Secondhand Smoke Exposure and Sleep-Related Breathing Problems in Toddlers

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ABSTRACT

BACKGROUND: Adequate sleep during childhood is an important component of overall health and wellbeing for children. Secondhand smoke (SHS) exposure has been linked to a greater risk of sleep-disordered breathing.

OBJECTIVE: Our objective was to investigate relationships between SHS exposure and sleep-related breathing problems in healthy toddlers aged 2 to 5 years. We hypothesized that there is an independent relationship between objectively measured SHS exposure and presence of sleep-related breathing problems by parental report.

METHODS: A convenience sample of 149 healthy children ages 2 to 5 years was recruited from an academic pediatric primary care center for this cross-sectional study; 138 had complete data that were analyzed. Current SHS exposure was determined by hair nicotine level. Presence of sleep-related breathing problems was assessed by 1 survey item. Inflammation was determined by serum C-reactive protein (CRP) level. Analysis in Stata 15 included a series of multivariate logistic regression models, controlling for individual-level demographics and body mass index z scores according to mediation analysis procedures for dichotomous outcomes.

RESULTS: Approximately 24% of parents reported their child snored, gasped, or had difficulty breathing at night sometimes, most of the time, or almost always. Regression models with mediation analysis indicate that SHS exposure significantly increased the odds of reporting the child had sleep-related breathing problems, and 18% of this relationship is explained by log serum CRP levels.

CONCLUSIONS: Although the cross-sectional nature of this study limits causality, evidence suggests a relationship exists between SHS exposure, as measured by log hair nicotine and sleep-related breathing problems at night.

KEYWORDS: hair nicotine; secondhand smoke; sleep-disordered breathing

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WHAT'S NEW

Sleep-related breathing problems in a group of toddlers were independently associated with an objective measure of secondhand smoke exposure and not with child overweight/obesity.

ADEQUATE SLEEP DURING childhood is an important component of overall health and wellbeing for children. Sleep-disordered breathing (SDB) is a term used to describe the spectrum of disorders ranging from intermittent snoring to documented obstructive sleep apnea.[1,2] Ultimate adult-health outcomes of SDB in childhood are not completely known due the lack of sufficient longitudinal studies[3] but likely include the risk of long-term cardiovascular comorbidities. During childhood itself, SDB, including the less-severe forms such as snoring, is associated with school problems,[4,5] poor cognitive function,[6] and behavior problems in preschool children.[2,7] In addition, relationships between SDB and impaired health-related quality of life during childhood have been reported.[8]

Secondhand smoke (SHS) exposure has been associated with SDB during childhood, although the mechanisms remain unclear. A systemic review of SHS exposure and SDB showed a significant association between SHS exposure and SDB in children younger than 18 years.[1] (Since the articles reviewed were all case-control studies, the overall grade in the systematic review was grade B based on the Oxford Centre of Evidence-Based Medicine.)[9] Proposed mechanisms for this finding include increased inflammation from the chronic tobacco exposure leading to mucosal edema and tonsillar

hypertrophy.[1] Yolton et al[10] found that SHS exposure measured by serum cotinine, a nicotine metabolite, was associated with SDB in children ages 6 to 12 years with asthma. Beebe et al[7] described a relationship between SHS exposure and persistent snoring, but these relationships were not found in adjusted models controlling for demographics. However, in a recent meta-analysis, there was a significant relationship between habitual snoring and SHS exposure (pooled odds ratio for maternal smoking was 1.87).[11] In a study of children evaluated for tonsillectomy, African-American race and SHS exposure by parental report were the only 2 independent factors associated with documented obstructive sleep apnea.[12] Zhu et al[13] reported a dose−response relationship between snoring frequency and log urinary cotinine concentrations in children 2 to 6 years old.

More than 40% of US children aged 3 to 11 years were exposed to tobacco smoke from 2011 to 2012, based on a biological marker of exposure, serum cotinine levels.[14] Of special concern are children from low-income homes and African-American children, because they have the greatest rates of biologically measured SHS exposure.[15] An inverse relationship between socioeconomic status and SHS exposure has been well documented,[15,16] and recent analyses have shown that for every decrease in family income ratio, serum cotinine levels increased by 1.18 ng/L among children.[15] We hypothesize that there is an independent relationship between objectively measured SHS exposure and presence of sleep-related breathing problems by parental report.

