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Tobacco Smoke Exposure and Fractional Exhaled Nitric Oxide Levels among U.S. Adolescents

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) can objectively guide clinical practice in the assessment, diagnosis, and treatment of eosinophilic airway inflammation. FeNO values may be affected by current smoking, but the role of tobacco smoke exposure (TSE) is understudied.

Objective: This study investigated the associations between biochemically validated and self-reported TSE and FeNO levels among U.S. nonsmoking adolescents without asthma.

Methods: National Health and Nutrition Examination Survey 2007-2012 data were used. TSE was assessed via serum cotinine and self-reported measures. We assessed FeNO continuously and using cutpoints of >35ppb and >50ppb to indicate likely eosinophilic inflammation in children and adults, respectively. We conducted linear and logistic regression adjusting for potential covariates.

Results: Overall, 34.0% of adolescents had low cotinine (0.05-2.99ng/ml), 6.2% had high cotinine (≥3.00ng/ml), and 11.9% had home TSE. Compared to adolescents with no/minimal cotinine, adolescents with high cotinine were at reduced odds to have FeNO >35ppb (adjusted odds ratio [aOR]=0.54, 95%CI=0.43,0.69). Adolescents with low cotinine had lower FeNO values (β=−2.05, 95%CI=−3.61,−0.49), and were also at decreased odds to have FeNO >35ppb

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Conflicts of Interest:

Ashley L. Merianos has no potential conflicts of interest to disclose.

Roman A. Jandarov has no potential conflicts of interest to disclose.

Mary Cataletto has no potential conflicts of interest to disclose.

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(aOR=0.74, 95%CI=0.66,0.83) and FeNO >50ppb (aOR=0.62, 95%CI=0.53,0.72). Adolescents with home TSE were at reduced odds to have FeNO >50ppb (aOR=0.72, 95%CI=0.57,0.91) than adolescents without home TSE. Adolescents with a higher number of cigarettes/day smoked inside their home were at reduced odds to have FeNO >35ppb (OR=0.98, 95%CI=0.97,0.99) and FeNO >50ppb (OR=0.98, 95%CI=0.96,0.99).

Conclusions: TSE was associated with decreased FeNO levels. The addition of TSE may be clinically important when interpreting thresholds for FeNO.

Keywords

tobacco smoke exposure; secondhand smoke; cotinine; adolescence

Introduction

Tobacco smoke exposure (TSE) is a pervasive public health issue which results in preventable morbidity in U.S. adolescents.[1] Although TSE prevalence has declined due to ongoing prevention and control initiatives, about 32% of 12-19-year-olds remain exposed to this known human carcinogen.[2,3] This is concerning since any level of exposure to tobacco smoke is considered unsafe for adolescents who are vulnerable to its related pulmonary morbidity, including but not limited to, respiratory symptoms and infections, asthma including more severe and frequent attacks, and slow lung growth.[1,3]

Fractional exhaled nitric oxide (FeNO), a non-invasive biomarker measured in exhaled human breath via a portable device, can be used to objectively guide clinical practice in the assessment, diagnosis, and treatment of eosinophilic airway inflammation.[4] FeNO is a clinical tool with moderate-to-strong diagnostic accuracy to assess asthma-related factors including risk of asthma development, timing of onset, treatment, and level of control including responsiveness to corticosteroids.[5,6] Children without asthma generally have lower FeNO values compared with children with asthma.[7] The American Thoracic Society's (ATS)[8] recent guidelines outline clinically meaningful FeNO cutpoints by age group that can be used to guide diagnosis (e.g., atopic asthma) when adolescents without diagnosed asthma have symptoms of cough, wheeze, and/or shortness of breath over the past six weeks at minimum, and guide management in adolescents with diagnosed asthma. Specifically among those without an asthma diagnosis, low FeNO (<20ppb and <25ppb in children and adults, respectively) implies that eosinophilic airway inflammation and responsiveness to inhaled corticosteroids is unlikely and high FeNO (>35ppb and >50ppb in children and adults, respectively) implies eosinophilic airway inflammation is present and likely to benefit from inhaled corticosteroids. There are several other potential confounding factors to consider while measuring and interpreting FeNO values including other demographics such as race/ethnicity, recent steroid use, recent respiratory illness, hay fever, and/or current smoking status.[8-10]

Low FeNO levels in individuals without asthma who have respiratory symptoms may suggest noneosinophilic inflammation and alternative pulmonary diagnoses (e.g., rhinosinusitis), nonpulmonary diagnoses (e.g., cardiac disease), or confounding factors (e.g., active smoking) that are not amenable to steroid therapy.[8] Thus, it is acknowledged that

current smoking among healthy individuals decreases FeNO levels.[11] This is likely due to tobacco smoke-related alterations to the endothelial function and structure of pulmonary arteries such as inhibited enzyme nitric oxide (NO) synthase, which may contribute to the development of respiratory-induced diseases and cardiovascular disease among smokers.[12,13] Acute TSE may also impair NO production,[14] but the association with chronic TSE is unknown. The literature on TSE and FeNO is inconsistent highlighting the need for more research.

