Research Paper

Concurrent prenatal drinking and smoking increases risk for SIDS: Safe Passage Study report

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ABSTRACT

Background: Sudden infant death syndrome (SIDS) is the leading cause of postneonatal mortality. Although the rate has plateaued, any unexpected death of an infant is a family tragedy thus finding causes and contributors to risk remains a major public health concern. The primary objective of this investigation was to determine patterns of drinking and smoking during pregnancy that increase risk of SIDS.

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1. Introduction

Sudden infant death syndrome (SIDS) is the leading cause of post-neonatal mortality in the United States, with an overall rate of 0.39/1000 births [1]. As these deaths are often unobserved, it is assumed the infants died during sleep or arousal from sleep. Despite the decline in SIDS following international campaigns in the early 90’s recommending supine infant sleep, the rate has plateaued over the last two decades [2]. Prenatal and postnatal exposures to alcohol and tobacco cigarettes have been identified as separate risk factors for SIDS in several studies [3–6]. Disentangling the effects of each substance, as well as the timing of exposure is complicated by the manner of data collection and frequent co-occurrence of smoking and drinking.

Large epidemiological population-based samples have focused more on the relationship between pre- and postnatal nicotine exposures and infant death. A recent publication in Pediatrics used a large birth cohort with linked birth/death data and found a linear relationship with increased risk for SIDS and maternal smoking per day in pregnancy. This increased risk was attenuated for those who quit or reduced their smoking during pregnancy, compared with those who continued to smoke [8]. Others have found significant associations between prenatal or postnatal nicotine exposure and SIDS, without consideration of prenatal alcohol exposure [9,10].

One challenge in many of these studies is prenatal alcohol use is often grossly underreported on birth certificates and in medical records, making inclusion in large retrospective data sets challenging [11]. A link between alcohol exposure and SIDS has not been as consistently reported in the literature. One retrospective study examining SIDS risk factors in pregnant American Indian women in the Northern Plains found first trimester binge drinking increased SIDS risk 8-fold [5]. Prenatal alcohol exposure was also found to significantly increase postnatal mortality risk in an analysis of 79,216 pregnancies in the Danish National Birth cohort when a woman’s weekly average intake was 4+ drinks or 3+ binge episodes at any point in pregnancy [7]. Other studies have not found a significant increase in SIDS risk with prenatal alcohol exposure, such as the Nordic Epidemiological SIDS Study of 244 SIDS infants and 869 living controls. This study found no increased risk associated with prenatal alcohol exposure after adjusting for maternal age, prenatal smoking exposure, and social variables [6]. Discrepancies in the results of the various studies may reflect differences in populations, the design of the study (retrospective or prospective), the quality of the exposure data, and whether or not a detailed pathologic assessment was performed in the fatal cases. Although both pre- and postnatal exposures have been found associated with SIDS, the triple risk model [12] suggests an underlying vulnerability for SIDS pathogenesis may originate in utero and is.

Methods: The Safe Passage Study was a prospective, multi-center, observational study with 10,888 women, 11,892 pregnancies, and 12,029 fetuses, followed to 1-year post delivery. Subjects were from two sites in Cape Town, South Africa and five United States sites, including two American Indian Reservations. Group-based trajectory modeling was utilized to categorize patterns of drinking and smoking exposure during pregnancy.

Findings: One-year outcome was ascertained in 94.2% infants, with 28 SIDS (2.43/1000) and 38 known causes of death (3.30/1000). The increase in relative risk for SIDS, adjusted for key demographic and clinical characteristics, was 11.79 (98.3% CI: 2.59–53.7, p < 0.001) in infants whose mothers reported both prenatal drinking and smoking beyond the first trimester, 3.95 (98.3% CI: 0.44–35.83, p = 0.14), for drinking only beyond the first trimester and 4.86 (95% CI: 0.97–24.27, p = 0.02) for smoking only beyond the first trimester as compared to those unexposed or reported quitting early in pregnancy.

Interpretation: Infants prenatally exposed to both alcohol and cigarettes continuing beyond the first trimester have a substantially higher risk for SIDS compared to those unexposed, exposed to alcohol or cigarettes alone, or when mother reported quitting early in pregnancy. Given that prenatal drinking and smoking are modifiable risk factors, these results address a major global public health problem.

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relevant since alcohol and tobacco use often co-occur. These data provide strong support for the public health message that prenatal drinking and smoking are among the most prevalent modifiable risk factors for adverse outcomes.

associated with suboptimal fetal development linked to these toxic exposures, although the underlying mechanism(s) remain unknown.

The multi-center longitudinal cohort Safe Passage Study, conducted by the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network, is the first prospective, large-scale study, to test the hypotheses that prenatal exposure to alcohol (drinking), tobacco cigarettes (smoking), or both (dual exposure) increases the risk for SIDS [13]. The Safe Passage Study provides a unique opportunity to analyze the risk of drinking and smoking alone and in combination on SIDS.

