

Race and ethnicity have significant influence on fractional exhaled nitric oxide



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ABSTRACT

Background: Race and ethnicity have been shown to influence fractional exhaled nitric oxide (FeNO). There is a need to investigate cutoff points for different races and ethnicities to improve clinical application.

Objective: To investigate cutoff points for different races and ethnicities by analyzing the FeNO data collected by the National Health and Nutrition Examination Survey from 2007 to 2012.

Methods: This study included 23,433 participants. After excluding participants with confounding factors, 11,084 participants were eligible for data analysis. Based on age and the probability of having allergic airway inflammation, participants were divided into 4 groups. The geometric mean and 5th, 50th, and 95th percentiles of FeNO in Hispanic, white, black, and other races were analyzed in all groups.

Results: Compared with white participants, the geometric mean for FeNO in black participants was 36% to 41% higher in children and 5% to 8% higher in adults. Hispanic children had significantly higher FeNO values (14% to 19%) compared with non-Hispanic white children; however, those differences were not significant in adults. Other races had significantly higher FeNO values in children (24–54%) and adults (9–29%) compared with white participants. Further, for normal healthy black children, the 95th percentile was 40.2 parts per billion (ppb), which is significantly higher than the cutoff point recommended by current guidelines.

Conclusion: Although there are significant differences in FeNO values among races and ethnicities, the current cutoff point at 50 ppb is sufficient to separate healthy from asthmatic populations in adults. However, for black children, we suggest increasing the cutoff point from 35 to 40 ppb to avoid unnecessary diagnosis and treatment.

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Introduction

The American Thoracic Society (ATS) has recommended using fractional exhaled nitric oxide (FeNO) to assess allergic airway inflammation, especially asthma, and to identify possible steroid-responsive individuals.¹ Since FeNO was first described in the laboratory setting in 1991,² FeNO testing has evolved to a point of care approved by the Food and Drug Administration. FeNO testing provides instant results with excellent patient cooperation, good repeatability, and reliability. A recent review showed FeNO testing can be routinely performed in basic clinical settings, and it is inexpensive and clinically useful.³

Like all other established clinical laboratory tests, FeNO concentration levels can be influenced by current or recent anti-

inflammatory medication usage, current or recent respiratory infection, smoking,^{4–6} and a diet rich in NO in addition to demographic factors (ethnicity, race, age, sex, weight, and height). FeNO concentration levels also can be influenced by laboratory factors (ie, analyzer used, measurement technique, exhalation flow rate, etc). Owing to inconsistent methodology, different populations, and inadequate sample sizes, the determination of normative FeNO values in different racial and ethnic groups has been challenged in many studies on adult and pediatric study populations.^{7–17} A recent systematic review based on current published data indicated that in other racial and ethnic groups, more than 5% of normal healthy children and adults had FeNO values above the normal Caucasian range. Therefore, it might be inappropriate to use the current Caucasian-based cutoff values for clinical interpretation in these groups.¹⁸

The aim of this study was to analyze the FeNO data collected by the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2012 to determine the reference range of FeNO values among major ethnic groups in the United States. With a highly consistent methodology and a large sample with a well-represented population using the NHANES, we analyzed the differences of FeNO

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values among major ethnic groups in the United States for children and adults.

Methods

Study Population

The NHANES is a survey research program conducted by the Centers for Disease Control and Prevention to assess the health and nutritional status of adults and children in the United States. It is composed of cross-sectional, nationally representative health and nutrition surveys of the US civilian noninstitutionalized population. To represent the US population, a complex, stratified, multistage probability cluster sampling design is used in the survey. For more details of the sampling design in the NHANES, see the supplemental Methods section.

The measurement of FeNO was sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The National Center for Health Statistics Research ethics review board approved all protocols.

Informed consent was obtained from all participants by the NHANES in accordance with section 308(d) of the Public Health Service Act (42 USC 242m). The consent form was signed by participants in the survey, and participants consented to storing specimens of their blood for future research.

