with SIDS. The risk curve was basically flat over much of the range of NO2 >0.05 to 0.24 ppm; however, infants living in these areas were at higher risk than those living in areas with 0.01 to 0.05 ppm. A threshold effect seemed to exist at 0.05 ppm.

Table 1  Factors relating to pollution exposure in SIDS cases and matched controls (n = 338)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>p</th>
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<tr>
<td>County of residence</td>
<td></td>
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<tr>
<td>Los Angeles</td>
<td>114 (67.5)</td>
<td>95 (56.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>San Bernardino</td>
<td>13 (7.7)</td>
<td>15 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>10 (5.9)</td>
<td>14 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Riverside</td>
<td>12 (7.1)</td>
<td>13 (8.9)</td>
<td></td>
</tr>
<tr>
<td>San Diego</td>
<td>19 (11.2)</td>
<td>25 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Other (Ventura, Kern, Monterey)</td>
<td>1 (0.6)</td>
<td>5 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Distance to pollution monitor (km)</td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>63 (37.3)</td>
<td>60 (35.5)</td>
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<td>&gt;0.5 to 5.0</td>
<td>61 (36.1)</td>
<td>58 (34.3)</td>
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<tr>
<td>&gt;5.0 to 10.0</td>
<td>26 (15.4)</td>
<td>35 (20.7)</td>
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<tr>
<td>&gt;10.0 to 15.0</td>
<td>10 (5.9)</td>
<td>11 (6.5)</td>
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<td>&gt;15.0</td>
<td>9 (5.3)</td>
<td>5 (3.0)</td>
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<tr>
<td>Season of last exposure date</td>
<td></td>
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<td>0.85</td>
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<td>Winter (December–February)</td>
<td>53 (31.4)</td>
<td>47 (27.8)</td>
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<td>Spring (March–May)</td>
<td>58 (34.3)</td>
<td>58 (34.3)</td>
<td></td>
</tr>
<tr>
<td>Summer (June–August)</td>
<td>31 (18.3)</td>
<td>32 (18.9)</td>
<td></td>
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<tr>
<td>Autumn (September–November)</td>
<td>27 (16.0)</td>
<td>32 (18.9)</td>
<td></td>
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<tr>
<td>Last exposure date during a weekend</td>
<td>45 (26.6)</td>
<td>44 (26.0)</td>
<td>1.00</td>
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Figure 1  Seasonal trends in monthly averaged CO and NO2 levels and monthly SIDS count. After the seasonal components of the variation were removed, CO and NO2 levels remain associated with SIDS count (p = 0.07 and p = 0.01, respectively).
Table 2 presents results from analyses of CO and NO₂ as dichotomous variables. High average CO was not associated with SIDS for any time during the infants’ exposure period in either univariate or multivariate analyses. High average NO₂ concentration during the infant’s lifespan, last 30 days, 7 days, and 3 days of life were also not statistically related to SIDS; albeit, they provide fairly persuasive evidence for an association, since the odds ratios were all gradually increasing in the same direction (that is, >1.00), with corresponding p values approaching significance as the time periods decreased to the last day of life.

In both univariate and multivariate models, high NO₂ during the last day of the infant’s exposure period was a significant risk factor for SIDS. The adjusted odds ratio was 2.34 (95% CI 1.13 to 4.87, p = 0.02), while adjusting for postnatal smoke exposure from all members, infant low birth weight and medical conditions, and maternal education. The odds ratio did not substantially change after adjusting for infant sleep position, maternal age, or weekend day (that is, Saturday or Sunday).

**DISCUSSION**

High levels of acute NO₂ exposure during the last day of life were found to be related to SIDS with an adjusted OR = 2.43 (95% CI 1.13 to 4.87), even after adjusting for tobacco smoke exposure. NO₂ is a product of tobacco smoke (which has been previously reported), and automobile exhaust. Studies have estimated that children spend approximately 80–90% of each day indoors, but NO₂ effectively penetrates indoors. High outdoor CO levels were not associated with an increased risk of SIDS.

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Competing interests: none

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There are potential limitations in this matched case-control study. Despite the fact that there is evidence that respiratory infection could be a contributory factor in a significant proportion of SIDS, respiratory infection rates were not collected in this study. In addition, the amount of time infants spent outdoors at different times of the day was not assessed.

The sample size may be inadequate to identify small associations between ambient pollutant exposure and SIDS outcome because: (1) 100 cases parents were never traced; and (2) a total of 62 case and control pairs were excluded because of missing data. Finally, the control infants lived in the same geographic area as the case babies, which could result in a conservative underestimation of the effect of air pollution on SIDS.

Future studies should attempt to account for the seasonal variation of respiratory infections and air pollution and SIDS, and conduct routine CO and NO₂ blood tests in the postmortem examination.
REFERENCES
12 StataCorp. Stata statistical software: release 8.0. College Station, TX: Stata Corporation, 2003.

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