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Snore-Associated Sleep Fragmentation in Infancy: Mental Development Effects and Contribution of Secondhand Cigarette Smoke Exposure

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ABSTRACT

OBJECTIVE. The link between sleep-disordered breathing and neurocognitive functioning in preschool and school-aged children now has been established clearly. Within these age groups, isolated studies have examined the potential effect of snoring without gas exchange abnormalities on aspects of cognitive competence. The goal of the study was to test the potential association between snoring and decrements in developmental performance among infants.

METHODS. Thirty-five healthy community infants (8.2 ± 0.4 months) were administered the Bayley Scales of Infant Development, including the Mental Development Index (MDI), after standard, overnight research polysomnography.

RESULTS. The apnea-hypopnea index for all infants was 0. Respiratory arousal index was significantly correlated with MDI. Snoring-associated arousals accounted exclusively for this relationship; spontaneous arousals and those that were associated with central apnea and oxyhemoglobin desaturation episodes (≥4%) were not significantly correlated with MDI. Living in a smoking household was not significantly associated with the presence of objectively recorded snoring but was associated with an increase in arousal frequency in snoring infants.

CONCLUSIONS. Infants with lower scores on a standardized mental development assessment had higher snoring-arousal indices. Because neither apnea nor hypopnea was present, these findings constitute additional evidence that snoring is not just an innocent noise during sleep in infants but may in fact represent the lower end of the disease spectrum associated with sleep-disordered breathing. Secondhand exposure to cigarette smoke may increase the deleterious effects of infant snoring.

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Key Words
infant, sleep, snoring, arousal, respiration, development, secondhand smoke

Abbreviations
SDB—sleep-disordered breathing
OSA— obstructive sleep apnea
AHI—apnea-hypopnea index
TST—total sleep time
Spo_2—arterial oxygen saturation
BSID-II—Bayley Scales of Infant Development, Version II
MDI—Mental Development Index
RespArI—respiratory arousal index

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THERE IS NOW substantial and compelling evidence indicating that sleep-disordered breathing (SDB) during early childhood is deleterious to cognition. Furthermore, SDB in early childhood leads to greater utilization of health care resources,[1] more frequent dose-dependent cardiovascular morbidity[2,3] and comorbid chronic illnesses,[4,5] as well as greater psychiatric and behavioral comorbidities.[6–10] Impairments associated with SDB have been shown on cognition and school performance.[6,9,11–16] The cumulative evidence points to at least partial reversibility of many of these effects in children[17–20] and in animal models,[21,22] highlighting the importance of early detection of pediatric SDB. Indeed, failure to thrive associated with SDB, which has been reported in up to 52% of patient samples, has been shown to be reversible in infants who are younger than 18 months after treatment.[23]

Although report of snoring history is insufficient for diagnosis of SDB, it is known that snoring is reliably present in children with obstructive sleep apnea (OSA).[24] The prevalence of SDB among school-aged children is estimated at 2% to 3%,[25,26] and symptoms that are consistent with risk for SDB have been reported between 6% and 27%.[4,12,15,26] An emerging body of work recently addressed the cognitive effects of mild SDB, or snoring exclusive of OSA, among school-aged children. Primary or habitual snoring may cause sufficient disruption of sleep architecture such that daytime functioning is affected in children.[27] Children who are aged 8 to 11 years and have apnea-hypopnea indices (AHI) of ≥ 1 and < 10 have impaired executive function.[28] Compared with nonsnoring control subjects, 5- to 8-year-olds who snore but have an obstructive AHI of < 1 per hour of total sleep time (TST) have impaired verbal and global IQ and selective and sustained attention and memory, with direct relationships between severity of impairment and mild oxyhemoglobin desaturations, obstructive hypopneas with desaturation, and respiratory arousals.[29] Habitual snoring among children who are aged 5 to 7 and have an obstructive AHI of < 1 per hour of TST have impaired performance on attention measures, as well as greater social problems and anxious/depressive symptoms.[16]

Prevalence rates of snoring similar to those of preschool- and early school-aged children have been reported among infants. Indeed, habitual snoring was found in 5% of 2- to 4-month-olds[30] and in 6- to 12-month-olds,[26] with higher rates in infants who are aged 1 to 8 months (16–26%).[31] More recently, we found habitual snoring in 1% to 9% of infants and toddlers (2–24 months of age).[32] However, the influence of snoring on the developing infant is unknown. Accordingly, the primary goal of the present study was to test the association between snoring and cognitive development among 8-month-old infants.