2. Patients and methods

2.1. Study design, populations, and settings

Between August 2007 and January 2015, 10,088 women, with 11,892 pregnancies and 12,029 fetuses were recruited in two residential areas within Cape Town, South Africa; and from five sites, including two American Indian Reservations, in the United States (South and North Dakota). These sites were selected for high rates of prenatal alcohol use and SIDS (Fig. 1), [13] and to include populations where the marked ethnic and socioeconomic disparities in SIDS remains understudied. Written informed consent was obtained from each participant at the time of recruitment, which occurred between six weeks gestation up to but not including delivery. Depending on gestational age, women meeting eligibility criteria were enrolled and completed up to three additional prenatal visits at 20–24, 28–32 and 34+ gestational weeks; maternal-infant dyads were assessed at delivery, one month, and 1-year post delivery. When a sudden infant demise occurred, the local medical examiner ordered an autopsy. The participant was asked for written informed consent for release of autopsy and death scene investigation reports of the infant demise to the study.

Institutional review board (IRB) approvals, including tribal review boards for reservation-based sites in the Northern Plains, were obtained for all PASS entities (clinical sites, and centers for data coordination, pathology and physiology) [13,14]. The research was overseen by the network’s Steering Committee and an external Advisory and Safety Monitoring Board.

2.2. Outcomes

Infants were followed to 1-year post delivery. Infant demises occurring after hospital discharge were adjudicated by a multidisciplinary committee to determine causes of death. SIDS, the primary outcome, was defined as the sudden unexpected death of an infant, less than 1-year of age, whose cause of death remained unexplained after review of all available information, including performance of a complete autopsy, examination or report of the death scene, and review of the clinical history [15]. Deaths were classified as undetermined when there were inconclusive results, equivocal results or missing critical information (e.g., no autopsy). The demises classified as undetermined were not included in the current analyses. Infants dying of known (explained) causes of death (KCOD) were also evaluated.

2.3. Exposure measures

Methods used to collect and characterize alcohol and tobacco cigarette exposure during pregnancy have been previously described [16,17]. Briefly, self-reported drinking and smoking were obtained at the recruitment interview, including reports of exposure around last menstrual period (LMP), at up to three prenatal visits after recruitment, and at one month post-delivery, using a modified timeline follow-back [16] interview for alcohol use and frequency and quantity of smoking. Group-based trajectory modeling was utilized to categorize patterns of quantity and frequency of drinking and smoking over each month of pregnancy; five drinking and seven smoking trajectories were defined [17]. Because of the small number of demise outcomes, the five and seven level trajectories of drinking and smoking were collapsed to create two 2-level variables for drinking and smoking separately, defined as None or Quit Early - no exposure during pregnancy or quit prior to the end of the first trimester or Continuous or Quit Late - continuous exposure during pregnancy or quit after the first trimester. The primary exposure measures combined the 2-level drinking and the 2-level smoking variables to determine the impact of no, single or dual exposure to drinking and smoking, defined as None or Quit Early for both drinking and smoking; Drinking Only - continuous or quit late for drinking and none or quit early for smoking; Smoking Only - continuous or quit late for smoking and none or quit early for drinking; and Dual – continuous or quit late for both drinking and smoking (Fig. S1, see supplement).

2.4. Confounding

Propensity scores (PS) were developed to reduce biases that could arise because factors that predict exposure might underlie the association with SIDS rather than the exposure itself. The PS scores derived for the Safe Passage Study contained eight enrollment characteristics that differed among women that were dually, singly or unexposed: recruitment location (site), maternal age, race, marital status, education, history of diabetes, parity, and maternal arm circumference (proxy of body mass index), as well as statistical interactions (see supplement).

At one-month postnatal age (corrected for prematurity) mothers were interviewed regarding postnatal drinking and smoking behaviors and infant sleep environment; specifically, bed-sharing and sleep position last placed. Postnatal exposure was defined as any drinking or smoking over the past month and quantity was defined per exposure day. In the event of an infant death, the reported position found was recorded (see supplement).

2.5. Statistical analyses

The analysis set included women with infants known to be alive at 1-year or have a demise outcome of SIDS (primary) or KCOD (secondary). Crude associations between each demise outcome compared to those alive at 1-year were expressed as risk per 1000 pregnancies by maternal demographics, medical and obstetric history and infant characteristics. Statistical significance between groups was determined using Chi-square or Fisher’s exact test. Log binomial regression using generalized linear models and generalized estimating equations to account for correlation (exchangeable) among reenrollments were utilized to estimate crude and adjusted relative risks to quantify associations between exposure and outcome; odds ratios were used if there were not a sufficient number of events. Adjustment in multi-variable models included the PS described above, gestational age at enrollment, gestational age at delivery and multi-fetal pregnancy. For both demise outcomes, there were three planned comparisons; None or Quit Early versus Drinking Only, Smoking Only or Dual exposure. Statistical significance (alpha) was set at 0.0167 based on Bonferroni correction (0.05/3 tests). Otherwise, statistical significance was determined at 0.05 level and 95% confidence intervals were provided. There were minimal missing data (only 1 missing exposure trajectory) and 1.1% missing PS, no methods were used to account for
missing data. However, 39.3% of the mothers with SIDS infants and 12.3% of the mothers of infants alive at 1-year did not complete the 1-month postnatal interview. Information regarding the sample size and further details regarding the statistical methods are provided in the supplement. Analyses were performed using SAS/STAT® software, Version 9.4.