Prior studies have found that TSE is associated with low FeNO levels,[15,16] while other research reports no differences,[17-19] but this association has not yet been examined specifically among adolescents without asthma. Most studies have assessed adolescent TSE and respiratory health outcomes by relying on self-reported measures of TSE and respiratory-related symptomatology,[20,21] or the use of spirometry measures to assess lung function.[22-24] FeNO levels assess airway inflammation and reactivity in real-time,[25] which is detectable before clinical symptomatology. This differs from spirometric measurements that assess airway caliber, other dimensions of airway disease.[4] The existing literature that has assessed TSE with FeNO levels to measure airway inflammation has examined this relationship among children and adolescents with asthma,[15,16,26-28] in samples with broad age ranges (e.g., 6-79 years),[29-31] and/or in small clinical samples.[14,32] Prior studies have used National Health and Nutrition Examination Survey (NHANES) 2007-2012 data to assess passive and active tobacco smoking with FeNO measurements, and the current study expands upon this work. For example, one prior study focused solely on children and adolescents with asthma,[27] and another study included a wide age range of participants ages 6-79 years with and without asthma.[30] Both of these studies categorized individuals with cotinine ≥10ng/ml as current smokers, irrespective of their self-reported responses.[30] However, nonsmoking children and adolescents who are exposed to tobacco smoke can have cotinine well above 10ng/ml.[33,34] Therefore, it is also important to assess the association of objectively measured, varying TSE levels including those ≥10ng/ml with FeNO levels among adolescents without asthma.

Our study objective was to assess the association between biochemically measured TSE as assessed with cotinine and FeNO levels among U.S. nonsmoking adolescents without asthma. Based on the potential biological plausibility that tobacco smoking results in endothelial dysfunction,[12,13] we hypothesized that nonsmoking adolescents with low cotinine and high cotinine levels would have decreased FeNO values and be at reduced odds of having high FeNO (>35ppb or >50ppb) than adolescents with no/minimal cotinine levels. We also assessed self-reported TSE and FeNO levels, and posited that adolescents who lived with a smoker who smoked inside the home (i.e., home TSE) and those who had a higher number of cigarettes/day smoked inside their home would have decreased FeNO values and decreased likelihood of having high FeNO (>35ppb or >50ppb).

Methods

Participants and Procedures

We used NHANES 2007-2012 data, described elsewhere in detail.[35] In brief, NHANES recruited a representative sample of the U.S. non-institutionalized civilian population using

a multistage probability cluster design to assess health information across the nation.[35] Prior to participation, informed consent was obtained from adults ≥18 years old, and parental permission and child assent was obtained for children <18 years old. NHANES 2007-2012 included an interview (e.g., self-reported TSE) and medical examination (e.g., FeNO measurement).

Of the 30,442 NHANES 2007-2012 participants, we delimited our analyses to 2,631 nonsmoking adolescents without asthma from 12-19 years old. Prior to analyses, we first excluded participants of other ages (n=26,592) and who were missing data on the outcome of interest, FeNO (n=436). Then, we excluded 12-19-year-olds who reported current cigarette smoking within the past 5-days (n=146) and past 30-days (n=275) or were missing these data (n=13), and currently had asthma (n=342) or were missing these data (n=7). We excluded children 3-11 years old with cotinine data due to typically having higher TSE levels,[2] being physiologically more susceptible to the effects of exposure when compared with adolescents,[36] and because self-reported current cigarette smoking questions were only asked among participants ages ≥12 years. We also excluded participants with asthma due to having higher NO levels in exhaled breath and varying confounding factors affecting the interpretation of FeNO levels compared to populations without asthma.[8] We received a "not human subjects" determination from a university-based IRB due to using public NHANES data.

Measures

Serum Cotinine.—We objectively assessed TSE status using serum cotinine obtained during the medical examination and measured by the laboratory via the isotope-dilution liquid chromatography-tandem mass spectrometry method.[37] Serum cotinine is a major nicotine metabolite that is a commonly used index of TSE due to a half-life of cotinine in serum of approximately 16 hours.[38] An analysis of NHANES 1999-2004 data indicated the optimal serum cotinine cutpoint to distinguish adolescents who do not smoke from those who smoke as 2.99ng/ml with a sensitivity of about 87% and specificity of 93%.[39] Therefore, we used cotinine cutpoints widely used in NHANES research,[22,40-42] to differentiate between no/minimal TSE (cotinine <0.05ng/ml), low TSE (cotinine 0.05-2.99ng/ml), and high TSE (cotinine ≥3.00ng/ml).

Self-Reported TSE.—We included self-reported items to measure potentially chronic TSE. Adolescents were asked about home TSE, "Does anyone smoke inside the home" (no, yes). Adolescents who responded "yes" and had home TSE were asked a follow-up question about the total number of cigarettes/day smoked inside the home by all smokers (continuous).

FeNO.—During NHANES 2007-2012, collected respiratory health examination data included a NO exam. A detailed manual of FeNO measurement procedures is available elsewhere.[43] Briefly, we used FeNO measurements produced by the noninvasive NO exam originally collected to assess baseline measurements in healthy individuals and those with respiratory conditions, and the prevalence of undiagnosed airway inflammation.[43] FeNO was measured using an FDA-approved, hand-held analyzer to detect NO levels in

the exhaled breath; analyzers followed the ATS and European Respiratory Society 2005 equipment recommendations.

