Plasma cotinine levels and sleep disturbances in children exposed to environmental tobacco smoke

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ABSTRACT

Background. The relationship between sleep disturbances and exposure to environmental tobacco smoke (ETS) in children is a growing health concern. This study aimed to evaluate the association between ETS exposure and sleep disorders in healthy children, and to determine whether there is a difference in this relationship between secondhand smoke (SHS) and thirdhand smoke (THS) exposure.

Methods. Healthy children aged 4–12 years who presented to the pediatric outpatient department were consecutively enrolled in this cross-sectional study. Plasma cotinine levels were measured to validate the exposure. The Children's Sleep Habits Questionnaire was used to assess sleep disorders in all children.

Results. Of the 203 children we evaluated, with a median (Q1-Q3) age of 8.3 (6–10) years, 99 (49.8%) were female. Children exposed to ETS had significantly more sleep disturbances than children who were not exposed to ETS (p = 0.042). However, there was no significant difference in the plasma cotinine levels (p = 0.239) or the prevalence of sleep disorders (p = 0.648) between children exposed to SHS and those exposed to THS.

Conclusions. Exposure to both SHS and THS is associated with an increase in plasma cotinine and a higher prevalence of sleep disorders in children. These findings highlight the importance of reducing children's exposure to all forms of ETS to promote healthy sleep and overall well-being.

Key words: children, cotinine, environmental smoke exposurei sleep, thirdhand smoking.

Environmental tobacco smoke (ETS) consists of the side stream and exhaled mainstream smoke from cigarettes and pipes. ETS exposure includes both secondhand and thirdhand smoke: secondhand smoke (SHS) refers to smoke passively inhaled by non-smokers, whereas thirdhand smoke (THS) refers to the residual contamination that persists after SHS has dispersed.[1] The World Health Organization estimates that 40% of children worldwide are exposed to ETS.[2] In a study conducted with adolescents in Hong Kong, 23.2% were exposed to SHS at home. When THS was also considered, this proportion rose to 63.3%. Exposure to SHS and THS within the home was linearly associated with respiratory symptoms.[3]

Adequate sleep quality and duration are critical for children's health and development. Insufficient sleep can lead to poor academic performance, behavioral issues, and mental health problems.[4] Identifying modifiable factors that compromise sleep is therefore essential. Sleep problems associated with active smoking and the use of smokeless tobacco include reduced sleep duration, difficulty initiating and maintaining sleep, and disruptions in sleep architecture.[5] Polysomnography studies—evaluating acute nicotine patches in healthy, non-smoking adults via transdermal nicotine patches—provide strong evidence of nicotine's negative effects on sleep.[6,7]

Two main hypotheses have been proposed regarding the causal relationship between nicotine and sleep disturbances. The first suggests that nicotine disrupts the regulation of the sleep-wake cycle and that a decrease in blood nicotine levels during sleep may lead to nocturnal cravings and withdrawal symptoms, thereby disrupting sleep. In addition, irritation of the upper airway caused by tobacco smoke has been suggested to contribute to overall sleep disturbances.[8]

Studies conducted in adult populations[9,10] have demonstrated a positive association between SHS exposure and poor sleep. However, research on the relationship between ETS exposure and sleep problems in children remains limited. Although case-control studies have reported a statistical association between passive cigarette smoke exposure and sleep-disordered breathing in children, only a few have verified smoking exposure using a biomarker.[11,12] To the best of our knowledge, no study has directly compared the effects of SHS and THS on sleep disorders in children.

This study therefore aimed to evaluate the association between ETS exposure and sleep disorders in healthy children, to determine whether this relationship differs between SHS and THS exposure, and to objectively quantify exposure by measuring plasma cotinine levels.

Materials and Methods

Ethics approval

This study was approved by the local ethics committee (Ankara University Ethics Board, Approval No. 10-805-19), in addition to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from the parents, and children over eight years of age.

Patient selection

Healthy children aged 4–12 years who were not taking any medications that affect sleep and who presented to the pediatric outpatient department of our hospital between June 2019 and March 2020 were consecutively enrolled in this cross-sectional study. Based on a previous report[13], the required sample size was calculated as 104 participants per group (exposed to ETS and not exposed to ETS), for a total of 208 participants, assuming a standard deviation of 12, a hypothesized effect size of 5, and a study power of 0.85.