Fig. 1. Safe Passage Study CONSORT Chart.
2.6. Role of the funding source

An NIH U01 was used for this project, which is a cooperative agreement award mechanism, in which substantial NIH programmatic involvement with the awardees occurred during the performance of all study related activities.

3. Results

3.1. Study cohort

A total of 11,892 pregnancies were enrolled, with 15.7% reenrolling with subsequent pregnancies. Pregnancy outcome was known in 11,695 (98.3%) resulting in 11,518 live born infants (Fig. 1). Of the 11,518 live born infants, 10,727 were alive at 1-year, 287 infants were known to be alive after 11-months but prior to 1-year; and 5.8% of infant outcomes were unknown at 1-year. There were 124 infant deaths; 45 pre- and 77 post-discharge and 2 withdrew consent. Of the 77 post-discharge infant demises, 28 were classified as SIDS (2.43/1000), 38 KCOD (3.30/1000) and 11 infant deaths were undetermined. The most frequent KCOD was respiratory infection occurring in 39.5% (Table 1). The primary analysis set included 10,755 infants (10,727 alive at 1-year, and 28 SIDS) and the secondary analysis set included 10,765 infants (10,727 alive at 1-year and 38 KCOD).

3.2. Participant characteristics

Mean gestational age at enrollment was 18.4 ± 6.6 weeks (mean ± standard deviation); 36.6% were nulliparous, 57.8% infants were from South Africa with 99.7% of coloured ancestry, 42.2% were from Northern Plains with 57.8% and 40.6% of white or American Indian ancestry, respectively. The unadjusted risk of SIDS was statistically significantly higher in South Africa (3.70/1000) as compared to the Northern Plains (1.10/1000, p = 0.009) (Table 2). Risks for KCOD were not significantly different by site and ancestry. Less well educated and those delivering infants with lower birthweights had a significantly higher risk of SIDS and KCOD (all p-values < 0.011).

3.3. Drinking and smoking behaviors

Women reporting dual or single exposures during pregnancies differed in their patterns of drinking and smoking; specifically, those reporting dual exposure, drank and smoked more than those reporting single exposure. For example, based on the 5 level drinking and 7 level smoking trajectories, among dually exposed pregnancies, 45% were low and 27% were high continuous drinkers as compared to 37% low and 13% high continuous drinkers in those only singly exposed to drinking. The proportion of quit-late drinkers was about half that in dually exposed pregnancies as compared to drinking only (29% vs. 49%). Among the dually exposed, 45% were moderate and 23% high or very high continuous smokers as compared to 40% and 19% in those only exposed to smoking [17].

3.4. Associations between prenatal exposures and outcomes

In crude analyses, accounting for reenrollments, the risk of SIDS was 5.01 (95% CI: 1.82 – 13.78) and 8.26 times higher (95% CI: (2.91 – 23.48)) for low and high continuous drinkers respectively, as compared to those not exposed to drinking. The relative risk was increased for both drinking or smoking when the exposure continued after the first trimester, or with continuous exposure as compared to those not exposed or who quit early (around the end of the first trimester) (Table 3, 2-level drinking and 2-level smoking variables). Further, after statistical adjustment for the PS, gestational age at enrollment, gestational age at delivery, multi-fetal pregnancy and reenrollment, the adjusted relative risk of SIDS was 2.59 (95% CI: 1.14 – 5.90, p = 0.024) and 3.84 (95% CI: 1.42 – 10.42, p = 0.008) times higher in infants of women who were in the Continuous or Quit Late drinking or smoking groups, respectively, as compared to those in the None or Quit Early group (interaction p-value=0.59, Table 4).

Of primary interest was the effect of dual exposure. Using the primary exposure 4-level drinking and smoking variable, the relative risk of SIDS was 11.79 (98.3% CI: 2.59 – 53.70, p-value < 0.001) times higher for infants dually exposed in pregnancy as compared to those not exposed or whose mothers quit early. Although not statistically

| Post Discharge Demise (n = 77). | Cause of death n (%) | Consent n (%) | Autopsy performed1 n (%) | Post conceptual age (days)2 Mean + Std. Dev. Median (min:max) |
|---------------------------------|----------------------|---------------|--------------------------|--------------------------------------------------|
| Post discharge demise*          | 77                   | 57 (74.0%)    | 56 (98.2%)               | 364.8 ± 83.3 351.0 (239.0:595.0) 340.0 ± 64.7 |
| SIDS                            | 28 (36.4%)           | 28 (100.0%)   | 28 (100%)                | 345.5 (239.0:541.0) 376.6 ± 100.2 |
| Undetermined/Unclassified       | 11 (14.3%)           | 4 (36.4%)     | 3 (75.0%)                | 367.0 (262.0:569.0) 379.6 ± 88.0 |
| KCOD                            | 38 (49.4%)           | 25 (67.6%)    | 25 (100.0%)              | 353.5 (257.0:595.0) |

SIDS: Sudden infant death syndrome, KCOD: Known cause of death.