To assess the outcome of interest, we used the NHANES-created continuous variable that averaged two reproducible FeNO measurements ranging from 3.5-217.5 parts per billion (ppb) in analyses. We also assessed high FeNO levels in a categorical nature based on the ATS'[8] recommended clinically significant cutpoint of FeNO >35ppb to indicate likely eosinophilic inflammation in children. We conducted a sensitivity analysis using the recommended cutpoint of FeNO >50ppb to determine eosinophilic inflammation in adults.[8]

Adolescent Characteristics.—Adolescent characteristics included demographics (age, sex, race/ethnicity), and standing height. We also assessed other characteristics that may influence FeNO results including past 2-day oral/inhaled steroid use, past 7-day respiratory illness, and past 12-month hay fever.

Statistical Analysis

We analyzed all data using R statistical software,[44] and adhered to the NHANES 2007-2012 analytic guidelines.[45,46] Guidelines included applying sample weights in all analyses to account for the complex study design, adolescent non-response, and post-stratification in order to obtain nationally representative estimates of the U.S. noninstitutionalized adolescent population. We assessed adolescent characteristics based on serum cotinine and self-reported home TSE by using chi-square tests, independent *t* tests, and analysis of variance (ANOVA). We conducted Pearson correlations to assess the associations between adolescent age and height with total number of cigarettes/day smoked inside adolescents' homes. We conducted linear regression analyses to assess the associations between serum cotinine with FeNO levels (continuous), while adjusting for adolescent age, sex, race/ethnicity, height, past 2-day steroid use, past 7-day respiratory illness, and past 12-month hay fever. Then, we conducted multivariable regression analyses to assess the associations between serum cotinine and the cutpoint of FeNO >35ppb (categorical) while adjusting for the same adolescent characteristics. We performed similar analyses to assess the associations between home TSE and number of cigarettes/day smoked inside the home and FeNO continuously (multiple regression) and categorically (multivariable regression), while adjusting for adolescent characteristics. We also conducted a sensitivity analysis using the cutpoint of FeNO >50ppb to assess the robustness of the FeNO >35ppb cutpoint. $P<0.05$ was used to determine statistical significance, and missing data were handled by removing incomplete cases prior to each analysis which were two-sided.

Results

The mean age (SD) of participants was 15.2 (0.04) years (Table 1). About half (49.8%) were female, and 57.0% were white, 20.6% Hispanic, 14.7% black, and 7.7% were another race/multiracial. Average (SD) standing height was 165.8 (0.19) cm. Less than one percent (0.7%) used steroids in the past 2-days, over one-fifth (23.6%) had a respiratory illness within the past 7-days, and 10.3% had hay fever within the past 12-months.

Serum Cotinine by Adolescent Characteristics

Overall, 34.0% had low cotinine and 6.2% had high cotinine. Adolescent age, sex, race/ethnicity, height, and past 2-day steroid use differed based on serum cotinine (see Table 1). Adolescents who were older, male, white or black, had higher mean height, and did not report past 2-day steroid use or past 12-month hay fever had significantly high proportions of low and high cotinine.

Cotinine by FeNO Levels

Multiple regression results indicated adolescents with low cotinine had lower FeNO levels (M=16.84, SE=0.59; β=−2.05, 95%CI=−3.61,−0.49, p>=0.01) than adolescents with no/minimal cotinine (M=18.58, SE=0.49; Table 2). A total of 9.0% and 6.8% of adolescents with low and high cotinine, respectively, had FeNO >35ppb. Logistic regression results indicated adolescents with low cotinine (adjusted odds ratio [aOR]=0.74, 95%CI=0.66,0.83, p<0.001) and high cotinine (aOR=0.54, 95%CI=0.43,0.69, p<0.001) were at reduced odds to have FeNO >35ppb than adolescents with no/minimal cotinine. A total of 3.8% and 4.6% of adolescents with low and high cotinine, respectively, had FeNO >50ppb. Adolescents with low cotinine were 0.62 times less likely to have FeNO >50ppb (95%CI=0.53,0.72, p<0.001) compared to adolescents with no/minimal cotinine.

Self-reported Home TSE

Approximately 11.4% of adolescents had self-reported home TSE, and of those, the mean (SD) number of cigarettes/day smoked inside their home was 1.41 (0.11) cigarettes. Adolescents who were white or black, had lower mean height, and no past 12-month hay fever had significantly high proportions of home TSE (see Table 1). Among adolescents with home TSE, adolescent race/ethnicity, mean height, and past 12-month hay fever similarly differed based on mean number of cigarettes/day smoked inside the home. Those who were white or black, and did not have past 12-month hay fever had a higher average number of cigarettes/day smoked inside their home. Adolescent standing height was positively correlated with number of cigarettes/day (r=−0.06), but no correlation was found between age and number of cigarettes/day (r=−0.03).