Children with a diagnosis of allergic rhinitis, asthma, attention deficit hyperactivity disorder, autism spectrum disorders, cystic fibrosis, dysmorphic disorders, infections, non-cystic fibrosis bronchiectasis, obesity, adenotonsillary hypertrophy, sleep-disordered breathing diagnosed with polysomnography, type 1 diabetes mellitus, or other chronic diseases were excluded. Children who declared active smoking were also excluded from the study. Parents of all eligible children received detailed information about the study, and those who provided informed consent were included.

Questionnaires

Two pediatricians conducted face-to-face questionnaire surveys. The first questionnaire collected information on parents' smoking habits, including the current smoking status

of the accompanying parent, the other parent, and any third parties (e.g., babysitters). Based on the parents' responses, the pediatricians classified children as having either "parent-reported ETS exposure" or "no parent-reported ETS exposure". Exposure to SHS and THS was differentiated according to whether smoking occurred in the presence of the child. Children living in households where smoking occurred indoors were classified as having SHS exposure, whereas those in households with no indoor smoking but with individuals who smoked outside and subsequently entered the home were classified as having THS exposure. In addition, parents were asked about their child's daily caffeine consumption with a yes/no question. For all participants, sex, current age, and body mass index (BMI), along with BMI z scores, were recorded.

The same evaluators administered an abbreviated, validated version of the Children's Sleep Habits Questionnaire (CSHQ) to assess sleep patterns and identify sleep problems.[13] CHSQ has been validated in our language and its validity and reliability has been tested.[14] The CSHQ includes 33 items relating to several key sleep domains that encompass major presenting clinical sleep complaints: bedtime behavior and sleep onset, sleep duration, anxiety around sleep, behavior occurring during sleep and night waking, sleep-disordered breathing, parasomnias, and morning waking/ daytime sleepiness. The CSHQ also inquires about the child's total daily sleep hours with an open-ended question. Parents were asked to recall their children's sleep behaviors over a typical week. Items were rated on a three-point scale as follows: "usually" if the sleep behavior occurred five to seven times per week, "sometimes" for two to four times per week, or "rarely" for none to once a week. The CSHQ yields a total sleep disturbance score (range, 33–99) and scores for the following eight scales: bedtime resistance (score range, 6–24), sleep onset delay (score range, 1–3), sleep duration (score range, 3–9), sleep anxiety (score range, 4–12), night waking (score range, 3–9), parasomnias (score range,

7–21), sleep-disordered breathing (score range, 3–9), and daytime sleepiness (score range, 8–24). A higher score is indicative of more sleep problems. As a previous receiver operating characteristic curve analysis suggested a cutoff score of 41 or higher yielded the best diagnostic confidence (i.e., correctly identified 80% of the clinical sample in the study), with children who obtained a score of ≥41 considered to "have sleep disturbances" and those who received a score <41 considered to "not have sleep disturbances." The following cutoff scores were observed for the eight scales: ≥7, "have bedtime resistance"; ≥2, "have sleep onset delay"; ≥4, "have sleep duration problem"; ≥5, "have sleep anxiety"; ≥4, "have night waking problems"; ≥8, "have parasomnias"; ≥4, "have sleep-disordered breathing"; and ≥10, "have daytime sleepiness."[13]

Measurement of plasma cotinine levels

Cotinine, a metabolite of nicotine, is a reliable biomarker of exposure to tobacco smoke. Plasma levels provide a view of exposure over the previous 48–72 hours. However, owing to the stability of exposure patterns over time, a one-time cotinine measurement is considered representative of typical daily exposure.[15]

Plasma was collected from every child using a standard phlebotomy procedure and stored at -20 °C until analysis (maximum of 3 months). The direct barbituric acid assay was modified by Barlow et al.[16] and was used to measure cotinine levels. Briefly, 200 µL of plasma, 100 µL sodium acetate buffer (4 M, pH 4.7), 40 µL of KCN in H_2O (1.5 M), 40 µl chloramine-T in H_2O (0.4 M), and 200 µL barbituric acid in acetone: H_2O (78 mM, 50% v/v) were sequentially added into 1 mL polypropylene tubes. The tubes were mixed and incubated at room temperature for 15 min. The reaction was stopped by the addition of 40 µL of sodium metabisulfite (1M in H_2O), and absorbance was measured at 490 nm using a spectrophotometer (Thermo, Germany), with H_2O serving as the blank. All results were expressed as 'cotinine equivalents ng/mL' by comparing the absorbance at 490 nm of each

unknown with that of a 100 ng/mL cotinine solution H$_2$O standard (BTLab, China). Results were expressed in ng/mL.