METHODS

HUMAN SUBJECTS RECRUITMENT

The current investigation is a secondary analysis from a larger study of the association of cardiovascular risk factors with smoke exposure in toddlers.[17] Participants were children aged 2 to 5 years, and parents provided informed consent. The Nationwide Children's Hospital institutional review board approved of the study. Subjects were recruited via convenience sampling through recruiting in Nationwide Children's Hospital Primary Care Network (Columbus, Ohio) and advertising via an internal hospital e-mail system. The Primary Care Network primarily serves low-income, urban children in Columbus. Inclusion criteria were healthy children both exposed and unexposed to SHS by parental report. Exclusion criteria were the presence of 1 or more of the following: acute febrile illness or other active infections, congenital heart disease, diabetes (type 1 or 2, as defined by elevated fasting glucose [>100 mg/dL]), use of daily prescription or specific nonprescription medications (including but not limited to the use of antihistamines, decongestants, nonsteroidal anti-inflammatory medications, and caffeine within 2 days of testing, and use of oral or inhaled steroids within 1 year of testing), and family history of hypercholesterolemia. This approach to enrollment thus avoided children with persistent asthma, because of the use of daily anti-inflammatory medication, which we considered confounding for the primary investigation.

STUDY PROCEDURES

The study was introduced to the mother or caregiver at a clinic visit. Subjects subsequently were scheduled for testing at a research site in the morning between 8 and 10 AM, after overnight fasting. This method therefore avoided studying children who were at the primary care clinic for an acute illness during that illness. The protocol was carried out as follows: 1) Study procedures were described and parental informed consent was obtained, 2) anthropomorphic measurements were obtained, 3) a structured interview with parent (demographics and SHS exposure history) was obtained, 4) a hair sample was obtained, and 5) a blood sample of 7 mL (for C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α], and cardiovascular impairment markers) was collected for biomarkers and covariates. Serum samples were then aliquoted within 4 hours of collection and stored at −80°C until the assays were performed. Further details regarding methods have been published.[17]

SHS EXPOSURE

Hair nicotine was used as a biological marker of SHS exposure to assess long-term evaluation of smoke exposure, since the nicotine is incorporated into the growing hair shaft over several months. Samples are easy to obtain, handle, and store. Approximately 20 to 40 hair shafts from the occipital area were cut at the root and 2 to 3 cm in length. Hairs were stored and later sent for assay at an established contract research facility (Johns Hopkins School of Public Health, Baltimore, Md). Hair was analyzed as previously described by Kim et al.[18] Between 10 and 30 mg of each hair sample was washed using 3 mL of dichloromethane and sonicated (Model 250HT; Aquasonic, Hayward, Calif) for 30 minutes before nicotine extraction and analysis. This process removed any nicotine adherent to the surface of the hair, limiting measurement of nicotine to that accumulated by inhalation, ingestion, and dermal absorption and subsequent incorporation into the growing hair. Hair nicotine analysis was performed using gas chromatography/mass spectrometry (GC-17/MS-QP5000; Shimadzu, Canby, Ore) in selected ion monitoring and splitless modes. For quality control, approximately 10% of the hair samples were subjected to duplicate analyses. Content is expressed as ng/mg of hair. Due to the skewed distribution of this measure, hair nicotine level was log transformed for statistical analysis.

MARKERS OF INFLAMMATION

C-REACTIVE PROTEIN

CRP was measured using a commercially available enzyme immunoassay test kit (cat. no. BC-1119; Bio-Check, Inc, Foster City, Calif). Intra- and interassay

variations are less than 5% and 11%, respectively. Due to the skewed distribution of this measure, CRP level was log transformed for statistical analysis.

Interleukin-6

IL-6 was determined using a highly sensitive ELISA kit (cat. no. DY206; R&D Systems, Minneapolis, Minn). Intra- and interassay variations are less than 8% and 10%, respectively.

Tumor Necrosis Factor-α

TNF-α was determined using a high-sensitivity ELISA kit (cat. no. DY210; R&D Systems). Intra- and interassay variations are less than 4% and 12%, respectively.