Self-reported Home TSE by FeNO Levels

A total of 8.6% and 3.2% of adolescents with home TSE had FeNO >35ppb and FeNO >50ppb, respectively (see Table 2). Mean (SD) number of cigarettes/day among adolescents with FeNO >35ppb and FeNO >50ppb were 0.82 (0.18) cigarettes and 0.68 (0.25) cigarettes, respectively. There was a significant difference found between adolescents with home TSE who had FeNO >50ppb (aOR=0.72, 95%CI=0.57,0.91, p=0.006) compared to adolescents with no home TSE.

Among adolescents with home TSE only, those with a higher number of cigarettes/day smoked inside their home were at reduced odds to have FeNO >35ppb (OR=0.98, 95%CI=0.97,0.99, p>=0.02) and FeNO >50ppb (OR=0.98, 95%CI=0.96,0.99, p=0.02).

Discussion

This U.S.-based study assessed the associations between TSE and FeNO measurements among a non-clinical sample of nonsmoking adolescents without asthma. The present study's results revealed that both objective and self-reported TSE were associated with FeNO measurements based on ATS' clinically significant cutpoints for high FeNO in our age range.[8] Aligning with our hypotheses, we found that adolescents with low cotinine had significantly reduced FeNO values and were at reduced odds to have FeNO >35ppb and >50pbb when compared to adolescents with no/minimal cotinine, while controlling for important covariates including demographics, standing height, recent steroid use, recent respiratory illness, and past 12-month hay fever. This aligns with prior work that found biochemically validated low TSE was associated with low FeNO levels among youth with asthma.[15]

The current study also found that adolescents with high cotinine were at decreased likelihood to have FeNO >35ppb. Previous studies indicate that increased cotinine levels result in progressively decreased FeNO levels in participants without asthma,[29] and with asthma.[26] A respiratory laboratory study among healthy adults found that high TSE, equivalent to seven cigarettes over one hour, resulted in a rapid decrease of FeNO that remained low for over one hour.[14] Xu et al.[30] found that NHANES 2007-2012 participants with and without asthma who were active smokers had reduced FeNO compared to nonsmokers, but results differed for TSE. Contrary to our findings, this study including participants ages 6-79 years found no differences based on self-reported TSE and FeNO levels among healthy participants, but found a decrease in FeNO levels among participants with asthma. Similarly, however, a dose-response relationship was found between cotinine and FeNO values. In addition to varying participant ages, one potential reason for the inconsistent results is that the prior study categorized nonsmokers using cotinine<10ng/ml irrespective of how participants ≥12 years old answered the self-reported questions. The current study used self-reported current smoking patterns to exclude adolescent smokers, and included adolescents with cotinine >10ng/ml since passive TSE levels can range well above this cutpoint.[33,34]

Aligning with the hypothesis on self-reported home TSE, the current study's results indicated that compared to adolescents who did not live with a smoker, those with home TSE were at reduced odds to have high FeNO >50ppb, the recommended cutpoint to determine airway inflammation among adults.[8] The mechanism responsible for our findings among those biochemically and self-reportedly exposed to tobacco smoke being at reduced likelihood of having high FeNO values may be similar to that of active smoking. Specifically, the decreased FeNO production observed in this study may be attributed to the negative feedback mechanism leading to decreased induced NO synthase gene expression and NO production from lung epithelial cells, which can lead to adverse health effects such as increased respiratory infections.[47] Further, another NHANES study delimited to children and adolescents with asthma found those with household smokers who smoked inside the home had significantly lower prevalence of high FeNO (9.4%) defined as >50pbb for 12-19-year-olds, than those with no TSE (19.6%).[27] Conversely, another study found that 16-year-olds who were daily or occasional smokers, as measured by self-report and

salivary cotinine, had significantly lower FeNO, but no difference was found based on TSE defined as parent smoking at least one cigarette/day.[24] Further, our results show that adolescents with a higher number of cigarettes/day smoked inside their home had reduced odds of FeNO values >35ppb and >50ppb. While we did not find differences between either self-reported TSE measure and continuous FeNO levels, a study among children with asthma found a negative association between parent-reported number of cigarettes/day smoked at home and FeNO levels after adjustment for important covariates, with this TSE measure accounting for one-third of the FeNO variance.[16] Our study expands on the current body of literature with results suggesting it may be important to take into account frequency of TSE and biochemically validating TSE while clinically interpreting FeNO levels. This would provide important assessment of potential confounders in addition to well-known confounders including adolescent age and other demographics, height, and recent steroid use, recent respiratory illness and hay fever.

