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Prenatal and childhood tobacco smoke exposure are associated with sleep-disordered breathing throughout early childhood

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Abstract

Objectives: To determine whether prenatal and childhood tobacco smoke exposure (TSE) are each independently associated with mild sleep-disordered breathing (SDB) symptoms throughout early childhood, and whether the association between childhood TSE and SDB differs according to the level of prenatal exposure.

Methods: Longitudinal cohort study, using data from the Avon Longitudinal Study of Parents and Children, a population-based birth cohort from the United Kingdom. Primary exposures were repeated measures of mother-reported prenatal and childhood TSE through age 7 years. Outcomes were mother-reported measures of mild SDB symptoms, including snoring, mouth breathing, and witnessed apnea, repeated annually through age 7 years.

Results: 12,030 children were followed for a median duration of 7 years. 24.2% were exposed to prenatal tobacco smoke, 46.2% were exposed at least once in childhood, and 20.6% were exposed during both periods. Both prenatal and childhood TSE were associated with SDB symptoms throughout early childhood (adjusted OR [aOR] for any prenatal TSE 1.23; 95% CI 1.08, 1.40; aOR for any childhood TSE 1.17; 95% CI 1.06, 1.29). We observed a dose-response effect between TSE and SBD symptoms, and found evidence of effect modification for those exposed during both time periods [combined high level exposure both prenatally and during childhood: aOR snoring 2.43 (95% CI 1.50, 3.93), aOR apnea 2.65 (95% CI 1.46, 4.82)].

Conclusions: Prenatal and childhood TSE were both independently associated with mild SDB symptoms throughout early childhood in a dose-dependent manner, further supporting the critical importance of maintaining a tobacco-free environment throughout gestation and childhood.

Keywords

ALSPAC; apnea; snoring; secondhand smoke; tobacco smoke; sleep-disordered breathing

Introduction

Sleep-disordered breathing (SDB) refers to the disruption of normal respiratory patterns and ventilation during sleep. It includes a spectrum of conditions ranging in symptom severity from milder symptoms like snoring and mouth breathing that affect up to 25% of children, to more severe conditions like obstructive sleep apnea (OSA), which affects 1-5% of children.[1,2] The spectrum of SDB conditions is associated with a wide range of comorbidities, including behavioral problems, impaired cognition and school performance, and long term cardiovascular comorbidities.[1-3]

Approximately 1 in 3 children in the United States are exposed to secondhand tobacco smoke, and up to 15% are exposed prenatally.[4,5] However, the association between tobacco smoke exposure (TSE) and SDB remains incompletely understood. Previous studies have found associations between TSE and SDB in childhood but have inadequately accounted for confounding by socioeconomic factors, and due to their cross-sectional nature, have not explored the temporal association between TSE and SDB symptoms.[6-9] Moreover, it is unclear whether children exposed prenatally are at increased risk of developing SDB, and whether they are more susceptible to the effects of childhood TSE on SDB symptoms. These

findings would have important implications for prenatal counseling and mechanistic studies of SBD symptoms.

Longitudinal studies can help clarify the long-term effects of prenatal TSE beyond infancy and disentangle the independent effects of prenatal and childhood TSE. Using a population-based birth cohort, we aimed to determine whether prenatal and childhood TSE are independently associated with mild SDB symptoms throughout early childhood, and whether prenatal TSE modifies the association between childhood TSE and SDB symptoms.

Methods

We performed a longitudinal analysis using data collected from 1990 to 1999 in the Avon Longitudinal Study of Parents and Children (ALSPAC). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples was collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The present study was considered exempt from review by the University of California, San Francisco Institutional Review Board because all data obtained by investigators were fully deidentified. Data analysis was performed from October 2018 to December 2019.

Participants

Pregnant women residing in Avon, United Kingdom, with expected dates of delivery between April 1st 1991 to December 31st 1992 were invited to take part in the ALSPAC study. A total of 14,541 pregnancies were enrolled, which resulted in 14,062 live births, of which 13,988 were alive at 1 year of age.[10,11] The analytic sample in the current study included 12,030 children alive at 1 year of age with TSE data available from at least one time point through age 7 years. The ALSPAC website contains details of all the data available through a fully searchable data dictionary and variable search tool.[12]

Exposures

The primary exposures were mother-reported prenatal and childhood TSE. Prenatal TSE was assessed by questions answered by the mother during each trimester of pregnancy about the number of cigarettes she smoked each day. The degree of prenatal TSE was characterized as none, low (less than half a pack per day, per trimester), moderate (half a pack to less than one pack per day, per trimester), or high (one pack or more per day, for at least two trimesters). Childhood TSE was assessed by standardized questions with categorical responses at 6 time points annually between ages 1.5 and 7 years asking the mother how often during the day the child spends in a room or enclosed place where people are smoking. The degree of childhood TSE was characterized as none, low (less than 3 hours per day), or high (3 or more hours per day).

Outcomes

The outcomes were mild symptoms of SDB, including mouth breathing, snoring, and apnea. The term apnea is used to refer to witnessed pauses in breathing or breath-holding, and does not refer to polysomnography-diagnosed OSA. These were mother-reported, and were assessed by the following standardized questions at 6 time points annually between ages 1.5 and 7 years (Figure 1): i) mouth breathing: “Does he/she breathe through his/her mouth rather than his/her nose?” (always/mostly vs. sometimes/rarely/never); ii) snoring: “Does he/she snore for more than a few minutes at a time?” (most nights/quite often vs. sometimes/rarely/never); iii) apnea: “When asleep, does he/she seem to stop breathing or hold his/her breath for several seconds at a time?” (often/sometimes vs. rarely/never).[13] These were modeled as a combined “Any SDB symptoms” binary variable and as individual binary variables.