Sleep-Related Breathing Problems

This was determined by response to a single-item question adapted from the Pediatric Sleep Questionnaire[19]: "When sleeping, does your child snore, gasp, or have difficulty breathing at night" with responses "never," "seldom," "sometimes," "most of the time," and "almost always." For analysis, the responses were dichotomized with "never" and "seldom" versus the other 3 responses. Because we used only 1 item from the Pediatric Sleep Questionnaire, we named this outcome variable "sleep-related breathing problems" and not "sleep-disordered breathing." This was defined as a response of breathing trouble at night (snoring, gasping, or difficulty breathing) sometimes, most of the time, or almost always.

Statistical Analyses

Statistical analyses were performed with Stata 15 (StataCorp. 2017 Stata Statistical Software: Release 15.0; Stata Corporation, College Station, Tex). Among the 149 children 2 to 5 years of age who were originally included in the study, 10 had missing information on maternal education, and 1 additional child had missing information on CRP. These children were omitted from the final analysis with listwise deletion, for a final analysis sample size of 138.

Categorical variables were used to indicate sex (female = 1, male = 0); race (African American, white, and other or biracial race); ethnicity (Hispanic or Latino = 1, Non-Hispanic = 0), insurance status (Medicaid benefits = 1, all other insurance = 0); and maternal education (less than high school, high school graduate or General Education Development, and some college, college graduate, or greater). Body mass index (BMI) was converted to a BMI z score. A program available in Stata, zscore06 was used to calculate anthropometric z scores. Length/height for-for-age, weight-for-height, BMI-for-age, and weight-for-age z scores were calculated. Sensitivity analyses substituting obesity and overweight status for BMI yielded similar results; therefore, results of continuous BMI z scores are presented.

Potential Confounders

We considered the following potential confounders—a clinical diagnosis of allergic rhinitis at the time of the study, laboratory evidence of environmental allergy based on allergy testing, an abnormal sleep study, and previous tonsillectomy/adenoidectomy before the study. A clinical diagnosis of allergic rhinitis was defined as either the presence of "allergic rhinitis," "seasonal allergic rhinitis," or "seasonal allergies" in the subjects' problem list or an active prescription for loratadine or cetirizine, both criteria at the time of the study. Subjects who had taken these prescriptions within 2 days of the study were excluded, but some subjects had active prescriptions but did qualify for enrollment (because they had not taken either loratadine or cetirizine within 2 days of the study).

Regression Modeling

A logistic regression–based power analysis indicated that for an alpha of 0.05, 109 cases were needed for 80% power and 123 cases were need for 85% power. Therefore, 138 cases was sufficient for logistic regression modeling. Our statistical approach included a series of multivariate logistic regression models, controlling for individual-level demographics, potential confounders of allergic rhinitis and tonsil or adenoid removal, and BMI z scores according to mediation analysis procedures for dichotomous outcomes. Single-mediation regression models were used to test whether SHS was associated with the presence of sleep-related breathing problems and whether this association was mediated by CRP. Mediation analysis is a valid tool, even in cross-sectional analysis, as long as confounding among key measures is not present and when reverse mechanisms are not possible. In our case it is not biologically possible for CRP to cause SHS exposure. Mediation was tested using 2 approaches: 1) causal steps and 2) medeff, a function for estimating mediation effects for a variety of data types, including binary outcomes.[20-22] Testing the causal steps requires 3 separate regressions: a regression of CRP on the SHS measure, a regression of sleep-related breathing problems on the SHS measure without controlling for CRP, and a regression of sleep-related breathing problems on the SHS measure and CRP. In addition, the magnitude of the coefficient relating SHS to sleep-related breathing problems must be larger in the model that does not control for CRP than in the model that does control for CRP. Models were then tested using the medeff procedure available in Stata, with clustering for family id and robust standard errors. The medeff procedure in Stata calculates the indirect effects, the direct effects, and the total effects. The percentage of mediation is then calculated as the proportion of indirect effect to total effect times 100.