Statistical analysis

The analysis used the Statistical Package for the Social Sciences (SPSS) version 22.0. Because the continuous variables did not show a normal distribution, data were presented as median (Q1-Q3). Categorical variables were expressed as frequencies and percentages. Comparisons between two independent groups were performed using the Mann–Whitney U test. Associations between categorical variables were analyzed using the chi-square test. The Spearman correlation test was employed to examine the relationship between two quantitative variables. Statistical significance was set at $p<0.05$.

Results

Characteristics of patients

Two hundred and eight consecutive participants were included in the study, but five participants had to be excluded due to missing data in their questionnaires. Of the 203 children we evaluated, with a median (Q1-Q3) age of 8.3 (6–10) years, 99 (49.8%) were female. Fifty-two (25.6%) children were in the preschool age group. The children's median z-score of BMI was 0 (-0.8 – 0.8). Parents reported that 192 (94.6%) children had daily caffeine intake. The median sleep time was 9.5 (9-10.5) hours. Of the 102 children exposed to ETS, 63 (61.8%) were exposed to SHS, while 39 (38.2%) were exposed to THS, according to parent reports. One hundred two children (50.2%) had parent-reported ETS exposure; 52 (25.6%) were exposed to paternal smoking, 14 (6.9%) to maternal smoking, 29 (14.3%) were exposed to both paternal and maternal smoking, and 7 (3.4%) were exposed to third-party smoking.

The median value of the total CSHQ score was 41 (38–46). One hundred eleven children (57.7%) were categorized in the "have sleep

disturbances" group based on their total CSHQ score. According to their scores on the eight scales, 128 (63.1%) children had bedtime resistance, 43 (21.2%) had sleep onset delay, 68 (33.5%) had problems with sleep duration, 141 (69.5%) had sleep anxiety, 96 (47.3%) had night waking problems, 79 (38.9%) had parasomnias, 31 (15.3%) had sleep-disordered breathing, and 131 (64.5%) had daytime sleepiness. The median plasma cotinine level was 6.2 (4–10.6) (Table I).

Table I. Demographic data, questionnaire and laboratory results of the study group (N=203).

Demographic Data	
Female sex, n(%)	99 (49.8)
Age (years), median (IQR)	8.3 (6-10)
Pre-school age group, n(%)	52 (25.6)
BMI z score, median (IQR)	0 (-0.8–0.8)
Daily caffeine intake, n (%)	192 (94.6)
Sleep time (hours), median (IQR)	9.5 (9–10.5)
Questionnaires	
Parent-reported ETS exposure, n (%)	102 (50.2)
Parent-reported SHS exposure, n (%)	63 (61.8)
Parent-reported THS exposure, n (%)	39 (38.2)
ETS exposure by the mother, n (%)	14 (6.9)
ETS exposure by the father, n (%)	52 (25.6)
ETS exposure by the mother and father, n (%)	29 (14.3)
ETS exposure by third party, n (%)	7 (3.4)
Sleep disturbance according to CHSQ, n (%)	111 (57.7)
Bedtime resistance, n (%)	128 (63.1)
Sleep onset delay, n (%)	43 (21.2)
Sleep duration problems, n(%)	68 (33.5)
Sleep anxiety, n(%)	141 (69.5)
Night waking problems, n (%)	96 (47.3)
Parasomnias, n (%)	79 (38.9)
Sleep-disordered breathing, n (%)	31 (15.3)
Daytime sleepiness, n (%)	131 (64.5)
Plasma cotinine levels (ng/mL), median (IQR)	6.2 (4–10.6)

BMI, body mass index; CHSQ, Children's Sleep Habits Questionnaire; ETS, environmental tobacco smoke; IQR, interquartile range; SHS, secondhand smoke; TSH, thirdhand smoke.

Comparison of groups with and without parent-reported ETS exposure

Differences between children with "parent-reported ETS exposure" and those with "no parent-reported ETS exposure" in terms of plasma cotinine levels, sleep time, and sleep disturbances, according to the CSHQ and its subgroups, are presented in Table II. Plasma cotinine level was statistically significantly higher in the parent-reported ETS exposure group than no parent-reported ETS exposure group (Medians 10.6 [10.1–11.1] vs 4 [3.4–4.4] ng/mL, p <0.001). Sleep disturbances according to CHSQ were statistically more common in the parent-reported ETS group exposure than no parent-reported ETS exposure group (61.8% vs 47.5%, p=0.042).