Furthermore, exposure to secondhand smoke is a known risk factor for snoring and SDB among school-aged children,[33] and significant differences have been shown in the histopathologic and ultrastructural evaluation of adenoid tissue from children who were exposed to passive smoking, indicating that this exposure is a primary contributor to repeated upper respiratory tract infection.[34] Passive smoking also was identified previously as a risk factor for snoring among infants.[31,35] Thus, a secondary study goal was to determine whether presence of smoking in the household had a contributing effect on snoring and arousal indices.

METHODS

The study was approved by the institutional review boards at the University of Louisville, Clark Memorial Hospital, Baptist Hospital East, Floyd Memorial Hospital, Norton Healthcare, Norton Suburban Hospital, and the University of Louisville Hospital. A preamble letter describing consent accompanied the screening survey; parent(s) signed informed consent and Health Information Portability and Accountability Act authorization for participation in overnight polysomnography and developmental assessment.

Postage-paid reply cards were included in the postpartum discharge packets at 6 local hospitals. Screening surveys then were sent to the homes of respondents when their infants reached 6 months and were returned to the research office via postage-paid mail. Qualifying families were invited to participate further when the infant reached 8 months.

Survey Instrument

The instrument assessed parent and child demographics, and a health history section included whether each parent snores or smokes (yes/no responses). Child sleep behaviors were assessed, including, "How often does your child snore?" with response options including "never" (never in the past 6 months), "rarely" (once a week), "occasionally" (2 times a week), "frequently" (3–4 times a week), and "almost always" (>4 times a week). These items were taken from a thoroughly validated and previously described instrument.[36]

Polysomnography and Scoring

Overnight polysomnography recordings were performed within the research unit of the Kosair Children's Hospital Sleep Medicine and Apnea Center using commercially available computerized multichannel data acquisition equipment (Medcare Systems, Inc, Amsterdam, Netherlands) that included 4 channels of electroencephalography (O1/O2, C3/C4), chin electromyography, bilateral electrooculogram, snore sound sensor, electrocardiogram, chest and abdominal inductance plethysmography; pulse oximetry was used to measure arterial oxygen saturation (Spo_2) and pulse wave form and thermistor-derived oronasal airflow. Simultaneous video monitoring was digitally recorded.

Stage scoring was performed using standard criteria for infants.[37] Time spent in active sleep, quiet sleep, and indeterminate sleep was calculated and expressed as a percentage of the TST. Respiratory events that lasted at least 2 breath-lengths were scored: central apneas were scored on the basis of cessation of oronasal flow and chest wall and abdominal movement; obstructive apnea was scored in the absence of oronasal airflow with continued chest wall and abdominal movement[38,39]; decreases in oronasal flow ≥50% with continued effort were scored as hypopneas. Minimal duration of 2 breath-lengths and an associated ≥4% Spo_2 desaturation and/or arousal were required for obstructive apnea and hypopnea scoring. Snoring was scored in the presence of a change in basal snore sensor levels that was verified by the polysomnographic technologist via both in-room checks and microphone transmission. Cardiorespiratory variables were scored as indices on the basis of the number of events per hour of TST. Average Spo_2 and nocturnal nadir were calculated from valid Spo_2 during TST with values during movement artifact being excluded.