Additional variables

Potential confounders and effect modifiers were identified from the literature and incorporated into a directed acyclic graph (Supplemental Figure 1).[1,9,14-17] These covariates included child gender, race/ethnicity and age, maternal age at delivery, mother’s partnership status, prematurity (gestational age < 37 weeks), low birth weight (birth weight < 2500 g), breastfeeding, parent-reported asthma or allergic rhinitis symptoms, number of children living in the household, and several measures of socioeconomic status, including maternal education level, social class based on occupation, financial difficulties score (assessing the mother’s self-reported difficulty to afford food, clothing, heating, rent or mortgage, and items necessary to care for her baby), and neighborhood stress score (assessing the mother’s self-reported concern about potential neighborhood and/or household problems, including ventilation, noise levels, litter, vandalism, and burglary).

Serum cotinine (ng/mL), a metabolite of nicotine and surrogate marker for tobacco exposure, was available for a subset of the population at age 7 years.[10] Maternal urine cotinine was measured during the first and third trimesters of pregnancy.[11,18]

Statistical analysis

Cross-sectional logistic regression analyses were performed to compare SDB outcomes between children with and without TSE at each time point. After checking for consistency across time points, longitudinal analyses were then conducted using mixed-effects logistic regression models. In these mixed-effects models we used repeated measures of the exposure and outcome. Most covariates were measured at the start of the study, though we included time-varying covariates measured at multiple time points when possible (i.e. asthma and allergic rhinitis symptoms, and number of children in the household). Mixed-effects models account for the correlation of repeated measures obtained on each individual over time, and we included random effects in our models (i.e. randomly varying slopes and intercepts for each individual). The minimally sufficient adjustment set to determine the direct association between TSE and SDB symptoms was determined using a directed acyclic graph (Supplemental Figure 1), and models were repeated with adjustment for potential confounders.

A stepwise modeling approach was used to distinguish the independent effects of prenatal TSE and childhood TSE. Models 1 and 2 examined the association between prenatal and childhood TSE and SDB symptoms, respectively, while adjusting for potential confounders. Model 3 adjusted for both prenatal and childhood TSE in addition to potential confounders. We then tested for interactions (effect modification) between the degree of childhood TSE and the degree of prenatal TSE.

We performed sensitivity analyses to examine whether there was a cumulative effect of childhood TSE on SDB symptoms, and to examine whether the specific trimester of prenatal exposure had an independent effect. We also evaluated the consistency of maternal report of TSE by examining correlations between mother-reported TSE and cotinine levels at selected time points using the Spearman's rank correlation coefficient. All statistical analyses were performed using Stata, version 15 (StataCorp Inc), and statistical significance was set at $p < 0.05$.

Missing data

As has been described in detail elsewhere, ALSPAC has both intermittent missing data and attrition, which vary by age.[10] Mixed-effects models were used to accommodate missingness in outcome data, and multivariable analyses were restricted to individuals with complete covariate data (missing data patterns shown in Supplemental Table 1). Covariate data were most likely to be missing at random; under this assumption, maximum likelihood-based analysis methods such as mixed-effects models are unbiased as the probability of missingness depends on the observed data.[19] Complete case analysis (with non-missing covariate data) is valid where missingness is independent of the outcome, conditional on the model covariates.[20] For primary longitudinal analyses, table footnotes display the mean number of observations per individual, which reflects the degree of missing outcome data, as well as the total number of individuals included in the model, which reflects the degree of missing exposure and covariate data.

Results

The ALSPAC cohort was composed of 13,988 children (7,217 male [51.7%], Table 1). The analytic sample was followed for a median duration of 7 (interquartile range 6-7) years. The proportion of missing covariate data ranged from 0.1% to 25.4% (Supplemental Table 1).

Sleep-disordered breathing symptoms

At any given age, 21.9% to 37.4% of all children reported at least one SDB symptom. Figure 1 demonstrates the prevalence of individual SDB symptoms across ages.

Prenatal tobacco smoke exposure

Overall, 24.2% of children were exposed to any prenatal tobacco smoke (Table 2). Table 3 shows the prevalence of maternal self-reported smoking according to the number of cigarettes smoked per day in each trimester of pregnancy. 11.9% of children had low prenatal exposure, 9.2% had moderate exposure, and 3.1% had high exposure. Among the 2,917 children exposed prenatally, 23.7% were exposed during only one trimester, 20.9%

were exposed during two trimesters, and 55.4% were exposed during all three trimesters. Only 121 of 1,736 (7.0%) children exposed in both the first and second trimesters were not exposed in the third trimester. Maternal urine cotinine levels in the first and third trimesters of pregnancy correlated with self-reported number of cigarettes smoked per day ($p < 0.001$, Table 4). As shown in Table 2, 3.7% of all children were exposed exclusively to prenatal TSE.