Results

Baseline Characteristics and Presence of Sleep Problems

Characteristics of the study subjects are shown in the Table. The average age was 3.2 years, and the majority (84%) were insured by Medicaid, although 43% of mothers had some college education or greater. Thirty-two (23%) gave a positive response to the survey item, "When

Table. Descriptive Statistics of All Variables Used in the Analyses (N = 138)

Subject Characteristics	Mean ± SD or n (%)
Demographics	
Age, y	3.22 ± 1.06
BMI	
kg/m^2	16.98 ± 2.28
z score	0.90 ± 1.39
Female	76 (55.07%)
Race	
African-American	75 (54.35%)
White	32 (23.02%)
Multiracial or other race	31 (22.63%)
Ethnicity	
Hispanic or Latino	12 (8.63%)
Family economic status	
Subject insured by Medicaid, n (%)	116 (84.06%)
Maternal education, n (%)	
Less than high school	43 (31.16%)
High school or GED	35 (25.36%)
Some college, college degree, or college graduate	60 (43.48%)
Allergic rhinitis	17 (12.32%)
Tonsils or adenoid removed	2 (1.45%)
Dependent variable	
Sleep-disordered breathing classification	
Positive response:	32 (23.19%)
Does your child sometimes, always, or almost always snore, gasp, or have difficulty breathing at night	
Independent variable	
Secondhand smoke exposure	
Log-transformed hair nicotine	0.23 ± 0.77
As collected hair nicotine, ng/mg, median (range)	1.86 (0.025–39.45)
Mediator variable	
CRP	
Log-transformed CRP	−1.60 ± 2.43
As collected CRP, median (range)	0.18 (0.0001–67.93)

SD indicates standard deviation; BMI, body mass index; GED, General Education Development; and CRP, C-reactive protein.

sleeping, does your child snore, gasp, or have difficulty breathing at night?" Of these responses, the breakdown of 'sometimes, most of the time, and almost always" was 20, 8, and 4 individuals in each category, respectively.

Smoke Exposure

The enrolled participants had a wide range in smoke exposure. Approximately two thirds (66.4%) of the subjects lived with a smoker, and 40 (26.8%) lived with 2 or more smokers. Maternal smoking was present in 62 (42.3%) of the enrolled subjects. The median hair nicotine level was 1.86 ng/mg with a wide range of exposure levels from 0.03 ng/mg (virtually no exposure) to 39.45 ng/mg. The mean log hair nicotine value was 0.23 with a range of −1.60 to 1.60 (Fig. 1).

Inflammatory Markers

Bivariate analysis showed that the only inflammatory marker with a relationship with smoke exposure (log hair nicotine) was CRP (Pearson coefficient 0.23, $P < .05$). Log CRP distributions are displayed in Figure 1. There was no correlation between IL-6 or TNF-α with log hair nicotine. Neither IL-6 nor TNF-α were significant independent variables or mediators when tested in the multivariate models. Therefore, results are presented for CRP only.

Presence of Potential Confounders

Seventeen subjects had a clinical diagnosis of allergic rhinitis at the time of the study. None had a history of allergy testing or a sleep study. Two had tonsillectomy and adenoidectomy before the study. One third of the group was either overweight (10.7%) or obese (22.8%), with a mean BMI of approximately 17.

Multivariate Analysis

Multivariate regression analyses examined the relationships among all individual-level demographics variables (sex, race, ethnicity, insurance status, and maternal education), potential confounders (allergic rhinitis and previous tonsillectomy/adenoidectomy), BMI z score, and sleep-related breathing problems. No significant association ($P < .05$) was found between any of the demographic variables or BMI z score and sleep-related breathing problems. Additional models added CRP to the multivariate regressions and the control demographics, and BMI z score maintained nonsignificant in relation to sleep-related breathing problems. One exception was white race was significant and negative in the final model (pathway b^4, $P = .041$), compared with other or mixed race.

SHS Exposure, Sleep-Related Breathing Problems, and Inflammation

We examined relationships between SHS exposure, sleep-related breathing problems, and CRP level. All models included all control variables described previously. Figure 2 depicts the results of the mediation analysis by displaying separate regression coefficients (b^1, b^2, b^3, b^4) for each model and corresponding significance tests. Regression model b^2 shows that log SHS significantly and positively increased log serum CRP (b$^2 = 0.70$, $P < .05$). In turn, log serum CRP positively increased the presence of sleep-related breathing problems (b$^3 = 0.19$, $P < .10$). Log SHS increased the presence sleep-related breathing problems directly (b^1), and 18% of this relationship was mediated by log CRP, as displayed by the reduction in coefficient b^4 to nonsignificance, compared with b^1. Regression models with mediation analysis indicated that SHS exposure, as measured by log hair nicotine, significantly increased the odds (approximately twice the odds [exp(b^2) = exp(0.70) = 2.02]) of reporting the child sometimes/any or almost always had sleep-related breathing problems, and a significant percentage (18%) of this relationship is explained by log serum CRP levels.