1 Of those consented.
2 Gestational age at delivery + postnatal age at demise.
Table 2
Crude associations between infant outcomes and enrollment characteristics.

| Maternal characteristics                                      | Total n = 10,792 | Alive at 1 Year n = 10,727 | SIDS n = 28 | SIDS risk/1000\(^a\) | Known cause n = 38 | Known cause Risk/1000\(^a\) | Known cause p-value\(^b\) |
|----------------------------------------------------------------|------------------|-----------------------------|-------------|---------------------|--------------------|-----------------------|-------------------------|
| Recruitment location                                           |                  |                             |             |                     |                    |                       |                         |
| Northern plains                                                | 4553 (42.2%)     | 4536 5 1.10                 |             |                     |                    |                       |                         |
| South Africa                                                   | 6240 (57.8%)     | 6191 23 3.70                |             |                     |                    |                       |                         |
| Maternal age (years)                                           |                  |                             |             |                     |                    |                       |                         |
| <20                                                            | 1736 (16.1%)     | 1729 2 1.16                 |             |                     |                    |                       |                         |
| 20 to <35                                                      | 8218 (76.2%)     | 8165 25 3.05                |             |                     |                    |                       |                         |
| 35+                                                            | 839 (7.8%)       | 833 1 1.20                 |             |                     |                    |                       |                         |
| Race                                                           |                  |                             |             |                     |                    |                       |                         |
| American Indian/Alaska native                                  | 1847 (17.1%)     | 1835 3 1.63                 |             |                     |                    |                       |                         |
| Colored                                                        | 6222 (57.7%)     | 6173 23 3.71                |             |                     |                    |                       |                         |
| White                                                          | 2631 (24.4%)     | 2626 2 0.76                 |             |                     |                    |                       |                         |
| Other/unknown                                                  | 93 (0.9%)        | 93 0 0.00                  |             |                     |                    |                       |                         |
| Hispanic or Latino                                             |                  |                             |             |                     |                    |                       |                         |
| No                                                             | 10,591 (98.1%)   | 10,529 28 2.65              |             |                     |                    |                       |                         |
| Yes                                                            | 202 (1.9%)       | 198 0 0.00                  |             |                     |                    |                       |                         |
| Married or partnered and living together                       |                  |                             |             |                     |                    |                       |                         |
| No                                                             | 4413 (41.0%)     | 4387 9 2.05                 |             |                     |                    |                       |                         |
| Yes                                                            | 6354 (59.0%)     | 6314 19 3.00                |             |                     |                    |                       |                         |
| Education                                                      |                  |                             |             |                     |                    |                       |                         |
| Any primary school                                             | 565 (5.2%)       | 557 3 5.36                 |             |                     |                    |                       |                         |
| Some high school                                               | 4996 (46.3%)     | 4957 20 4.02                |             |                     |                    |                       |                         |
| Completed high school                                          | 2205 (20.5%)     | 2191 3 1.37                |             |                     |                    |                       |                         |
| Beyond high school                                             | 3018 (28.0%)     | 3013 2 0.66                |             |                     |                    |                       |                         |
| Pre-pregnancy BMI (kg/m²)                                     |                  |                             |             |                     |                    |                       |                         |
| Underweight (<18.5)                                           | 569 (7.8%)       | 561 3 5.32                 |             |                     |                    |                       |                         |
| Normal (18.5 to <25.0)                                        | 3271 (44.9%)     | 3259 7 2.14                 |             |                     |                    |                       |                         |
| Overweight (25.0 to <30.0)                                    | 1712 (23.5%)     | 1705 4 2.34                 |             |                     |                    |                       |                         |
| Morbidly Obese (≥30.0)                                        | 953 (13.1%)      | 951 0 0.00                 |             |                     |                    |                       |                         |
| Arm circumference (mm)                                         | 775 (10.7%)      | 771 0 0.00                 |             |                     |                    |                       |                         |
| Gestational age at enrollment (<94 days)                      |                  |                             |             |                     |                    |                       |                         |
| First trimester (0 to 97 days)                                 | 2611 (24.3%)     | 2592 8 3.08                 |             |                     |                    |                       |                         |
| Second trimester (98 to 195 days)                             | 7098 (66.1%)     | 7063 17 2.40                |             |                     |                    |                       |                         |
| Third trimester (≥196 days)                                   | 1025 (9.6%)      | 1013 3 2.95                |             |                     |                    |                       |                         |
| Gestational age at delivery (<28,0 weeks)                     |                  |                             |             |                     |                    |                       |                         |
| <28,0                                                          | 25 (0.2%)        | 22 0 0.00                  |             |                     |                    |                       |                         |
| 28 to 31.6                                                     | 98 (0.9%)        | 93 4 4.24                  |             |                     |                    |                       |                         |
| 32 to 36.6                                                     | 1178 (10.9%)     | 1160 7 6.00                |             |                     |                    |                       |                         |
| ≥37                                                           | 9486 (87.9%)     | 9464 17 1.80               |             |                     |                    |                       |                         |
| Multi-fetal pregnancy                                         | 0.13             | 0.58                       |             |                     |                    |                       |                         |
| No                                                             | 10,549 (97.7%)   | 10,486 26 2.47             |             |                     |                    |                       |                         |
| Yes                                                            | 244 (2.3%)       | 241 2 8.23                 |             |                     |                    |                       |                         |
| Maternal medical history                                      |                  |                             |             |                     |                    |                       |                         |
| History of depression                                         | 9359 (87.0%)     | 9301 26 2.79               |             |                     |                    |                       |                         |
| History of hyperthyroidism                                     | 1401 (13.0%)     | 1394 2 1.43               |             |                     |                    |                       |                         |
| No                                                             | 10,660 (99.1%)   | 10,596 28 2.64             |             |                     |                    |                       |                         |
| Yes                                                            | 101 (0.9%)       | 100 0 0.00                 |             |                     |                    |                       |                         |
| History of hypothyroidism                                     |                  |                             |             |                     |                    |                       |                         |
| No                                                             | 10,490 (97.5%)   | 10,426 28 2.68             |             |                     |                    |                       |                         |
| Yes                                                            | 271 (2.5%)       | 270 0 0.00                 |             |                     |                    |                       |                         |
| History of diabetes                                           |                  |                             |             |                     |                    |                       |                         |
| No                                                             | 10,531 (97.9%)   | 10,468 28 2.67             |             |                     |                    |                       |                         |
| Yes                                                            | 230 (2.1%)       | 228 0 0.00                 |             |                     |                    |                       |                         |
| Maternal obstetric history                                    |                  |                             |             |                     |                    |                       |                         |
| Gravidity                                                      | 1 0.14           | 3.02                       |             |                     |                    |                       |                         |
| 3 0.05                                                        | 1098 (10.2%)     | 1084 3 2.76                |             |                     |                    |                       |                         |
| Parity                                                         | 0.15             | 0.001                      |             |                     |                    |                       |                         |
| 3942 (36.6%)                                                  | 3931 4 1.02      | 7 1.78                     |