In cross-sectional analyses, prenatal TSE was associated with SDB symptoms at all child ages (Supplemental Table 2). In unadjusted longitudinal analyses, children with any prenatal TSE were more likely to report any SDB symptoms (odds ratio [OR] 1.86; 95% confidence interval [CI] 1.69, 2.06). After adjusting for potential confounders, effect sizes were attenuated, but prenatal TSE remained associated with all SDB symptoms throughout early childhood (Table 5, Model 1). After additionally adjusting for childhood TSE, the association was further attenuated but remained significant for any SDB symptoms, mouth breathing, and apnea (Table 5, Model 3). For all outcomes, we found a significant dose-response effect according to the degree of prenatal TSE (linear test for trend, $p < 0.05$).

Childhood tobacco smoke exposure

Overall, 46.2% of children were exposed at least once between 1.5 and 7 years of age (Table 2). At any given age, 22.6% to 31.8% of children reported any childhood TSE (average across ages 28.5%), and the proportion of children exposed decreased with age (Figure 2). 18.2% to 20.8% were exposed to low TSE, with an average of 19.7% across ages. 4.4% to 11.5% were exposed to high TSE, with an average of 8.8% across ages (Figure 2). Child serum cotinine levels at age 7 years correlated with mother-reported TSE ($p = 0.001$, Table 4). As shown in Table 2, 25.6% of all children were exposed exclusively to childhood TSE, and 20.6% of all children were exposed to both childhood and prenatal TSE.

In cross-sectional analyses, childhood TSE was associated with SDB symptoms at all child ages (Supplemental Table 2). In unadjusted longitudinal analyses, children with any childhood TSE were more likely to report any SDB symptoms (OR 1.42; 95% CI 1.31, 1.55). After adjusting for potential confounders, effect sizes were attenuated, but childhood TSE remained associated with any SDB symptoms, snoring, and apnea throughout early childhood (Table 5, Model 2). After additionally adjusting for prenatal TSE, the association was further attenuated but remained significant for children exposed to high levels of tobacco smoke (Table 5, Model 3).

When we examined whether there was an interaction (or effect modification) between prenatal and childhood TSE, we found statistically significant effects for snoring and apnea ($p=0.004$ and $p=0.02$, respectively), but not for mouth breathing ($p=0.22$). For snoring and apnea, the associations were larger for children who were exposed to both prenatal and childhood TSE. Compared to children without any TSE, children with combined exposure to high levels of TSE both prenatally and during childhood had 2.43 times the odds of snoring (95% CI 1.50, 3.93) and 2.65 times the odds of apnea (95% CI 1.46, 4.82) (Supplemental Table 3).

Sensitivity analyses

We found evidence for a cumulative effect of childhood TSE on SDB symptoms (Supplemental Table 4). When we examined the timing of prenatal TSE according to trimester of gestation, prenatal TSE in the third trimester was significantly associated with any SDB symptoms independent of exposure in the first or second trimesters (Table 6). For the individual SDB symptoms, we observed a similar although non-significant trend with larger effect sizes for third trimester exposure.

Discussion

In a longitudinal analysis of 12,030 children from the ALSPAC cohort followed from birth through age 7 years, prenatal and childhood TSE were independently associated with mild SDB symptoms, including mouth breathing, snoring, and witnessed apnea. We observed a dose-response effect between TSE and SDB symptoms, and found that combined exposure both prenatally and during childhood resulted in higher levels of risk for snoring and apnea.

Our study was able to address important limitations of prior research. Several other studies have found a dose-response relationship between TSE and SDB symptoms, but were unable to assess individual symptoms of SBD, adequately address concerns about confounding, or examine the temporal relationship between TSE and SDB.[6-8,14,21] In particular, most existing studies have focused exclusively on snoring or a general measure of sleep-disordered breathing,[6-8,14,21] whereas our study was able to examine SDB symptoms individually. Our study also addresses the issue of confounding by socioeconomic characteristics, which are known to influence smoking patterns. The ALSPAC cohort includes rich measures of socioeconomic status; after controlling for these measures, the associations were attenuated but remained significant.

Another strength of this prospective, longitudinal study was that it enabled us to disentangle the independent effects of prenatal and childhood TSE. Few studies include measures of both prenatal and postnatal exposure, and report conflicting results, in part due to the high concordance of maternal smoking during pregnancy and infancy.[7,14,16,22] By using a repeated measure of TSE at multiple time points throughout childhood, we were able to account for the presence of concurrent childhood TSE when examining the association between prenatal TSE and SDB symptoms across early childhood. Most research studying the effects of prenatal TSE on sleep has focused on the role of smoke exposure in sudden infant death syndrome during the first year of life,[23] whereas our study design focused on children between 1.5 and 7 years of age.