Comparison of groups with SHS and THS exposure

Differences between children "with SHS exposure" and "with THS exposure" in terms of plasma cotinine levels, sleep time, CSHQ total sleep disturbance scores, and scores on the eight scales are presented in Table III. Sleep disturbances were present in 23 (59%) of children exposed to THS and 40 (63.5%) of children exposed to SHS. No statistically significant difference was found between the two groups (p=0.648).

Correlations between plasma cotinine levels and CSHQ total sleep disturbance scores

There were no significant correlations between plasma cotinine levels and CSHQ total sleep disturbance scores on the CSHQ in the overall study population (rho 0.070, p= 0.323).

Discussion

In this study investigating the effects of ETS on the sleep of healthy children, we found that children exposed to ETS were more likely to experience sleep disorders. Plasma cotinine levels were significantly higher in children with parent-reported ETS exposure compared to those without such exposure. However, no significant difference was found between the cotinine levels and sleep disturbances of children exposed to SHS and those exposed to THS.

Previous studies[17-20] have shown that SHS exposure increases the frequency of sleep-disordered breathing (SDB) in children and reduces sleep quality. To avoid this confounding

Table II. Comparison of groups with and without environmental tobacco smoke exposure.

	No parent-reported ETS exposure (n: 101)	Parent-reported ETS (n: 102)	p value
Plasma cotinine levels (ng/mL), median (IQR)	4 (3.4–4.4)	10.6 (10.1–11.1)	<0.001**
Sleep time (hours), median (IQR)	9.5 (8.6-10.5)	9.5 (8.9-10.5)	0.657
Sleep disturbance according to CHSQ, n (%)	48 (47.5)	63 (61.8)	0.042*
Bedtime resistance, n (%)	58 (57.4)	70 (68.6)	0.254*
Sleep onset delay, n (%)	22 (21.8)	21 (20.6)	0.313*
Sleep duration problems, n(%)	36 (35.6)	32 (31.4)	0.217*
Sleep anxiety, n (%)	67 (66.3)	74 (72.5)	0.377*
Night waking problems, n (%)	41(40.6)	55 (53.9)	0.152*
Parasomnias, n (%)	33 (32.7)	46 (45.1)	0.187*
Sleep-disordered breathing, n (%)	17 (16.8)	14 (13.1)	0.617*
Daytime sleepiness, n (%)	66 (65.3)	65 (63.7)	0.253*

*Chi-square test, ** Mann-Whitney U test
BMI, body mass index; CHSQ, the Children's Sleep Habits Questionnaire; ETS, environmental tobacco smoke; IQR, inter quartile range; SHS, secondhand smoke; THS, thirdhand smoke.

Table III. Comparison of groups with second- and thirdhand smoke exposure.

	Parent-reported SHS exposure (n: 63)	Parent-reported THS exposure (n: 39)	p value
Plasma cotinine levels (ng/mL), median (IQR)	10.6 (10–11.1)	10.6 (10.4–11.2)	0.239*
Sleep time (hours), median (IQR)	9.5 (8.5–10.3)	9.5 (9–10.5)	0.305*
CSHQ total sleep disturbance score, median, (IQR)	43 (33-56)	41 (33-62)	0.133*
Sleep disturbance according to CHSQ, n (%)	40 (63.5)	23 (59)	0.401**
Bedtime resistance, n (%)	43 (68.3)	27 (69.2)	0.549**
Sleep onset delay, n (%)	16 (25.4)	5 (12.8)	0.1**
Sleep duration problems, n (%)	16 (25.4)	16 (41)	0.76**
Sleep anxiety, n (%)	48 (76.2)	26 (66.7)	0.206**
Night waking problems, n (%)	33 (52.4)	22 (56.4)	0.424**
Parasomnias, n (%)	29 (46)	17 (43.6)	0.426**
Sleep-disordered breathing, n (%)	10 (15.9)	4 (10.3)	0.312**
Daytime sleepiness, n (%)	44 (69.8)	21 (53.8)	0.078**

*Mann-Whitney U test, **Chi-square test
CHSQ, the Children's Sleep Habits Questionnaire; ETS, environmental tobacco smoke; IQR, inter quartile range; SD, standard deviation; SHS, secondhand smoke; THS, thirdhand smoke.

effect, we excluded children diagnosed with SDB with polysomnography. Consequently, the number of participants with problems in the SDB subgroup of the CSHQ was the lowest among all subgroups in our study.