About 40% of our study population had biochemically validated TSE measured via cotinine, which is indicative of recent exposure to tobacco smoke from any source (e.g., friend, parent) and in any place (e.g., car, public place). Concerning home TSE, about 11% of adolescents lived with a smoker, with a mean number of 1.41 cigarettes/day smoked inside their homes. Overall, adolescents who were older, male, white or black, had higher mean standing height, and no past 2-day steroid use or no past 12-month hay fever had high proportions of low and high cotinine. Adolescents who had significantly high proportions of living with a smoker and had a higher mean number of cigarettes/day smoked inside the home were with or black, had lower mean standing height, and no past 12-month hay fever. While TSE disparities exist,[2] it is important to note that asthma prevalence is higher among non-Hispanic black individuals compared with white individuals.[48] Similar to other work,[40] the present study found that adolescents with biochemically validated or self-reported TSE had higher mean standing height, which is related to FeNO levels.[10]

Our study highlights the multifaceted relationship between TSE and FeNO levels using a nationally representative, non-clinical sample of nonsmoking adolescents without asthma. There are several study limitations. First, we used retrospective NHANES 2007-2012 data, which cross-sectionally captured TSE and FeNO at each time-point (2007-2008, 2009-2010, and 2011-2012). Therefore, we were unable to assess these measures longitudinally or in more recent years since FeNO was only measured during these three waves. Serum cotinine, a highly sensitive and comprehensive measure of TSE, has a relatively short half-life of about 16 hours.[38] We included self-reported TSE to account for potential chronic TSE specific to the home setting, but were unable to assess TSE in other settings since this was not measured in NHANES 2007-2012 continuous waves. Additionally, NHANES did not provide data on prenatal TSE, which may contribute to respiratory morbidity during adolescence.[49] While we included self-reported past 12-month hay fever to consider atopy, NHANES 2007-2012 did not provide information on IgE-mediated sensitization to inhalant and food allergens to objectively measure allergic sensitization, a central risk factor of atopic disease development.[50] We relied on self-reported data for asthma diagnoses and current smoking to determine our inclusion/exclusion criteria, which might have been inaccurately reported by adolescents. Notwithstanding limitations, our results provide credence for healthcare professionals to consider TSE while interpreting FeNO

measurements, and to consider referring adolescents with asthma symptoms for formal diagnosis when appropriate.

In conclusion, this study demonstrated that U.S. nonsmoking adolescents without asthma diagnoses who were tobacco smoke-exposed had reduced FeNO values compared with unexposed adolescents. Low cotinine was associated with decreased FeNO measurements, beyond important covariates. We also found that adolescents with biochemically validated TSE and self-reported TSE, including home TSE and number of cigarettes/day smoked inside the home, were at reduced odds to have the higher cutpoint of FeNO >50ppb, which varied from our analysis of FeNO >35ppb. Specifically, there were associations found based on FeNO >35ppb for high cotinine versus no/minimal cotinine, but home TSE was not associated with this lower FeNO cutpoint. Findings highlight the need to take into consideration the frequency and amount of TSE when interpreting FeNO evidence-based guidelines for adolescents in the clinical and research settings.

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References

1. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
2. Brody DJ, Lu Z, Tsai J. Secondhand Smoke Exposure Among Nonsmoking Youth: United States, 2013-2016. NCHS Data Brief 2019;(348):1–8.
3. U.S. Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2006.
4. Duong-Quy S Clinical utility of the exhaled nitric oxide (NO) measurement with portable devices in the management of allergic airway inflammation and asthma. J Asthma Allergy. 2019;12:331–341. doi: 10.2147/JAA.S190489. [PubMed: 31632093]
5. Tang S, Xie Y, Yuan C, Sun X, Cui Y. Fractional exhaled nitric oxide for the diagnosis of childhood asthma: a systematic review and meta-analysis. Clin Rev Allergy Immunol. 2019;56(2):129–138. doi: 10.1007/s12016-016-8573-4 [PubMed: 27444490]
6. Guo Z, Wang Y, Xing G, Wang X. Diagnostic accuracy of fractional exhaled nitric oxide in asthma: a systematic review and meta-analysis of prospective studies. J Asthma. 2016;53(4):404–412. doi: 10.3109/02770903.2015.1101132 [PubMed: 26796787]
7. Paraskakis E, Brindicci C, Fleming L, et al. Measurement of bronchial and alveolar nitric oxide production in normal children and children with asthma. Am J Respir Crit Care Med. 2006;174(3):260–267. doi: 10.1164/rccm.200506-962OC [PubMed: 16627868]
8. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602–615. doi: 10.1164/rccm.9120-11ST [PubMed: 21885636]
9. Mehari A, Enwerem N, Odeyemi Y, Gillum RF. Effect modification by race-ethnicity of environmental tobacco smoke exposure on airway inflammation in US children. Ann Allergy Asthma Immunol. 2015;115(6):477–480. doi: 10.1016/j.anai.2015.09.010 [PubMed: 26443435]