This longitudinal design thus allowed us to examine the long-term effects of prenatal TSE beyond infancy and identify a cumulative effect of childhood TSE on SDB symptoms, which has not previously been studied.[6] In addition, the cohort included a large number of children exposed to TSE exclusively in childhood but not prenatally, which allowed us to address the aforementioned limitations of concordance of maternal smoking during pregnancy and childhood. Finally, our finding of a significant effect modification between childhood and prenatal TSE is novel. Children exposed to high levels of both prenatal and childhood TSE

were at higher risk of snoring and witnessed apnea, with adjusted odds of SDB symptoms similar in magnitude to those reported in adult active smokers.[24]

Several possible mechanisms may contribute to the observed associations. Nicotine readily crosses the placenta, inducing molecular, epigenetic, and morphologic changes affecting lung development and brain structures associated with control of breathing.[25-28] In animal models, nicotine binds acetylcholine receptors in airway epithelial cells and fibroblasts, resulting in structural changes such as increased collagen deposition, thickened airway walls, and decreased elastin.[26-28] These structural changes are thought to underlie the airflow obstruction and other changes in pulmonary function observed in children exposed to prenatal tobacco smoke,[26,27] and similar mechanisms may contribute to increased upper airway resistance. The critical period for the detrimental effects of nicotine exposure on fetal lung development is hypothesized to occur in mid- to late-gestation.[27] Similarly, we found preliminary evidence for an independent effect of exposure during the third trimester of pregnancy, and this finding warrants further investigation. Postnatally, tobacco and other ingredients in cigarette smoke lead to chronic irritant exposure, causing mucosal edema and upper airway inflammation; this in turn, may lead to adenotonsillar hypertrophy and predispose to airway narrowing and collapse.[6,7,29] Animal studies also suggest that both prenatal and postnatal TSE may impair upper airway neuromuscular protective reflexes and mechanisms to maintain airway patency.[29] Finally, smoke exposure prenatally and postnatally has been shown to adversely affect infant arousal and recovery from hypoxia, which may impair the usual stimulus to trigger an arousal during an apneic episode,[23,28,29] thus leading to more severe symptoms. Indeed, Weinstock et al. reported an association between TSE and polysomnography-diagnosed OSA severity among adenotonsillectomy candidates aged 5 to 10 years.[9]

As in all large-scale longitudinal studies, attrition occurred over time and the cohort contained missing data. However, in previous work with this cohort we have shown that imputing missing exposure and covariate data did not significantly alter our findings, helping to address concerns of potential selection bias.[30] Another limitation is the absence of body-mass index (BMI) data for the majority of participants in the ALSPAC cohort prior to 7 years of age. However, previous studies have not found a relationship between obesity and SDB symptoms in early childhood;[8,9,16] in contrast, elevated BMI may be a more important risk factor in later childhood and adolescence. We also used parent-reported measures of SDB symptoms, rather than objective measures such as polysomnography that are used to diagnose OSA specifically. The current study focused on the constellation of milder, more prevalent SDB symptoms that affect a much larger proportion of children in the general population than OSA. Finally, although our cohort is fairly representative of the United Kingdom population,[10] the extent to which our results are generalizable to other more diverse settings is unclear. Previous work suggests that the effects of TSE on SDB symptoms may vary according to race,[9,16] and more research is needed to understand the effects of TSE on SDB symptoms in diverse populations.

Another limitation of the current study is the use of mother-reported measures of prenatal and childhood TSE. However, these measures correlated with cotinine levels at selected time points, and the overall prevalence of childhood TSE in our study was consistent with current

population-based estimates using nationally representative data.[4,31] Urine cotinine levels among mothers who reported smoking during pregnancy were well above validated cutoffs for active adult pregnant smokers.[32,33] Similarly, serum cotinine levels at age 7 among children exposed to TSE in our study were consistent with cotinine levels among children aged 4 to 11 years old exposed to secondhand smoking in the nationally representative National Health and Nutrition Examination Survey,[34] in which parent-reported TSE in the home correlated well with youth serum cotinine levels.[35] Finally, parental report typically underestimates true tobacco use,[36] and maternal urine cotinine levels in our study were relatively high in non-smokers,[32,33] suggesting these mothers underreported their smoking habits or were exposed to secondhand smoke themselves. This misclassification would be non-differential with regards to the outcome, so this would likely bias our results towards the null.

Our findings have several clinical implications. Pediatricians can identify children at higher risk of SDB symptoms by screening for prenatal and current TSE, especially in children with non-modifiable risk factors, including prematurity, chronic lung disease, neuromuscular conditions, and craniofacial abnormalities.[1] In addition, our results suggest that tobacco cessation as late as the third trimester has the potential to improve sleep outcomes, which has important implications for prenatal counseling. For clinicians caring for pregnant women, continued efforts to encourage tobacco cessation throughout the duration of pregnancy are warranted. Despite the limitation that these data were collected in the 1990s, our findings remain relevant in the context of the current vaping epidemic.[37,38] From a mechanistic standpoint, nicotine in TSE is thought to play an important role in the observed associations,[23,25-29] and vaped nicotine both prenatally and during childhood may contribute to SDB symptoms. Our findings are particularly concerning given the rising prevalence of e-cigarette use in youth and pregnant women,[37,38] and future work should investigate whether vaping is associated with SDB symptoms.

In conclusion, prenatal and childhood TSE were both independently associated with mild SDB symptoms throughout early childhood in a dose-dependent manner, and the associations with snoring and witnessed apnea were larger for children with combined prenatal and childhood exposure. In addition to known morbidities from TSE, these findings highlight another pathway through which TSE is associated with long-term adverse health outcomes that persist well beyond infancy, further supporting the critical importance of maintaining a tobacco-free environment throughout gestation and childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new

Both prenatal and childhood tobacco smoke exposure were each independently associated with sleep-disordered breathing symptoms throughout early childhood. Combined exposure both prenatally and during childhood resulted in higher risks of apnea and snoring.