Because criteria for arousals have not yet been established for infants and children, arousals were scored manually as defined by the American Sleep Disorders Association Task Force report; briefly, an abrupt change in electroencephalography that lasted 3 to 14 seconds with a concurrent change in electromyography in rapid eye movement sleep[40] was scored as spontaneous or respiratory related (occurring immediately subsequent to an apnea, hypopnea, desaturation, or snore). Arousals and respiratory events were scored as indices on the basis of occurrence per hour of TST. Scoring of respiratory events and desaturations was initially automated, all events and signals then were individually scorer validated. Polysomnography records were scored by a single blinded analyst; Cronbach's α and significance for intraclass correlations for interscorer reliability on previous work in the laboratory were .975 ($P < .001$) for sleep stage percentages, .821 ($P < .05$) for arousal subtypes, .957 ($P < .01$) for periodic leg movements subtypes, and .975 ($P < .001$) for apnea subtypes and hypopneas. For overall combined polysomnography measures, $\alpha = .996$ ($P < .001$).[41]

Developmental Assessment

The Bayley Scales of Infant Development II (BSID-II) were performed the morning after polysomnography by a blinded administrator; parents were asked not to discuss the polysomnography with the administrator. The BSID was originally standardized in the United States under the auspices of the National Institutes of Health on children from 1 to 42 months of age[42] and renormed in 1993.[43] The BSID is made up of the Mental Development Index (MDI) and the Motor Scale. When administered within the first year, the MDI is an assessment of sensory-perceptual acuity, discriminations, and response abilities and tests acquisition of object constancy as well as memory, learning, and problem-solving abilities. Vocalizations and the beginnings of verbal communication are measured as early evidence of the ability to form generalizations and classifications, which are a basis of abstract thinking.

Results are expressed as a standard score ranging from 50 to 150 and encompassing 3 SDs (15 points) on either side of the mean (100 points). When administered at the same age, there is a correlation between the MDI and the Stanford-Binet IQ test.[42] The BSID at 4, 8, 12, 18, and 24 months is correlated with Stanford-Binet Intelligence Scales at 30 and 36 months, with the perceptual items being more predictive at early months.[44] The MDI at 2 years is correlated with the Stanford-Binet IQ at 3 and 5 years.[45] No study was performed on a night when a child had an acute illness such as fever or nasal discharge.

Statistical Analyses

Descriptive statistics were calculated. Regression analyses were conducted for continuous variables. χ^2 was used to examine bimodal frequencies; Fisher exact probability test was used for tests with expected frequency value(s) <5. One-way analysis of variance was used for means comparisons. Cohen's d was calculated to determine effect sizes. Data were analyzed using SPSS 13.0 (SPSS Inc, Chicago, IL), and $P < .05$ was considered significant.

RESULTS

Forty-four infants were recruited into the study, with 9 lost as a result of intolerance of polysomnography instrumentation. Thirty-five infants underwent full overnight polysomnography recordings and developmental assessment and were available for analysis (Table 1). Four pregnancies were complicated by gestational diabetes, pregnancy-induced hypertension, preeclampsia, and preterm labor, respectively. Six infants had medical conditions diagnosed before participation: bronchitis at 2 months, respiratory syncytial virus bronchiolitis (at 5 weeks, 3 months, and 5 months, respectively), gastro-

TABLE 1 **Demographics and Family Characteristics**

N	35
Age (SD; range), mo	8.2 (±0.44; 7.2–9.5)
Female, %	47
White, %[a]	80
Birth weight (SD), lb	7.6 (1.1)
Gestational age (SD), wk at birth	38.8 (1.5)
Primipara, %	43
Maternal age (SD), y	29.3 (5.3)
Maternal education (SD), y	15.1 (3.1)
≥1 parent snores, %	59
≥1 parent smokes, %	33

[a] Nonwhite: black (1), Hispanic (1), biracial (3), other (2).

esophageal reflux disease, and eczema; 1 infant received a diagnosis of glycogen storage disease type IX after participation. Ten infants had medication administered within 24 hours before polysomnography: acetaminophen ($n = 3$), ophthalmic antibiotic ($n = 2$), decongestant and antihistamine ($n = 2$), metoclopramide ($n = 1$), ibuprofen ($n = 1$), and topical hydrocortisone ($n = 1$). Glycogen storage disease type IX can cause developmental delay, but this infant's MDI was average (96) and the data were retained.

Infants spent 5.8 to 10.7 hours asleep with an average of 1.1 hour awake after initial sleep onset. The average total arousal index was 8.9 per hour of TST, and respiratory arousal index (RespArI) was 0.67 per hour of TST. No infant had any obstructive apneas or hypopneas; all but 9 infants had central apneas, with indices ranging from 0.12 to 4.02. Central apneas were not associated with significant desaturations (Table 2).