In total, 23,433 participants 6 to 80 years old were recruited for NHANES FeNO testing from 2007 to 2012. Exclusion criteria consisted of participants without valid FeNO measurements, were defined as “smoker,” were defined as “household smoker,” exercised strenuously within 1 hour before the test, ate NO-rich vegetables or meats within 3 hours before the test, or used oral or inhaled steroids at least 48 hours before the test. After applying the exclusion criteria, 11,084 participants were included in the final analysis. For definitions of “smoker” and “household smoker” used in this study, see the supplemental Methods section.

Groups

To evaluate the influence of race and ethnicity on FeNO values in the healthy and unhealthy populations, participants were divided into “normal” and “abnormal” groups based on their probability of having allergic airway inflammation.^{12,19–21} The normal group was defined as not having physician-diagnosed and self-reported diseases including asthma, emphysema, or chronic bronchitis and no hay fever in the past 12 months before the test. The abnormal group was defined as having at least 1 of these conditions.

Based on recommendations from current ATS guidelines,¹ participants younger than 12 years composed the child population and those at least 12 years old composed the adult population. Four groups, “normal children,” “abnormal children,” “normal adults,” and “abnormal adults,” were analyzed separately. Figure 1 presents the flow diagram of participants’ enrollment.

Race and Ethnicity

Participants in each of these 4 groups were further stratified into 4 subgroups according to their race or ethnicity interview report in the NHANES: “Hispanic,” “white,” “black,” and “other.” Table 1 presents the characteristics of the different races and ethnicities in the present study population. For details about the interview setting and group criteria for race or ethnicity, see the supplemental Methods section.

FeNO Measurement

Fractional exhaled NO was measured using the Aerocrine NIOX MINO (Aerocrine AB, Solna, Sweden) with a stabilized flow rate at 50 mL/s. Participants who had produced 2 reproducible FeNO measurements, in accordance with testing procedures recommended by the manufacturer and similar to those published by the ATS and the European Respiratory Society, were considered eligible.^{22,23} Two reproducible FeNO measurements were defined as having 2 valid FeNO measurements below 30 parts per billion (ppb) and the measurements were within 2 ppb of each other or the 2 measurements were over 30 ppb and within 10% of each other. FeNO testing was conducted in mobile examination centers, which are traveling clinics. Spirometry was conducted after FeNO testing in each participant. There was no repeated forced vital capacity maneuver immediately before FeNO determination.²⁴ For detailed FeNO measurements, see the supplemental Methods section.

Statistical Analysis

Because FeNO values were positively skewed,^{25,26} to assess differences in FeNO values, log-transformed FeNO values or geometric means were used to compare and derive *P* values among the racial and ethnic groups. To account for the complex, stratified, multistage probability sampling design in the NHANES, the Proc survey methodology in SAS 9.4 (SAS Institute Cary, North Carolina) was applied for all statistical analyses. For participants’ characteristics, SAS PROC SURVEYMEANS and SURVEYFREQ were performed to estimate weighted means and weighted frequencies, respectively. Because studies have shown how age significantly influences FeNO values,^{25,26} for adults (age 12–80 years), SAS SURVEYREG was applied to estimate age-adjusted means and derive *P* values, in which the proximate proportions based on the 2010 US population census (Table 2) were used in the age adjustment analyses; for children (age 6–11 years), SAS SURVEYREG without age adjustment was used to estimate means and derive *P* values because of the narrow age range. In addition, SAS PROC SURVEYMEANS was conducted to estimate FeNO means and 5th, 50th, and 95th percentiles. A *P* value less than .05 was considered statistically significant.

Results

In total, 23,433 participants 6 to 79 years old were recruited for NHANES FeNO testing. Of those, 19,800 participants who had 2 reproducible FeNO measurements were included in the present study. After participants who had potential confounded FeNO measurements were excluded, 11,084 participants were included in the final analysis.