Yolton et al.[8] evaluated 232 children with asthma who were exposed to SHS, and reported that 92.7% of the children had sleep disorders. In our study, this rate was considerably lower. The strong association between asthma and sleep disorders is well established[21,22], likely due to complex bidirectional interaction. Therefore, children with asthma were excluded from our sample; we believe this contributed to the lower prevalence of sleep disorders observed.

Although we found a statistically significant difference in cotinine levels between the ETS-exposed group and the non-ETS-exposed group based on parent reports, no correlation was observed between cotinine levels and CSHQ scores. Yolton et al.[8] reported significant associations between log-transformed serum cotinine levels and several sleep domains, including bedtime resistance, sleep anxiety, parasomnias, sleep-disordered breathing, daytime sleepiness, and total sleep disturbance,

although they found no associations with sleep onset latency or sleep duration.

In our study, parents who smoked were asked whether they did so inside or outside their homes; Approximately 38% reported smoking outdoors. These children were classified as having THS exposure only. No significant difference in plasma cotinine levels was found between children THS and SHS-exposed. Consistent with previous studies[23,24], avoiding smoking in the child's presence reduces SHS exposure but does not eliminate ETS exposure. Many parents may underestimate THS risks, believing children are unaffected by ETS if smoking occurs in another location. Studies have shown that the proportion of parents who recognize THS is harmful ranges from 42.4% to 91%, yet this awareness is not consistently associated with implementing home or car smoking bans.[25]

The effects of THS, a relatively recent component in ETS research, remain poorly understood. Children are believed to be more vulnerable to THS than adults due to spending more time indoors and having developing respiratory systems.[26] Lidón-Moyano et al.[27] demonstrated

that salivary cotinine levels in adults exposed to THS at home were comparable to those exposed to SHS. Matt et al.[28] reported that children living in homes where adults smoked outside had ETS exposure levels 5–7 times higher than those in non-smoking homes, and children in homes with indoor smoking had levels 3-8 times higher than those with outdoor-only smoking. Similarly, Protano et al.[29] demonstrated that median urinary cotinine concentrations in children increased significantly with higher levels of household ETS exposure.

Nicotine uptake from SHS and THS can be assessed using several metabolites, with cotinine being the most commonly used. A study[30] of 4485 non-smokers aged 3–17 years participating in the 2013–2016 National Health and Nutrition Examination Survey used random forest models to identify the best combination of biomarkers and reported exposures to distinguish ETS-exposed children. The strongest predictors were the number of smokers in the home, serum cotinine, serum hydroxycotinine, and urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Reliable serum cotinine measurement methods include gas chromatography, high-performance liquid chromatography, radioimmunoassay, and enzyme-linked immunosorbent assay.[16,31] However, these require expensive equipment, limiting routine use in low- and middle-income countries. In our study, plasma cotinine measurement was chosen for its simplicity, speed, and low cost, but the lack of a cutoff value for ETS exposure in plasma cotinine measurements remains a limitation.

Risk factors for pediatric sleep problems can be classified as biological (e.g., sex, age, body weight), environmental (e.g., ETS, heavy metals, air pollution), and social (e.g., family life, socioeconomic status, screen exposure).[32] Potential contributors, such as heavy metal and air pollution exposure, socioeconomic status, co-sleeping, and screen exposure, could be investigated through parent questionnaires. The absence of these variables in our analysis may have limited our ability to identify additional risk factors. Future research should

measure SHS and THS exposure with greater precision to better clarify their impact on sleep disturbances. Plasma cotinine measurement may serve as a practical screening tool in low- and middle-income countries if validated in larger studies and accompanied by standardized cutoffs. There are studies on certain foods and medications thought to affect cotinine levels.[33] One of the limitations of our study was that we did not ask about these foods and medications. Combining objective sleep assessments, such as polysomnography or actigraphy, with parent-reported questionnaires could also improve the accuracy of findings.

In conclusion, ETS exposure increases the risk of sleep disturbances in children, and both SHS and THS contribute to elevated plasma cotinine levels. Efforts to reduce ETS exposure in children should address both SHS and THS exposure patterns to effectively protect pediatric sleep health.

Ethical approval

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GÖ, NÇ, ÖY; data collection: NEÇİ, FG, FBA; analysis and interpretation of results: GÖ, FZ ; draft manuscript preparation: GÖ, NÇ, ÖY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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