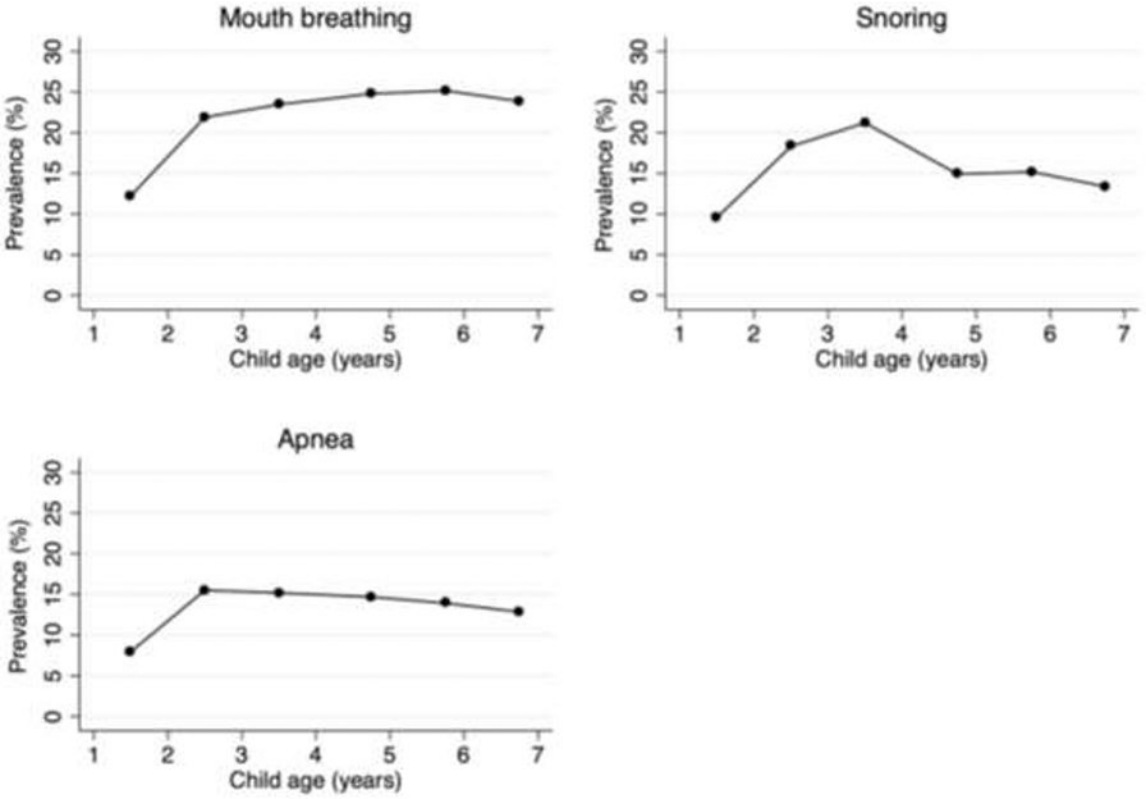

Figure 1:
Prevalence (%) of SDB symptoms according to child age

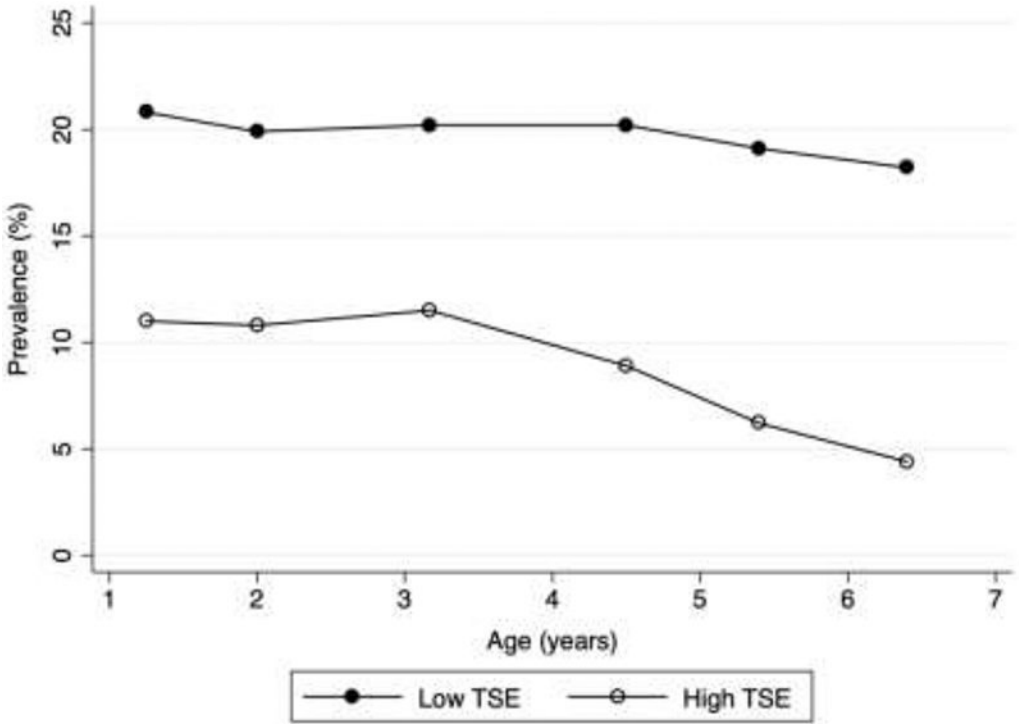

Figure 2:
Prevalence (%) of low and high TSE according to child age

Table 1:

Cohort characteristics

	Analytic sample * (N = 12,030)		
Characteristic	**No TSE**	**Any prenatal TSE** **	**Any childhood TSE** **
	No. / Total available (%) ***		
Child gender			
Male	3,078 / 6,033 (51.0)	1,905 / 3,561 (53.5)	2,869 / 5,554 (51.7)
Female	2,955 / 6,033 (49.0)	1,656 / 3,561 (46.5)	2,685 / 5,554 (48.3)
Child race/ethnicity			
White	5,525 / 5,762 (95.9)	2,802 / 2,981 (94.0)	4,733 / 4,987 (94.9)
Non-white	237 / 5,762 (< 5.0)	179 / 2,981 (6.0)	254 / 4,987 (5.1)
Maternal age at delivery			
≤ 20 years old	97 / 6,033 (< 5.0)	483 / 3,561 (13.6)	572 / 5,554 (10.3)
21-34 years old	5,153 / 6,033 (85.4)	2,832 / 3,561 (79.5)	4,557 / 5,554 (82.1)
≥ 35 years old	783 / 6,033 (13.0)	246 / 3,561 (6.9)	425 / 5,554 (7.7)
Mother's partnership status			
Has partner	5,856 / 5,892 (99.4)	3,110 / 3,297 (94.3)	5,067 / 5,280 (96.0)
Does not have partner	36 / 5,892 (< 5.0)	187 / 3,297 (5.7)	213 / 5,280 (< 5.0)
Gestational age			
< 37 weeks	344 / 6,033 (5.7)	238 / 3,561 (6.7)	333 / 5,554 (6.0)
≥ 37 weeks	5,689 / 6,033 (94.3)	3,323 / 3,561 (93.3)	5,221 / 5,554 (94.0)
Birth weight			
< 2500 grams	336 / 6,033 (5.6)	307 / 3,561 (8.6)	378 / 5,554 (6.8)
≥ 2500 grams	5,697 / 6,033 (94.4)	3,254 / 3,561 (91.4)	5,176 / 5,554 (93.2)
Breastfeeding [a]			
Ever breastfed	4,761 / 5,669 (84.0)	1,715 / 2,646 (64.8)	3,221 / 4,827 (66.7)
Never breastfed	908 / 5,669 (16.0)	931 / 2,646 (35.2)	1,606 / 4,827 (33.3)
Asthma or allergic rhinitis [b]			
Ever had symptoms	1,037 / 5,926 (17.5)	593 / 2,888 (20.5)	1,101 / 5,381 (20.5)
Never had symptoms	4,889 / 5,926 (82.5)	2,295 / 2,888 (79.5)	4,280 / 5,381 (79.5)
Maternal highest education [c]			
CSE/None	602 / 5,843 (10.3)	1,071 / 3,130 (34.2)	1,418 / 5,152 (27.5)
Vocational	431 / 5,843 (7.4)	391 / 3,130 (12.5)	643 / 5,152 (12.5)
O level	1,963 / 5,843 (33.6)	1,053 / 3,130 (33.6)	1,920 / 5,152 (37.3)
A level	1,648 / 5,843 (28.2)	476 / 3,130 (15.2)	881 / 5,152 (17.1)
Degree	1,199 / 5,843 (20.5)	139 / 3,130 (< 5.0)	290 / 5,152 (5.6)
Social class [d]			

	Analytic sample * (N = 12,030)		
Characteristic	**No TSE**	**Any prenatal TSE** **	**Any childhood TSE** **
Unskilled	42 / 5,707 (< 5.0)	107 / 3,085 (< 5.0)	128 / 4,887 (< 5.0)
Partly skilled	229 / 5,707 (< 5.0)	376 / 3,085 (12.2)	492 / 4,887 (10.1)
Skilled manual	440 / 5,707 (7.7)	643 / 3,085 (20.8)	919 / 4,887 (18.8)
Skilled non-manual	1,615 / 5,707 (28.3)	975 / 3,085 (31.6)	1,637 / 4,887 (33.5)
Managerial and technical	2,568 / 5,707 (45.0)	895 / 3,085 (29.0)	1,506 / 4,887 (30.8)
Professional	813 / 5,707 (14.3)	89 / 3,085 (< 5.0)	205 / 4,887 (< 5.0)
Financial difficulties quartile [e]			
Lowest	2,820 / 5,861 (48.1)	742 / 3,163 (23.5)	1,507 / 5,193 (29.0)
Mild	848 / 5,861 (14.5)	332 / 3,163 (10.5)	632 / 5,193 (12.2)
Moderate	1,512 / 5,861 (25.8)	1,098 / 3,163 (34.7)	1,700 / 5,193 (32.7)
Highest	681 / 5,861 (11.6)	991 / 3,163 (31.3)	1,354 / 5,193 (26.1)
Neighborhood stress score quartile [f]			
Lowest	1,663 / 5,389 (30.9)	501 / 2,365 (21.2)	1,067 / 4,586 (23.3)
Mild	1,669 / 5,389 (31.0)	609 / 2,365 (25.8)	1,195 / 4,586 (26.1)
Moderate	1,295 / 5,389 (24.0)	607 / 2,365 (25.7)	1,198 / 4,586 (26.1)
Highest	762 / 5,389 (14.1)	648 / 2,365 (27.4)	1,126 / 4,586 (24.6)
Number of children in the household [g]			
1 child	2,405 / 5,529 (43.5)	1,108 / 2,624 (42.2)	2,026 / 4,865 (41.6)
2 children	2,141 / 5,529 (38.7)	901 / 2,624 (34.3)	1,774 / 4,865 (36.5)
3 or more children	983 / 5,529 (17.8)	615 / 2,624 (23.4)	1,065 / 4,865 (21.9)

Notes:

* Among the ALSPAC cohort of 13,988 children alive at 1 year of age, 1,948 children did not have tobacco smoke exposure data available from at least one time point between ages 1.5 and 7 years, and 10 withdrew consent. The analytic sample included the remaining 12,030 children.