There was a significant, negative correlation between MDI and RespArI ($r = -.43$; F = 7.3; $P = .011$; Fig 1). Because there were no obstructive apneas or hypopneas, RespArI was made up of arousals that resulted from central apneas, oxyhemoglobin desaturation (Spo_2 ≥4%) episodes, and snoring. Among these, snoring-related arousals accounted exclusively for the correlation between MDI and RespArI ($r = -.43$; F = 7.3; $P = .011$). Spontaneous arousals and those that were associated with central apneas and desaturations were not significantly correlated with MDI. Variance among maternal education years was low; MDI and maternal education were not significantly correlated. Motor Scale scores on the BSID were not significantly associated with polysomnography measures.

Fifty-nine percent of infants had at least 1 parent who reported snoring. χ^2 values were nonsignificant for a relationship between parental snoring and the presence of either infant snoring or respiratory-related arousals on polysomnography.

TABLE 2 **Mean (SE) Polysomnography and MDI Values**

TST, h	7.90 (0.20)
Sleep efficiency, %	84.2 (1.2)
Sleep latency, min	6.04 (2.3)
Wake after sleep onset, min	66.67 (7.3)
Quiet sleep, %	25.20 (0.008)
Active sleep, %	31.50 (0.008)
Indeterminant sleep, %	43.40 (0.009)
Spontaneous arousal index	7.65 (0.47)
Apnea arousal index	0.36 (0.27)
Desaturation arousal index	0.01 (<0.00)
Snore arousal index	0.58 (0.18)
Total arousal index	8.85 (0.37)
RespArI	0.67 (0.19)
Central apnea index	0.98 (0.20)
Mean Spo_2	97.73 (0.15)
Spo_2 nadir	90.14 (1.0)
MDI	98.03 (1.2)

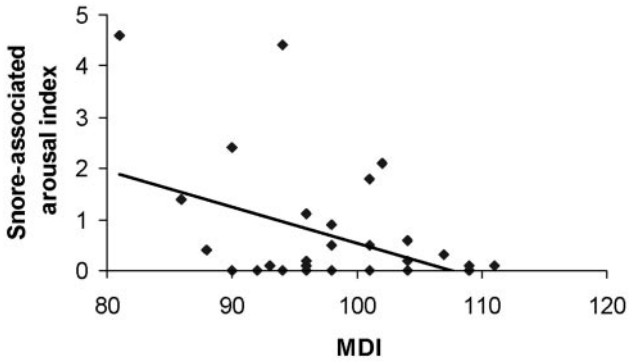

FIGURE 1
Regression between snore-associated arousal index and MDI ($R^2 = 0.18$; $P = .011$).

Thirty-three percent of infants were from a cigarette-smoking household (in which at least 1 parent smoked: both parents smoked in 17% of homes, only the father smoked in 9%, and only the mother smoked in 6%). χ^2 for parental smoking and presence of infant snoring on polysomnography approached significance; snoring was observed in 41% of infants from a nonsmoking household and in 73% of those from a smoking household ($\chi^2 = 3.0$; $P = .08$).

Infants from a smoking household were significantly more likely to have respiratory-related arousals during polysomnography recordings. RespArI >0 was present among 50% of infants from nonsmoking households and among 100% of infants from smoking households (Fisher's $P = .005$). Maternal-only and paternal-only smoking were also both significantly related to RespArI >0 (Fisher's $P = .03$, each). MDI did not differ significantly between infants from smoking and nonsmoking households (F = 2.0; $P = .16$). There were no significant correlations or differences as a function of TST or sleep efficiency on RespArI or MDI.

DISCUSSION

The data presented herein indicate that even among infants and toddlers, the concept of habitual snoring's being an innocent phenomenon without adverse consequences probably needs to be viewed as obsolete. Indeed, snoring may present a developmental hazard in young children, particularly when snore-associated arousals are present. Furthermore, we show that exposure to environmental smoke increases the risk for snoring-related sleep fragmentation.