For normal children, 1,564 participants were analyzed: 661 were Hispanic (42%), 466 were white (30%), 290 were black (19%), and 147 were other (9%). The geometric mean (95% confidence interval [CI]) of FeNO values (parts per billion [ppb]) was 8.6 (8.1–9.1) in the Hispanic group, 7.6 (7.1–8.1) in the white group, 10.3 (9.3–11.3) in the black group, and 9.4 (7.8–11.3) in the other group. Using the white group as a comparison, the percentage of the geometric mean was 114% (104%–125%, *P* = 0.006) for the Hispanic group, 136% (123%–150%, *P* < 0.0001) for the black group, and 124% (102%–151%, *P* = 0.0287) for the other group. The 95th percentile of FeNO values was 27 ppb in the Hispanic group, 21.6 ppb in the white group, 40.2 ppb in the black group, and 31.5 ppb in the other group (Fig 2).

For abnormal children, 862 participants were analyzed: 324 were Hispanic (38%), 233 were white (27%), 200 were black (23%), and 105 were other (12%). The geometric mean (95% CI) of FeNO values (ppb) was 14.1 (12.7–15.6) in the Hispanic group, 11.8 (10.5–13.4) in the white group, 16.7 (14.5–19.3) in the black group, and 18.3 (15.7–21.3) in the other group. Using the white group as a