Tonsillectomy/Adenoidectomy, Allergic Rhinitis, and Sleep-Related Breathing Problems

In addition to log hair nicotine and CRP, having had tonsils or adenoids removed was positive and significant in the pathway between log hair nicotine and CRP only ($P = .041$). Presence of a clinical diagnosis of "allergic

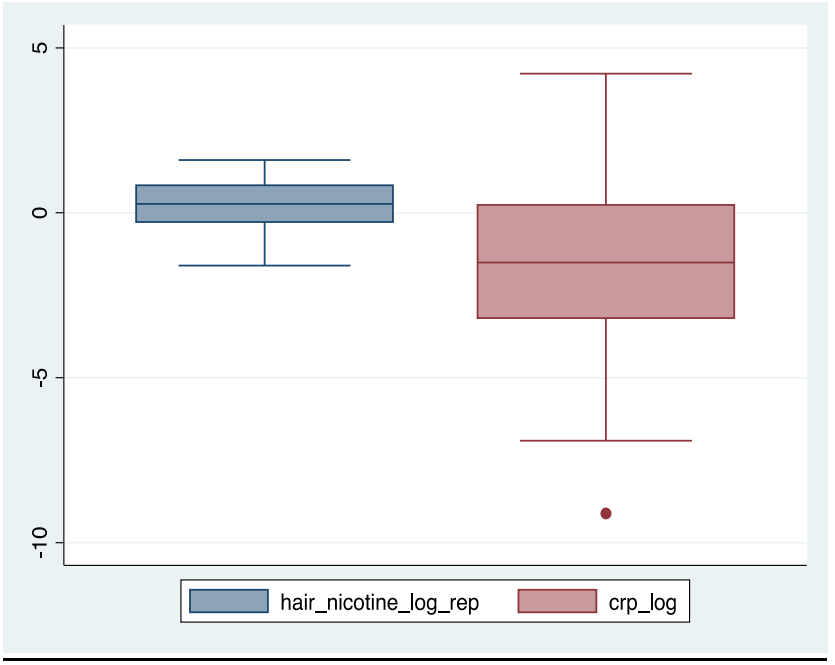

Figure 1. *Box and whisker plot of log distributions of hair nicotine and CRP. The ends of the box are the upper and lower quartiles (interquartile range). The median is marked by the line inside the box. The whiskers are the lines outside that box that extend to the highest and lowest points. CRP indicates C-reactive protein.*

rhinitis" was significantly and positively associated with sleep-related breathing problems (pathway b^3, $P = .018$) as well as the final model (pathway b^4, $P = .017$).

DISCUSSION

We found a positive relationship between objectively measured SHS exposure and sleep-related breathing problems in this preliminary cross-sectional study of healthy toddlers. A clinically used measure of systemic inflammation, CRP, was found to mediate about one fifth of this relationship. Other markers of inflammation (IL-6 and TNF-α) did not demonstrate this relationship.

One third of our subjects were either overweight or obese; we did not find a relationship between child BMI and sleep-related breathing problems in this group of young children. With the increased prevalence of overweight and obesity among young children,[23,24] it has been hypothesized that the rate of severe sleep-related breathing problems such as obstructive sleep apnea may be increasing. Iannuzzi et al[25] found that children who were obese had a 3.3 times greater probability of having obstructive sleep apnea than children who were not obese. However, our findings correspond to Beebe et al,[7] who reported no relationship between BMI z score and presence of snoring in preschool children. Relationships between elevated BMI and sleep-related breathing problems may be more pronounced in school-