** Categories are not mutually exclusive

*** Numerator corresponds to the number of individuals with a certain characteristic, and denominator corresponds to the total number of individuals with available (i.e. non-missing) data for the given covariate and TSE status.

[a] By 6 months of age

[b] At least 2 reports of symptoms by 7 years of age

[c] United Kingdom educational levels: CSE (Certificate of Secondary Education), certificate after passing national school examinations at 16 years of age; vocational; O level, qualification after passing national school examinations at 16 years of age, higher than CSE; A level, qualification after passing national school examinations at 18 years of age; degree, university degree, or higher

[d] Highest of either parent, based on occupation

[e] Assessing the mother's self-reported difficulty to afford food, clothing, heating, rent or mortgage, and items necessary to care for her baby

[f] At 1.75 years of age, assessing the mother's self-reported concern about potential neighborhood and/or household problems, including ventilation, noise levels, litter, vandalism, and burglary

[g] At 8 months of age, including study participant

Table 2:

Prevalence (%) of prenatal and childhood TSE among analytic sample

	Childhood TSE		
Prenatal TSE	None	Any	**Total**
None	6,033 (50.1%)	3,080 (25.6%)	**9,113 (75.8%)**
Any	443 (3.7%)	2,474 (20.6%)	**2,917 (24.2%)**
Total	**6,476 (53.8%)**	**5,554 (46.2%)**	**12,030**

Table 3:

Prevalence (%) of maternal self-reported smoking according to trimester of pregnancy

	1st trimester	2nd trimester	3rd trimester
Any smoking	22.7	17.9	19.7
Number of cigarettes smoked per day			
None	77.3	82.1	80.3
1-9 cigarettes per day	10.3	8.2	7.7
10-19 cigarettes per day	9.1	7.1	8.9
≥ 20 cigarettes per day	3.3	2.6	3.1

Table 4:

Cotinine levels according to maternal tobacco use in pregnancy and child TSE

Self-reported maternal cigarette use in the 1st trimester of pregnancy*	**N**	**Median (IQR) urine cotinine levels (ng/mL)**
None	3,180	22.0 (5.0 - 62.6)
1-9 cigarettes per day	402	1395.9 (375.9 - 3484.7)
10-19 cigarettes per day	334	3016.2 (1248.1 - 4884.1)
≥ 20 cigarettes per day	119	4128.0 (1697.3 - 6923.8)
Self-reported maternal cigarette use in the 3rd trimester of pregnancy*	**N**	**Median (IQR) urine cotinine levels (ng/mL)**
None	2,572	92.6 (48.6 - 205.1)
1-9 cigarettes per day	238	1489.1 (557.7 - 3123.9)
10-19 cigarettes per day	260	2982.4 (1516.8 - 5754.9)
≥ 20 cigarettes per day	100	3715.7 (1385.5 - 7365.0)
Mother-reported child TSE at age 7 years**	**N**	**Median (IQR) serum cotinine levels (ng/mL)**
None	3,575	1.0 (0.5 - 1.4)
Low TSE	684	1.8 (1.2 - 2.9)
High TSE	134	2.8 (1.9 - 4.4)

Notes:

IQR, interquartile range

*Spearman correlation coefficient = 0.62, $p < 0.001$

**Spearman correlation coefficient = 0.40, $p < 0.001$

Table 5:

Adjusted odds of SDB symptoms among children with prenatal and childhood TSE

	Any SDB symptoms	Mouth breathing	Snoring	Apnea
Model 1 – Prenatal TSE, adjusted for confounders				
No prenatal TSE	Ref.	Ref.	Ref.	Ref.
Any prenatal TSE	**1.23 (1.08, 1.40)** [a]	**1.23 (1.07, 1.42)** [b]	**1.23 (1.04, 1.45)** [c]	**1.40 (1.14, 1.73)** [d]
Low	1.05 (0.89, 1.24)	1.09 (0.91, 1.31)	1.07 (0.86, 1.33)	1.24 (0.94, 1.63)
Moderate	**1.38 (1.14, 1.68)**	**1.36 (1.10, 1.68)**	1.25 (0.97, 1.61)	**1.41 (1.03, 1.94)**
High	**1.73 (1.26, 2.37)**	**1.52 (1.08, 2.14)**	**2.03 (1.36, 3.03)**	**2.32 (1.40, 3.82)**
Model 2 – Childhood TSE, adjusted for confounders				
No childhood TSE	Ref.	Ref.	Ref.	Ref.
Any childhood TSE	**1.17 (1.06, 1.29)** [e]	1.06 (0.95, 1.17) [f]	**1.15 (1.01, 1.31)** [g]	**1.29 (1.11, 1.50)** [h]
Low	1.10 (0.99, 1.22)	1.06 (0.95, 1.19)	1.08 (0.94, 1.24)	**1.26 (1.08, 1.47)**
High	**1.46 (1.26, 1.70)**	**1.38 (1.16, 1.64)**	**1.47 (1.20, 1.79)**	**1.45 (1.14, 1.85)**
Model 3 – Prenatal and childhood TSE, adjusted for confounders				
No TSE	Ref.	Ref.	Ref.	Ref.
Any prenatal TSE	**1.15 (1.01, 1.32)** [i]	**1.17 (1.01, 1.36)** [j]	1.15 (0.96, 1.38) [k]	**1.26 (1.00, 1.58)** [l]
Low	1.02 (0.86, 1.21)	1.07 (0.88, 1.28)	1.05 (0.84, 1.32)	1.13 (0.85, 1.50)
Moderate	**1.28 (1.04, 1.57)**	**1.29 (1.03, 1.62)**	1.13 (0.87, 1.49)	1.25 (0.89, 1.75)
High	**1.58 (1.13, 2.20)**	1.42 (0.99, 2.04)	**1.83 (1.20, 2.78)**	**2.13 (1.27, 3.60)**
Any childhood TSE	1.11 (1.00, 1.23) [i]	1.04 (0.93, 1.16) [j]	1.10 (0.95, 1.26) [k]	**1.22 (1.05, 1.43)** [l]
Low	1.06 (0.96, 1.18)	1.01 (0.90, 1.13)	1.05 (0.91, 1.21)	**1.21 (1.03, 1.42)**
High	**1.35 (1.15, 1.58)**	**1.25 (1.04, 1.49)**	**1.36 (1.10, 1.68)**	**1.32 (1.03, 1.70)**

Notes: Reported as odds ratio (95% confidence interval). Results from adjusted multivariable mixed-effects logistic regression models examining the association between prenatal and childhood tobacco smoke exposure (TSE) and four measures of sleep-disordered breathing (SDB) symptoms at 6 time points (18, 30, 42, 57, 69, and 81 months) between ages 1.5 and 7 years, compared to children without TSE. Models 1 and 2 adjusted for potential confounders, including child gender, child age, child race/ethnicity, child asthma or allergic rhinitis symptoms (time-varying), prematurity, low birth weight, breastfeeding, maternal age at delivery, mother's partnership status, maternal educational level, social class, financial difficulties score, neighborhood stress score, and number of other children in the household (time-varying). Model 3 adjusted for potential confounders and for both prenatal and childhood TSE.

[a]Model with 8,732 individuals; mean (range) of 5.0 (1.0 - 6.0) observations per individual.

[b]Model with 8,603 individuals; mean (range) of 4.6 (1.0 - 6.0) observations per individual.

[c]Model with 8,682 individuals; mean (range) of 4.7 (1.0 - 6.0) observations per individual.

[d]Model with 8,573 individuals; mean (range) of 4.4 (1.0 - 6.0) observations per individual.

[e,i]Model with 8,651 individuals; mean (range) of 4.8 (1.0 - 6.0) observations per individual.

[f,j]Model with 8,506 individuals; mean (range) of 4.5 (1.0 - 6.0) observations per individual.

[g,k]Model with 8,594 individuals; mean (range) of 4.6 (1.0 - 6.0) observations per individual.

[h,l]Model with 8,482 individuals; mean (range) of 4.3 (1.0 - 6.0) observations per individual.

Table 6:

Adjusted odds of SDB symptoms among children with prenatal TSE according to trimester of gestational exposure

	Any SDB symptoms	Mouth breathing	Snoring	Apnea
No prenatal TSE	Ref.	Ref.	Ref.	Ref.
1st trimester, any TSE	0.95 (0.74, 1.21)	1.07 (0.81, 1.40)	0.92 (0.66, 1.29)	1.05 (0.70, 1.59)
2nd trimester, any TSE	0.94 (0.68, 1.29)	0.85 (0.60, 1.21)	1.02 (0.66, 1.56)	1.07 (0.63, 1.82)
3rd trimester, any TSE	**1.42 (1.04, 1.94)**	1.37 (0.97, 1.94)	1.38 (0.92, 2.09)	1.28 (0.77, 2.12)

Notes: Reported as odds ratio (95% confidence interval). Results from adjusted multivariable mixed-effects logistic regression models examining the association between any prenatal tobacco smoke exposure (TSE) during each trimester of pregnancy and sleep-disordered breathing (SDB) symptoms at 6 time points (18, 30, 42, 57, 69, and 81 months) between ages 1.5 and 7 years, compared to children without prenatal TSE. Models adjusted for potential confounders, including child gender, child age, child race/ethnicity, child asthma or allergic rhinitis symptoms (time-varying), prematurity, low birth weight, breastfeeding, maternal age at delivery, mother's partnership status, maternal educational level, social class, financial difficulties score, neighborhood stress score, and number of other children in the household (time-varying), and additionally adjusted for the degree of childhood TSE. Models mutually adjusted for any prenatal TSE in all three trimesters of pregnancy. Of note, 1,615 of 2,288 (70.6%) children exposed in the first trimester were also exposed during the second and third trimesters. 1,615 of 1,943 (83.1%) of children exposed in the third trimester were also exposed during the first and second trimesters.