In the present study, we did not find conclusive evidence suggesting that living in a cigarette-smoking household increased the risk for snoring per se. However, Mitchell and Thompson[31] found that among nearly 2000 infants from 1 to 8 months of age, parental report of snoring was increased with concurrent reporting of maternal cigarette smoking, along with the presence of male gender, prone or supine sleeping, respiratory in-

fections, and the presence of snoring during the first month after birth. These findings suggest that multiple modifiers may contribute to the occurrence of snoring in the first year of life.

More important, we still do not know much about the natural history of snoring and snore-induced arousals in infancy. Zucconi et al[46] found that among 18- to 24-month-olds who were evaluated for nightly snoring and referred for surgical treatment, the parents of >50% reported that the habitual snoring had developed during the child's first year of life, and 16% reported an onset in the first month of life. Furthermore, habitual snoring may persist over a 1-year period in 49% of primary school children. It is interesting that household cigarette smoking was identified as a risk factor for both initial onset of snoring and its continued presence over time.[35] Thus, we speculate that exposure to secondhand cigarette smoke not only may account for more snore-related arousals but may also contribute to the development of SDB among very young snorers.

Some of the study limitations merit discussion. First, the survey response rate is unknown because of the implementation of a prohibition on tracking the number of nonparticipants subsequent to Health Insurance Portability and Accountability Act legislation. Response cards were distributed to postpartum patients through local hospitals at the discretion of the nursing and clerical staff, so a response percentage cannot be calculated; among those who returned the response card and were sent a survey, the response rate was 57.1%. Thus, a self-selection bias clearly is possible, and our ability to generalize the results is limited. Second, the survey was not designed to gather extensive and comprehensive information about exposure to secondhand cigarette smoke. However, the previous studies reported above and current findings emphasize the need and the importance of future research into the mechanisms that influence snore-related arousals in infants and whether this effect is exposure dependent. Finally, 1 of the original goals of the study was to screen infants at the age of 8 months for objective evidence of SDB while minimizing intrusion into the natural sleep pattern and mother-infant interactions during the recording period. At the same time, home-based studies using currently available instrumentation for sleep recordings in infants are vulnerable to data losses, and preliminary trials using this approach confirmed such concerns. Thus, we used a sleep laboratory–based approach that enabled a high rate of data integrity with minimal intrusion to the infant and the parent. Although the percentage of wake time subsequent to sleep onset was higher than would be expected in a naturalistic setting, it should be emphasized that no relationships were found between RespArI or MDI and TST or sleep efficiency. Thus, we do not expect that administration of the BSID after polysomnography had on influence on MDI scores as a function of sleep loss.

This study and others clearly support the need for identification and evaluation of the youngest children with recognizable risk factors for SDB. This may pose a formidable challenge when we consider that the symptoms of SDB, such as snoring, are less frequently the presenting complaint in such children when compared with associated comorbidities, such as recurrent upper respiratory tract infections and delays in growth and development.[47] In addition, the recently published American Academy of Pediatrics 2003 guidelines for diagnosis and management of SDB in childhood specifically exclude children who are younger than 1 year because these cases are considered too complex for the scope of the recommendations and require specialist consultation.[48] Finally, awareness of SDB symptoms on the part of parents and physicians is very low.[49,50] Indeed, using an exit-interview strategy after pediatrician consultation, Blunden and colleagues[50] reported that among children with a significant history of snoring, only 8% of parents mentioned this symptom during the concurrent clinical evaluation, and only 15% had done so previously. The robustness of our findings on the relationship between sleep fragmentation (as evidenced by snore-associated arousals) and the variance in mental development among healthy infants highlights the need to overcome these diagnostic screening challenges. Furthermore, we are unaware of any study that has examined potential mechanisms underlying this correlation, and, as such, we do not know whether such decrements in developmental achievement will persist or completely reverse on implementation of measures that aim to treat snoring in these infants. The possibility exists that if such infants are left untreated, then they may go on subsequently to develop SDB and its associated morbidities.

CONCLUSIONS

Snoring without evidence of apnea and/or hypopnea in 8-month-old infants is associated with decreased scores on the MDI of the BSID-II when such snoring induces sleep fragmentation, the latter being apparently facilitated by cigarette-smoke exposure. We postulate that substantial reductions or elimination of exposure to secondhand cigarette smoke may ameliorate the developmental outcomes of snore-related arousals among some children.

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