10. Buchvald F, Baraldi E, Carraro S, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol. 2005;115(6):1130–1136. doi: 10.1016/j.jaci.2005.03.020 [PubMed: 15940124]
11. Nadif R, Matran R, Maccario J, et al. Passive and active smoking and exhaled nitric oxide levels according to asthma and atopy in adults. Ann Allergy Asthma Immunol. 2010;104(5):385–393. doi: 10.1016/j.anai.2010.03.013 [PubMed: 20486328]
12. Kharitonov SA, Robbins RA, Yates D, Keatings V, Barnes PJ. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. Am J Respir Crit Care Med. 1995;152(2):609–612. doi: 10.1164/ajrccm.152.2.7543345 [PubMed: 7543345]
13. Barberà JA, Peinado VI, Santos S, Ramirez J, Roca J, Rodriguez-Roisin R. Reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers. Am J Respir Crit Care Med. 2001;164(4):709–713. doi: 10.1164/ajrccm.164.4.2101023 [PubMed: 11520741]
14. Yates DH, Breen H, Thomas PS. Passive smoke inhalation decreases exhaled nitric oxide in normal subjects. Am J Respir Crit Care Med. 2001;164(6):1043–1046. doi: 10.1164/ajrccm.164.6.2005043 [PubMed: 11587994]
15. de la Riva-Velasco E, Krishnan S, Dozor AJ. Relationship between exhaled nitric oxide and exposure to low-level environmental tobacco smoke in children with asthma on inhaled corticosteroids. J Asthma. 2012;49(7):673–678. doi: 10.3109/02770903.2012.701363 [PubMed: 22799435]
16. Laoudi Y, Nikasinovic L, Sahraoui F, Grimfeld A, Momas I, Just J. Passive smoking is a major determinant of exhaled nitric oxide levels in allergic asthmatic children. Allergy. 2010;65(4):491–497. doi: 10.1111/j.1398-9995.2009.02190.x [PubMed: 19804439]
17. Kovesi TA, Dales RE. Effects of the indoor environment on the fraction of exhaled nitric oxide in school-aged children. Can Respir J. 2009;16(3):e18–e23. doi: 10.1155/2009/954382 [PubMed: 19557209]
18. Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. J Pediatr. 2006;149(2):220–226. doi: 10.1016/j.jpeds.2006.04.001. [PubMed: 16887438]
19. Dinakar C, Lapuente M, Barnes C, Garg U. Real-life environmental tobacco exposure does not affect exhaled nitric oxide levels in asthmatic children. J Asthma. 2005;42(2):113–118. [PubMed: 15871443]
20. Merianos AL, Jandarov RA, Mahabee-Gittens EM. Association of secondhand smoke exposure with asthma symptoms, medication use, and healthcare utilization among asthmatic adolescents. J Asthma. 2019;56(4):369–379. doi: 10.1080/02770903.2018.1463379 [PubMed: 29641269]
21. Merianos AL, Jandarov RA, Mahabee-Gittens EM. Adolescent tobacco smoke exposure, respiratory symptoms, and emergency department use. Pediatrics. 2018;142(3):e20180266. doi: 10.1542/peds.2018-0266 [PubMed: 30082449]
22. Merianos AL, Jandarov RA, Mahabee-Gittens EM. Tobacco smoke exposure, respiratory health, and health-care utilization among US adolescents. Chest. 2020;158(3):1104–1114. doi: 10.1016/j.chest.2020.03.038 [PubMed: 32272115]
23. Wang Z, May SM, Charoenlap S, et al. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2015; 115(5):396–401.e2. doi: 10.1016/j.anai.2015.08.005 [PubMed: 26411971]
24. Thacher JD, Schultz ES, Hallberg J, et al. Tobacco smoke exposure in early life and adolescence in relation to lung function. Eur Respir J. 2018;51(6):1702111. doi: 10.1183/13993003.02111-2017 [PubMed: 29748304]
25. Leung TF, Ko FW, Wong GW. Recent advances in asthma biomarker research. Ther Adv Respir Dis. 2013;7(5):297–308. doi: 10.1177/1753465813496863 [PubMed: 23907809]
26. Bobrowska-Korzeniowska M, Stelmach I, Brzozowska A, Jerzyńska J, Mital M, Stelmach W. The effect of passive smoking on exhaled nitric oxide in asthmatic children. Nitric Oxide. 2019;86:48–53. doi: 10.1016/j.niox.2019.01.012 [PubMed: 30779991]