(continued)
significant after Bonferroni correction, the relative risk of SIDS was increased, 3.95 (98.3% CI: 0.44–35.83, \( p = 0.14 \)) for infants exposed to prenatal drinking only and 4.86 (98.3% CI: 0.97–24.27, \( p = 0.02 \)) for infants prenatally exposed to smoking only, compared to those unexposed or whose mothers quit early. The risk of having an infant dying of SIDS for those who were dually exposed was 8.09/1000; 3.50/1000 for those reporting smoking only; 2.19/1000 for those reporting drinking only; and 0.54/1000 for those reporting no exposure or quit early (Table 4). For KCOD groups, the adjusted odds ratios were not statistically significant after Bonferroni correction in infants exposed to drinking only, smoking only, or dually exposed during pregnancy, and were 0.42 (98.3% CI: 0.03–5.43, \( p = 0.42 \)), 2.08 (98.3% CI: 0.72–6.02, \( p = 0.10 \)) and 2.00 (98.3% CI: 0.60–6.63, \( p = 0.17 \)), as compared to those infants whose mothers were not exposed or quit early in pregnancy, respectively.

### 3.5. Association between SIDS and postnatal exposure, sleep position and bed sharing

There was no significant association between maternal report of any postnatal drinking or smoking use between mothers of SIDS infants (88.2%) and mothers of infants alive at 1-year (79.2%) (\( p > 0.56 \)). Further, there were no significant associations between sleep position (last placed) or bed sharing the night before and incidence of SIDS (both \( p \)-values > 0.12) (Fig. S2 – in supplement).

### 4. Discussion

This is the first prospective, multi-center longitudinal cohort study to provide evidence that infants prenatally exposed to alcohol and tobacco cigarettes continuing beyond the first trimester have substantially higher risk for SIDS as compared to those unexposed or exposed only in the first trimester. The risk for SIDS was found to be increased almost 12-fold in infants whose mothers both drank and smoked beyond the first trimester as compared to those unexposed or only exposed in the first trimester of pregnancy. These results suggest that combined, exposures had a synergistic effect on risk, given that dual exposure was associated with substantially higher risk than either exposure, considered individually. It is critical to note that this significant increase in risk attributable to dual prenatal exposures was unique to SIDS and not to KCOD. These findings are tempered somewhat by the small sample sizes, resulting in a large range in confidence intervals, however, the sample size is not atypical for studies on SIDS [5,18].