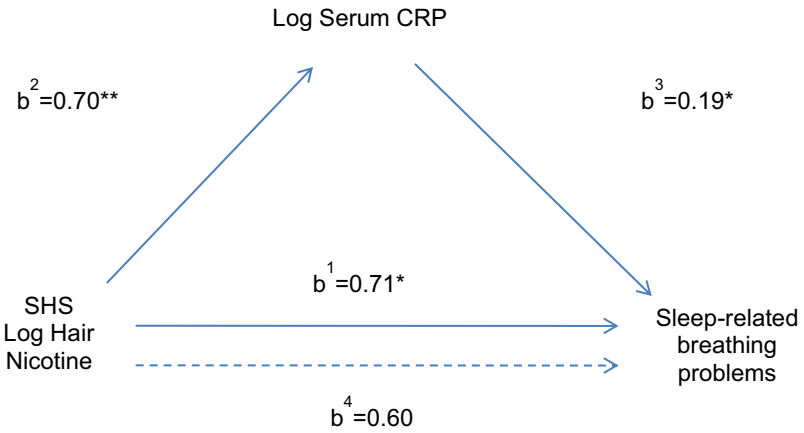

Figure 2. *Mediation analysis path diagram (N = 138). All models include demographic control variables and regression coefficients (not odds ratios) are reported to show the reduction in coefficients for mediation analysis. b^1 is the direct effect of SHS on breathing difficulty. b^2 is the direct effect of SHS on CRP. b^3 is the direct effect of CRP on breathing difficulty. b^4 Dashed line indicates the effect of SHS on breathing difficulty when CRP is included in the model, as displayed by regression coefficient b^4. *P < .10, **P < .05. CRP indicates C-reactive protein; SHS, secondhand smoke.*

aged children and adolescents rather than preschool children. While pediatricians are increasingly aware of the health consequences of childhood obesity, it is important not to ignore relationships with other potential modifiable risk factors such as smoke exposure.

This study has several limitations. We used only 1 question to assess the presence of sleep-related breathing problems by parental report and did not have any objective measure of sleep-related breathing problems, such as a polysomnogram, which was beyond the scope of this project. SDB is defined as a spectrum of disorders, ranging from intermittent snoring to sleep apnea, and therefore the question we used assessed the less severe end of that spectrum. As noted earlier, behavioral and cognitive problems are associated with milder forms of SBD[5-7] so that relationships noted between SHS exposure and sleep-related breathing problems have clinical relevance.

Another limitation is our restriction to children without persistent asthma in recruitment criteria. We did not include these children because we wanted to exclude subjects taking inhaled corticosteroids, as these might confound measurements of systemic inflammation. Consequently, we may have actually underestimated the association between SHS exposure, inflammation, and sleep-related breathing problems because we did not study the children with the greatest amount of airway inflammation. It was thus notable that we found these relationships in relatively well children.

Our subjects were a convenience sample from a clinic serving primarily an underserved urban minority population. Therefore, our generalizability is limited to that population and should not be extrapolated to low-income rural populations. However, by studying highly exposed, low-income, city-dwelling children we are actually focused on a group of children who are vulnerable to the harms of smoke exposure. Smoking and smoke exposure varies inversely by socioeconomic status,[14] so we chose a relevant group to study. In addition, although it is impossible to ensure causality from the cross-sectional design used, a clear weakness to this design, the mediation analysis we used remains a valuable tool for understanding potential pathways for biological effects.

The major strength of the study is the use of a biological measure of child SHS exposure. Hair nicotine is a reliable[26] measure of several months of smoke exposure. Parents are known to underestimate such exposure in a clinical setting[27] for reasons of social desirability. Therefore, relationships between SHS exposure by survey questions and a potential health outcome may not be detected unless biological measures are used.

Another strength is the measurement of inflammatory markers. CRP is a commonly recognized marker of systemic inflammation to examine potential pathways of these relationships. CRP is also an independent predictor of risk for future cardiovascular morbidity in adults.[28] Iannuzzi et al[25] reported a positive significant relationship between the presence of obstructive sleep apnea and CRP levels in children aged 5 to 15 years. However, this relationship lost significance when adjusted for BMI z score. In contrast, we found that in the preschool age group, the relationship between CRP and sleep-related breathing problems was not mediated by BMI.

In this preliminary study, we have demonstrated an independent relationship between objectively measured SHS exposure and sleep-related breathing problems in children aged 2 to 5 years. We did not find a relationship with BMI. SHS exposure is a modifiable risk factor and must be recognized as such. Pediatricians counseling parents of children with sleep-related breathing problems should emphasize the importance of establishing and maintaining a complete smoke-free home to improve their child's sleep and ultimately wellbeing. As the American Academy of Pediatrics recommends, parents should be screened for tobacco use and receive assistance from their children's pediatrician in quitting smoking to help create an optimal environment for healthy children.[29]

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