27. Nguyen DT, Kit BK, Brody D, Akinbami LJ. Prevalence of high fractional exhaled nitric oxide among US youth with asthma. Pediatr Pulmonol. 2017;52(6):737–745. doi: 10.1002/ppul.23672 [PubMed: 28524604]
28. Gill R, Krishnan S, Dozor AJ. Low-level environmental tobacco smoke exposure and inflammatory biomarkers in children with asthma. J Asthma. 2014;51(4):355–359. doi: 10.3109/02770903.2013.823446 [PubMed: 24580138]
29. Jacinto T, Malinovschi A, Janson C, Fonseca J, Alving K. Differential effect of cigarette smoke exposure on exhaled nitric oxide and blood eosinophils in healthy and asthmatic individuals. J Breath Res. 2017;11(3):036006. doi: 10.1088/1752-7163/aa746b [PubMed: 28825404]
30. Xu X, Hu H, Kearney GD, Kan H, Carrillo G, Chen X. A population-based study of smoking, serum cotinine and exhaled nitric oxide among asthmatics and a healthy population in the USA. Inhal Toxicol. 2016;28(14):724–730. doi: 10.1080/08958378.2016.1264502 [PubMed: 27973944]
31. See KC, Christiani DC. Normal values and thresholds for the clinical interpretation of exhaled nitric oxide levels in the US general population: results from the National Health and Nutrition Examination Survey 2007-2010. Chest. 2013;143(1):107–116. doi: 10.1378/chest.12-0416 [PubMed: 22628492]
32. Kalliola S, Pelkonen AS, Malmberg LP, et al. Maternal smoking affects lung function and airway inflammation in young children with multiple-trigger wheeze. J Allergy Clin Immunol. 2013;131(3):730–735. doi: 10.1016/j.jaci.2013.01.005 [PubMed: 23380219]
33. Merianos AL, Jandarov RA, Mahabee-Gittens EM. High cotinine and healthcare utilization disparities among low-income children. Am J Prev Med. 60(2):267–275. doi: 10.1016/j.amepre.2020.06.018
34. Mahabee-Gittens EM, Mazzella MJ, Doucette JT, et al. Comparison of liquid chromatography mass spectrometry and enzyme-linked immunosorbent assay methods to measure salivary cotinine levels in ill children. Int J Environ Res Public Health. 2020;17(4):1157. doi: 10.3390/ijerph17041157.
35. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National Health and Nutrition Examination Survey: plan and operations, 1999-2010. Vital Health Stat 1. 2013;(56):1–37. [PubMed: 25078429]
36. World Health Organization. WHO summary of principles for evaluating health risks in children associated with exposure to chemicals. Geneva, Switzerland: World Health Organization; 2011.
37. National Center for Health Statistics. Laboratory procedure manual, cotinine. Centers for Disease Control and Prevention; 2008.
38. Benowitz NL, Bernert JT, Foulds J, et al. Biochemical verification of tobacco use and abstinence: 2019 update. Nicotine Tob Res. 2020;22(7):1086–1097. doi: 10.1093/ntr/ntz132 [PubMed: 31570931]
39. Benowitz NL, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. Am J Epidemiol. 2009;169(2):236–248. doi: 10.1093/aje/kwn301 [PubMed: 19019851]
40. Merianos AL, Jandarov RA, Khoury JC, Mahabee-Gittens EM. Tobacco smoke exposure association with lipid profiles and adiposity among U.S. adolescents. J Adolesc Health. 2018;62(4):463–470. doi: 10.1016/j.jadohealth.2017.10.001 [PubMed: 29224987]
41. Merianos AL, Hossain MM, Khoury JC, Matt GE, Mahabee-Gittens EM. Serum cotinine and Hemoglobin A1c among a national sample of adolescents without known diabetes. Nicotine Tob Res. 2018;20(4):474–481. doi: 10.1093/ntr/ntx115 [PubMed: 28575471]
42. Merianos AL, Jandarov RA, Mahabee-Gittens EM. Secondhand smoke exposure and pediatric healthcare visits and hospitalizations. Am J Prev Med. 2017;53(4):441–448. doi: 10.1016/j.amepre.2017.03.020 [PubMed: 28532658]
43. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES): respiratory health ENO procedures manual. Centers for Disease Control and Prevention; 2011.
44. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013. http://www.R-project.org/.

45. Johnson CL, Paulose-Ram R, Ogden CL, et al. National Health and Nutrition Examination Survey: analytic guidelines, 1999-2010. Vital Health Stat. 2013;2(161):1–24.

46. National Center for Health Statistics. National Health and Nutrition Examination Survey: analytic guidelines, 2011-2014 and 2015-2016. Centers for Disease Control and Prevention; 2018

47. Hoyt JC, Robbins RA, Habib M, et al. Cigarette smoke decreases inducible nitric oxide synthase in lung epithelial cells. Exp Lung Res. 2003;29(1):17–28. doi: 10.1080/01902140303759 [PubMed: 12652813]

48. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief. 2012;(94):1–8.

49. Gibbs K, Collaco JM, McGrath-Morrow SA. Impact of tobacco smoke and nicotine exposure on lung development. Chest. 2016;149(2):552–561. doi: 10.1378/chest.15-1858 [PubMed: 26502117]

50. Salo PM, PhD, Arbes Samuel J., DDS,MPH, PhD, Jaramillo R, MStat, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350–359. doi: 10.1016/j.jaci.2013.12.1071 [PubMed: 24522093]

Highlights

- Adolescent serum cotinine levels were associated with decreased FeNO values.
- Adolescent report of tobacco smoke exposure was associated with decreased FeNO.
- Adolescent tobacco smoke exposure should be considered for FeNO interpretation.

Table 1.

Characteristics of Nonsmoking Adolescents without Asthma Based on Tobacco Smoke Exposure, NHANES 2007-2012