The influence of the postnatal environment, including sleep position and postnatal exposures, and SIDS risk has been studied extensively. A limitation of the Safe Passage Study is that postnatal information was available on only 60.8% of mothers whose infants succumbed to SIDS, primarily due to timing of the infant demise (see supplement Fig. S2). In this current study, there were no statistically significant differences in maternal report of postnatal drinks per drinking day for mothers of infants with SIDS as compared to infants alive at 1-year; and no association between reported postnatal cigarettes per day for mothers of infants with SIDS as compared to infants alive at 1-year (Fig. S2). Given the high proportion of bed-sharing in our study cohort and the similar postnatal drinking and smoking behaviors among mothers of SIDS and living infants, we are unable to assess the interaction between postnatal exposure and bed sharing. Moreover, the similarity of postnatal adverse exposures between mothers of SIDS infants and those alive at one year suggest that the major contribution of drinking and smoking to SIDS risk in this particular cohort occurred prenatally. Although lack of postnatal exposure information on the full cohort is a limitation, it should be noted that the first prospective study of SIDS and sleep position, published in 1995, which demonstrated a link between prone sleep position and SIDS, was similar in the proportion of available postnatal data. That study included a cohort of 3110 infants, with 23 infants later dying from SIDS; postnatal sleep position data was only available in 15 of these deaths (65.2%) [18]. The compelling results were considered major evidence to support the launch of numerous campaigns promoting supine sleeping.

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**Table 2 (Continued)**

| Total | Alive at 1 Year | SIDS | SIDS risk/1000 | SIDS p-value | Known cause | Known cause Risk/1000 | Known cause p-value |
|-------|----------------|------|----------------|--------------|-------------|----------------------|---------------------|
|       | \( n = 10,792 \) | \( n = 10,727 \) | \( n = 28 \) | \( n = 38 \) | \( n = 38 \) | \( n = 38 \) |                           |
| 1     | 3268 (30.4%)   | 3247 | 10             | 3.07         | 11          | 3.38                 |                     |
| 2     | 1932 (18.0%)   | 1918 | 8              | 4.15         | 6           | 3.12                 |                     |
| 3     | 963 (9.0%)     | 955  | 4              | 4.17         | 4           | 4.17                 |                     |
| \( \geq 4 \) | 661 (6.1%) | 650  | 2              | 3.07         | 9           | 13.66                |                     |
| Nulliparous                     | 0.01 |                |             | 0.03         |            |                      |                     |
| No   | 6824 (63.4%)   | 6770 | 24             | 3.53         | 30          | 4.41                 |                     |
| Yes  | 3942 (36.6%)   | 3931 | 4              | 1.02         | 7           | 1.78                 |                     |
| Previous Stillbirths            | 0.19 |                |             | 0.06         |            |                      |                     |
| No   | 6883 (96.8%)   | 6835 | 23             | 3.35         | 25          | 3.64                 |                     |
| Yes  | 226 (3.2%)     | 221  | 2              | 8.97         | 3           | 13.39                |                     |
| Prevalent infant demise         | 0.55 |                |             | 0.01         |            |                      |                     |
| No   | 6884 (96.8%)   | 6836 | 24             | 3.50         | 24          | 3.50                 |                     |
| Yes  | 225 (3.2%)     | 220  | 1              | 4.52         | 4           | 17.86                |                     |

**Infant characteristics**

| Birth weight (g) | \(< 1500\) | 107 (1.0%) | 98   | 5   | 48.54 | 4     | 39.22 |
|                 | \(1500 \leq \text{birth weight} < 2500\) | 1015 (9.8%) | 1015 | 6   | 5.88  | 14    | 13.61 |
|                 | \(2500 \leq \text{birth weight} < 4000\) | 8611 (81.7%) | 8598 | 16  | 1.86  | 17    | 1.86  |
|                 | \(\geq 4000\) | 796 (7.5%) | 794  | 0   | 0.00  | 2     | 2.51  |
| SGA (as reported on MCA) | 0.06 | | | | | | |
| No   | 10,376 (98.5%) | 10,316 | 25  | 2.42 | 35    | 3.38  |                     |
| Yes  | 156 (1.5%)    | 152   | 2   | 12.99 | 2    | 12.99 |                     |
| Female | 0.28 | | | | | | |
| No   | 5348 (49.6%)  | 5316  | 11  | 2.06 | 21    | 3.93  |                     |
| Yes  | 5436 (50.4%)  | 5402  | 17  | 3.14 | 17    | 3.14  |                     |

**BMI: Body mass index.**

**SGA: Small for gestational Age.**

**MCA: Medical chart abstraction.**

1. Of total.
2. \#demise/\#alive at 1 year*1000.
3. Fisher’s exact test or chi-square test.
The strengths of the Safe Passage Study are its prospective design and rigorous assessment of quantity, frequency and timing of exposure that allowed for the development of trajectories, and adjustment of propensity scores to account for confounding. In addition, each demise went through an in-depth multidisciplinary expert review to determine cause of death. The Safe Passage Study was designed to include populations with known high rates of SIDS, maternal alcohol intake and maternal smoking during pregnancy. This raises questions

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**Table 3**

Unadjusted associations between infant demise and drinking and smoking (accounting for reenrollments).