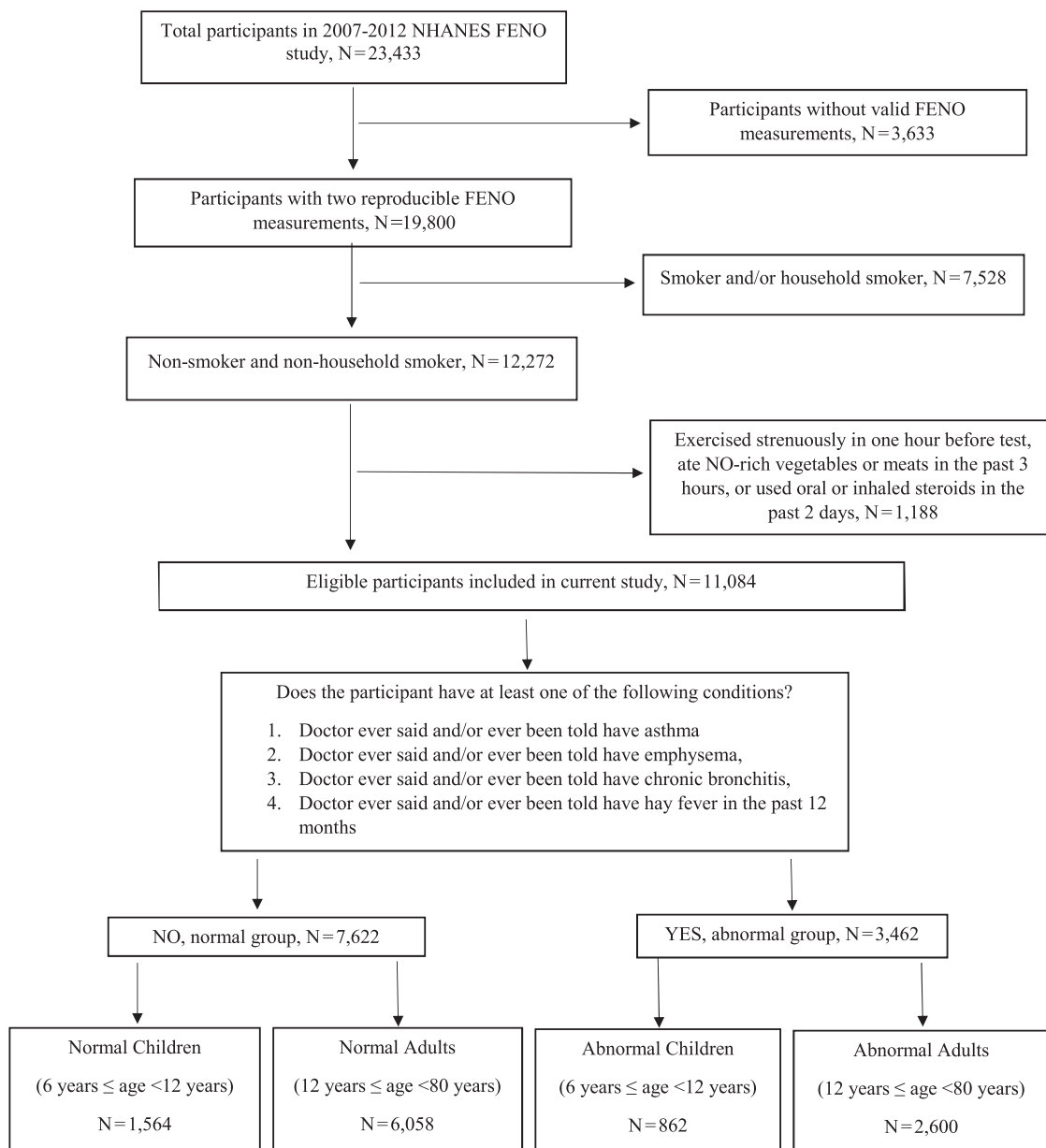


Figure 1. Flow diagram of participants' enrollment. FeNO, fractional exhaled nitric oxide; NHANES, National Health and Nutrition Examination Survey; NO, nitric oxide.

comparison, the percentage of the geometric mean was 119% (103%–138%, $P=0.02$) for the Hispanic group, 141% (120%–167%, $P<0.0001$) for the black group, and 154% (125%–190%, $P<0.0001$) for the other group. The 95th percentile of FeNO values was 64.8 ppb in the Hispanic group, 55.6 ppb in the white group, 68.3 ppb in the black group, and 71.5 ppb in the other group (Fig 3).

For normal adults, 6,058 participants were analyzed: 2,122 were Hispanic (35%), 1,983 were white (33%), 1,333 were black (22%), and 620 were other (10%). The geometric mean (95% CI) of FeNO values (ppb) was 14.1 (13.5–14.7) in the Hispanic group, 13.4 (13.0–13.9) in the white group, 14.1 (13.6–14.7) in the black group, and 14.6 (13.8–15.5) in the other group. Using the white group as a comparison, the percentage of geometric mean was 105% (100%–111%, $P=0.073$) for the Hispanic group, 109% (101%–111%, $P=0.028$) for the black group, and 124% (102%–116%, $P=0.008$) for the other group. The 95th percentile of FeNO values was 37.9 ppb in the Hispanic group, 32.4 ppb in the white group, 43.3 ppb in the black group, and 39.4 ppb in the other group (Fig 4).

For abnormal adults, 2,600 participants were analyzed: 700 were Hispanic (27%), 983 were white (38%), 603 were black (23%), and 314 were other (12%). The geometric mean (95% CI) was 17.2 (16.2–18.2) in the Hispanic group, 16.9 (16.1–17.8) in the white group, 18.3 (17.1–19.7) in the black group, and 21.9 (19.7–24.3) in the other group. Using the white group as a comparison, the percentage of geometric mean for the Hispanic group was 101% (95%–109%, $P=0.681$) for the Hispanic group, 108% (101%–111%, $P=0.054$) for the black group, and 129% (102%–116%, $P<0.0001$) for the other group. The 95th percentile of FeNO values was 72.2 ppb in the Hispanic group, 54 ppb in the white group, 78.3 ppb in the black group, and 75.9 ppb in the other group (Fig 5).