Characteristic	Overall (N=2,631)	Serum Cotinine (*n*=2,369)				Home TSE (*n*=2,618)			No. of Cigarettes/Day Smoked Inside the Home by All Smokers (*n*=2,631)	
		No/Minimal (<0.05ng/ml)	Low (0.05-2.99ng/ml)	High (≥3.00ng/ml)		No	Yes			
	n (%)[a]	*n* (%)[b]	*n* (%)[b]	*n* (%)[b]	*P*[c]	*n* (%)[b]	*n* (%)[b]	*P*[c]	*M (SE)*	*P*[c]
Adolescent Age, *M*±SE	15.21 (0.04)	15.04 (0.06)	15.36 (0.08)	16.58 (0.17)	<0.001	15.21 (0.05)	15.10 (0.13)	0.39	-	0.19
Adolescent Sex										
Male	1,332 (50.2)	678 (55.8)	441 (35.8)	89 (8.4)	<0.001	1,176 (88.8)	151 (11.2)	0.76	1.37 (0.15)	0.68
Female	1,299 (49.8)	720 (64.0)	395 (32.2)	46 (3.8)		1,136 (88.4)	155 (11.6)		1.46 (0.16)	
Adolescent Race/Ethnicity										
White	715 (57.0)	331 (58.5)	250 (34.3)	53 (7.2)	<0.001	593 (87.3)	116 (12.7)	<0.001	1.91 (0.25)	<0.001
Black	678 (14.7)	232 (39.4)	318 (52.9)	45 (7.7)		558 (82.4)	119 (17.6)		1.51 (0.18)	
Hispanic	950 (20.6)	657 (75.2)	196 (21.7)	29 (3.1)		889 (94.0)	56 (6.0)		0.41 (0.09)	
Other Race/Multiracial	288 (7.7)	178 (65.5)	72 (30.5)	8 (4.0)		272 (95.1)	15 (4.9)		0.24 (0.10)	
Adolescent Height (cm)	165.81 (0.19)	165.44 (0.26)	166.13 (0.36)	169.75 (0.87)	<0.001	165.97 (0.21)	164.56 (0.61)	0.02	-	<0.001
Steroid Use in Past 2-Days										
No	2,618 (99.3)	1,389 (59.6)	834 (34.2)	135 (6.2)	0.03	2,300 (88.5)	305 (11.5)	0.28	1.42 (0.11)	0.32
Yes	13 (0.7)	9 (93.1)	2 (6.9)	0 (0.0)		12 (96.5)	1 (3.5)		0.11 (0.16)	
Respiratory Illness in Past 7-Days										
No	1,971 (76.4)	1,061 (60.7)	611 (33.0)	100 (6.3)	0.21	1,736 (88.8)	229 (11.2)	0.56	1.48 (0.13)	0.31
Yes	660 (23.6)	337 (57.1)	225 (37.1)	35 (5.8)		576 (87.9)	77 (12.1)		1.21 (0.18)	
Hay Fever in Past 12-Months										
No	2,384 (89.7)	1,250 (58.7)	764 (35.0)	124 (6.3)	0.005	2,088 (88.1)	283 (11.9)	0.02	1.50 (0.12)	0.03
Yes	245 (10.3)	148 (69.3)	70 (25.6)	11 (5.1)		222 (92.7)	23 (7.3)		0.71 (0.22)	

Abbreviations: NHANES, National Health and Nutrition Examination Survey; *M*, mean; SE, standard error.

[a] *n* refers to raw sample size and % refers to weighted valid column percent unless noted otherwise.

[b] *n* refers to raw sample size and % refers to weighted valid row percent unless noted otherwise.

[c] *P* <0.05 indicates statistical significance.

Table 2.

Tobacco Smoke Exposure and Fractional Exhaled Nitric Oxide Levels among Nonsmoking Adolescents without Asthma, NHANES 2007-2012

TSE Variable	FeNO (Continuous)		FeNO >35ppb		FeNO >50ppb	
	M (SE)	β (95% CI)[a]	*n* (%)[b]	aOR (95% CI)[a]	*n* (%)[b]	aOR (95% CI)[a]
Serum Cotinine (*n*= 2,369)						
No/minimal cotinine (<0.05ng/ml)	18.58 (0.49)	Ref	183 (11.0)	Ref	106 (6.0)	Ref
Low cotinine (0.05-2.99ng/ml)	16.84 (0.59)	−2.05 (−3.61, −0.49) *	99 (9.0)	0.74 (0.66, 0.83) ***	43 (3.8)	0.62 (0.53, 0.72) ***
High cotinine (≥3.00ng/ml)	18.10 (1.75)	−0.85 (−3.90, 2.19)	13 (6.8)	0.54 (0.43, 0.69) ***	7 (4.6)	0.86 (0.65, 1.15)
Home TSE (*n*= 2,618)						
No	18.06 (0.38)	Ref	290 (10.2)	Ref	156 (5.2)	Ref
Yes	15.98 (0.79)	−1.10 (−3.2, 1.0)	30 (8.6)	0.94 (0.81, 1.10)	13 (3.2)	0.72 (0.57, 0.91) **
No. of Cigarettes/Day Smoked Inside the Home by All Smokers (*n*= 2,631)	17.80 (0.35)	−0.08 (−0.20, 0.04)	-	0.98 (0.97, 0.99) *	-	0.98 (0.96, 0.99) *

Abbreviations: NHANES, National Health and Nutrition Examination Survey; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; TSE, tobacco smoke exposure; *M*, mean; SE, standard error; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference group.

*** $p<0.001$,

** $p<0.01$,

* $p<0.05$.

[a] Regression adjusting for adolescent age, sex, race/ethnicity, standing height, past 2-day steroid use, past 7-day respiratory illness, and past 12-month hay fever.

[b] *n* refers to raw sample size and % refers to weighted valid row percent.