| 5-level Drinking Trajectory | % of alive at 1 Year n = 10,727 | SIDS and alive at 1 Year n = 10,755 | Known cause of death and alive at 1 Year n = 10,764 |
|-----------------------------|---------------------------------|----------------------------------|----------------------------------|
| None                        | 5149 (48.0%)                    | 7 (0.14%)                        | 19 (0.37%)                      |
| Moderate quit early         | 2767 (25.8%)                    | 4 (0.14%)                        | 7 (0.25%)                       | 0.68 (0.29, 1.62) |
| High quit later             | 1028 (9.6%)                     | 2 (0.19%)                        | 1 (0.10%)                       | 0.27 (0.04, 1.92) |
| Low continuous              | 1166 (10.9%)                    | 8 (0.68%)                        | 5 (0.12)                        | 0.46 (0.11, 1.99) |
| High continuous             | 616 (5.7%)                      | 7 (1.12%)                        | 8.26 (2.91, 23.48)              | <0.001            |
| 7-level smoking trajectory  |                                 |                                  |                                 |                   |
| None                        | 5601 (52.23%)                   | 4 (0.07%)                        | 12 (0.21%)                      |
| Moderate quit early         | 930 (8.7%)                      | 1 (0.11%)                        | 0.71                            | 2 (0.21%)         | 1.01 |
| High quit later             | 368 (3.4%)                      | 0.54%                            | 0.02                            | 1 (0.27%)         | 0.99 |
| Low continuous              | 1190 (11.1%)                    | 4 (0.34%)                        | 4.71                            |
| Moderate continuous         | 1759 (16.4%)                    | 14 (0.79%)                       | 7.15                            |
| High continuous             | 720 (6.7%)                      | 3 (0.41%)                        | 5.83                            |
| Very High continuous        | 158 (1.5%)                      | 0 (0.00%)                        | 1 (0.63%)                       | 2.92              | 0.30 |
| 2-level drinking measure    |                                 |                                  |                                 |                   |
| None, quit early            | 7916 (73.8%)                    | 11 (0.14%)                       | 26 (0.33%)                      |
| Continuous, quit late       | 2810 (26.2%)                    | 17 (0.60%)                       | 12 (0.43%)                      |
| 2-level Smoking Measure     |                                 |                                  |                                 |                   |
| None, quit early            | 6531 (60.9%)                    | 5 (0.08%)                        | 1.0                             |
| Continuous, quit late       | 4195 (39.1%)                    | 23 (0.55%)                       | <0.001                          |
| 2-level drinking measure and 2-level smoking measure | | | | |
| Drinking; continuous, quit late | 2810 (26.2%) | 17 (0.60%) | 2.54 | 0.02 | 12 (0.43%) | 0.91 (0.44, 1.86) |
| Smoking; continuous, quit late | 4195 (39.1%) | 23 (0.55%) | 24 (0.57%) | 2.73 (1.36, 5.46) |

**Primary exposure measure: 4-level drinking and smoking measure**

| None, quit early | 5386 (52.2%) | 3 (0.05%) | 1.0 | 12 (0.21%) | 1.0 |
| Drink only (continuous, quit late) | 935 (8.7%) | 2 (0.21%) | 3.96 | 0.13 | 2 (0.21%) | 1.00 |
| Smoke only (continuous, quit late) | 2320 (21.6%) | 8 (0.34%) | 6.39 | 0.006 | 14 (0.60%) | 2.80 |
| Dual (continuous, quit late) | 1875 (17.5%) | 15 (0.79%) | 14.75 | <0.001 | 10 (0.53%) | 2.47 |

RR: relative risk, CI: confidence interval, OR: odds ratio.

2-level drinking measure and 2-level smoking measure.

Drinking measure:
- None, quit early: No drinking or quitting by end of the 1st trimester.
- Continuous, quit late: Drinking after the 1st trimester.

Smoking measure:
- None, quit early: No smoking or quitting by end of the 1st trimester.
- Continuous, quit late: smoking after the 1st trimester.

Primary exposure measure: 4-level drinking and smoking measure.
- None: No smoking or drinking during pregnancy or quitting by the end of the 1st trimester.
- Drinking Only: Drinking after the 1st trimester of pregnancy and no smoking or quitting by the end of the 1st trimester.
- Smoking Only: Smoking after the 1st trimester of pregnancy and no drinking or quitting by the end of the 1st trimester.
- Dual: Drinking and smoking after 1st trimester of pregnancy.

1 Of total alive at 1 year (10,726 with complete data).
2 (# demise)/(# demise + alive at 1 year)*100.
3 95% CI estimated from RR using log binomial regression utilizing generalized linear models and generalized estimating equations accounting for reenrollments.
4 95% CI estimated from OR (as approximation to RR) using logistic regression due to convergence issues with log binomial regression.
5 Test for interaction between 2-level drinking and 2-level smoking not significant (SIDS p-value=0.59, ICOD p-value=0.88). Estimated RR and 95% CI do not include interaction term, reference group (None, Quit Early) not provided.
about generalizability of the main findings. However, it is important to note the results held even after adjustment for other known risk factors for SIDS, e.g., lower socioeconomic status and less education, suggesting relevance across populations.

Future research into how the prenatal toxins of alcohol and smoke interact to lead to sleep-related sudden death in a critical postnatal period is necessary. The independent biological effects of prenatal alcohol and nicotine exposure converge at multiple levels including: (1) neurochemical, affecting properties of nicotinic acetylcholine receptors (nAChRs) and other neurotransmitters that affect cardiorespiratory control, sleep, arousal, and other vital functions; [19–22] (2) hormonal, activating neuroendocrine pathways associated with the hypothalamic-pituitary-adrenal axis and homeostatic stress responses; [23–26] and (3) immunological, affecting immune, inflammatory, and infectious responses [27–29]. Maternal smoking and alcohol consumption also have direct effects on the placenta including placental perfusion, weight, and structure [27,28,30]. Whether and to what extent these physiological actions converge in a fetus to adversely affect its development and survival are currently unknown as are the effects of precise timing and amount of the dual exposures.

In conclusion, the Safe Passage Study provides new information about the role of dual exposures to prenatal smoking and drinking as risk factors for SIDS. The Safe Passage Study results show that the quantity, frequency and timing of exposures played a critical role in risk of SIDS. These findings support the Center for Disease Control and Prevention, the United States Surgeon General, and the World Health Organization’s recommendation of no smoking or drinking during pregnancy and emphasize the importance of dual exposure, which provides the greatest risk for infant mortality. Given that many women quit drinking and smoking after pregnancy recognition, this finding has great public health impact for screening for substance use early and intervening as soon as possible. Stronger public health messaging regarding the dangers of drinking and smoking during pregnancy may alter the current plateau and further decrease SIDS rates.

**Declaration of Competing Interest**

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RDF reports grants from NICHD, during the conduct of the study.

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**Table 4**

| 2-level drinking measure and 2-level smoking measure (in model together; 95% Confidence Intervals)** | % of alive at Year n = 10,727* | SIDS and alive at Year n = 10,755 | Known cause of death and alive at Year n = 10,765 |
|---|---|---|---|
| | SIDS n = 282 | RR (CI) | p-value |
| | | | |
| Drink (None, quit early) | 7752 (73.8%) | 11 (0.14%) 1 | 25 (0.32%) 1 |
| Drink (Continuous, quit late) | 2752 (26.2%) | 17 (0.61%) 1 | 11 (0.4%) 0.6 |
| Smoke (None, quit early) | 6387 (60.8%) | 5 (0.08%) 1 | 12 (0.19%) 1 |
| Smoke (Continuous, quit late) | 4117 (39.2%) | 23 (0.56%) 1 | 24 (0.58%) 0.9 |

Primary exposure measure: 4-level drinking and smoking measure (98 3%: Confidence Intervals Adjusted for Bonferroni correction α = 0.0167)** |

| | Known COD n = 382 | OR (CI) | p-value |
|---|---|---|---|
| None, Quit Early | 5574 (52.1%) | 3 (0.05%) 1 | 11 (0.2%) 1 |
| Drink only (Continuous, Quit Late) | 913 (8.7%) | 2 (0.22%) 1 | 1 (0.11%) 0.3 |
| Smoke only (Continuous, Quit Late) | 2278 (21.7%) | 8 (0.35%) 1 | 14 (0.61%) 0.2 |
| Dual (Continuous, Quit Late) | 1839 (17.5%) | 15 (0.81%) 1 | 10 (0.54%) 0.2 |

RR: Relative risk; CI: confidence interval; OR: odds ratio.

2-level Drinking Measure and 2-level Smoking Measure |

Drinking measure.

-None, quit early: No drinking or quitting by end of the 1st trimester.
-Continuous, quit late: drinking after the 1st trimester.

Smoking measure.

-None, quit early: No smoking or quitting by end of the 1st trimester.
-Continuous, quit late: smoking after the 1st trimester.

Primary exposure measure: 4-level drinking and smoking measure.

-None: No smoking or drinking during pregnancy or quitting by the end of the 1st trimester.
-Drinking only: Drinking after the 1st trimester of pregnancy and no smoking or quitting by the end of the 1st trimester.
-Drinking only: Drinking after the 1st trimester of pregnancy and no drinking or quitting by the end of the 1st trimester.
-Dual: Drinking and smoking after 1st trimester of pregnancy.

1 Of total alive at 1 year (10,504 with complete data).
2 (# demise)/(#demise + alive at 1 year)*100.
3 95% and 98 3% CI estimated from RR using log binomial regression utilizing generalized linear models and generalized estimating equations accounting for reenrollments.
4 95% and 98 3% CI estimated from OR (as approximation to RR) using logistic regression due to convergence issues with log binomial regression.
5 Adjusted for gestational age at enrollment, gestational age at delivery, multi-fetal gestation and one propensity score developed based on the 2-level drinking and one propensity score based on the 2-level smoking measures. Each propensity score included the following variables: recruitment location, maternal age, race, married or partnered status, education, arm circumference, history of diabetes and parity, as well as interaction terms (race*education, race*arm circumference, arm circumference*education, race*married/partnered status, race*parity).
6 Adjusted for reenrollment, gestational age at enrollment, gestational age at delivery, multi-fetal gestation and three propensity scores developed based on the 4-level exposure variable. The propensity score included the following variables: recruitment location, maternal age, race, married or partnered status, education, arm circumference, history of diabetes and parity, as well as interaction terms (race*education, race*arm circumference, arm circumference*education, race*married/partnered status, race*parity).
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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2019.100247.

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