Discussion

The FeNO values from 11,084 participants were analyzed in this study. Race or ethnicity was shown to affect FeNO values significantly in normal and abnormal children (6–11 years old). For adults

Table 1
Characteristics of Different Races and Ethnicities in Present Study Population

	Hispanic	White	Black	Other
A. Normal children (age 6–11 y)				
Age (y), mean	8.7	8.7	8.9	8.4
BMI (kg/m ²), mean	19.3	18.1	19.4	17.7
Height (cm), mean	135.2	136.8	139.6	133.2
Male, %	49.3	48.1	43.2	41.5
B. Abnormal children (age 6–11 y)				
Age (y), mean	8.7	8.8	8.8	8.7
BMI (kg/m ²), mean	19.6	18.2	19.7	17.8
Height (cm), mean	135.5	137.7	138.3	135.0
Male, %	53.4	56.9	56.9	51.5
C. Normal adults (age 12–80 y)				
Age (y), mean	41.3	41.4	41.4	41.3
BMI (kg/m ²), mean	28.5	27.4	30.3	25.2
Height (cm), mean	162.6	169.7	168.3	163.6
Male, %	46.0	46.3	41.7	42.2
D. Abnormal adults (age 12–80 y)				
Age (y), mean	41.3	41.4	41.4	41.2
BMI (kg/m ²), mean	29.5	28.6	31.1	26.9
Height (cm), mean	162.9	169.8	168.1	166.0
Male, %	48.8	45.5	44.6	52.9

Abbreviation: BMI, body mass index.

(12–80 years old), the influence of race or ethnicity on FeNO values was statistically significant when the black and other groups were compared with the white group; however, the degree of difference was much less than in children. We found that race or ethnicity influences FeNO values in children and adults in the healthy populations and populations that have potentially allergic airway diseases.

Fractional exhaled NO testing has evolved into a noninvasive point-of-care method that is a good indicator of allergic airway inflammation.^{1,27–29} Since 2011, the ATS has published guidelines regarding the interpretation of FeNO values for clinical applications. FeNO testing has been helping physicians identify patients with airway inflammation responsive to inhaled corticosteroids. The incorporation of FeNO testing into the management of patients with asthma has been shown to lower exacerbation rates.^{30–33}

However, because of multiple confounding factors and overlap between healthy populations and populations with allergic airway diseases, previous publications have prevented the routine application of reference values in the clinical setting.¹ Thus, the ATS committee suggested the use of cutoff points rather than reference values when interpreting FeNO values.¹ Among possible non-modifiable factors that can affect FeNO values (age, sex, height, weight, and race and ethnicity), only age is included in current ATS guidelines. Race or ethnicity has been shown to potentially affect FeNO values in adults and children in previous publications.^{34,35} One recently published systematic review concluded that race or ethnicity affects FeNO values, suggesting a need to establish FeNO reference values for those populations.¹⁸

The NHANES is a national standard database of a comprehensive survey drawing from a large and diverse sample of participants to represent the general US population. The NHANES is well known for its design to avoid volunteer bias encountered frequently in most surveys. Highly standardized procedures and high-quality data collecting and recording systems further increase data reliability. By using data from the NHANES, modifiable factors such as the analyzer used, measurement technique, exhalation flow rate, sample bias, etc, which affected results from previous publications, are generally avoided. Our study using the NHANES database clearly showed race or ethnicity has a significant effect on FeNO values. Using survey weights and accounting for complex sampling, we obtained the distribution of FeNO values in different racial or ethnic groups in children and adults, which will provide more accurate guidance when interpreting FeNO values during clinical practice.

In the general US population, the black population has consistently higher FeNO values than the white population. This difference is more prominent in children than in adults. Our study showed that FeNO values in the black population can range from 36% to 41% higher than in white children and from 5% to 8% higher than in white adults. For populations of Hispanic origin, during childhood the FeNO values can range from 14% to 19% higher than in those of non-Hispanic origin. However, for unknown reasons, this difference subsides once adulthood has been reached. For the “other” group,

Table 2
Adjusted Proportions for Adult Participants (Age 12–80 y) According to 2010 US Population Census (<https://www.census.gov/2010census/>)

Age (y)	12–14	15–19	20–24	25–29	30–34	35–39	40–44
Proportion	0.049887	0.088627	0.0868	0.084853	0.08027	0.081144	0.084005
Age (y)	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Proportion	0.091314	0.089663	0.079074	0.067627	0.05003	0.037308	0.029426

FeNO value in normal children

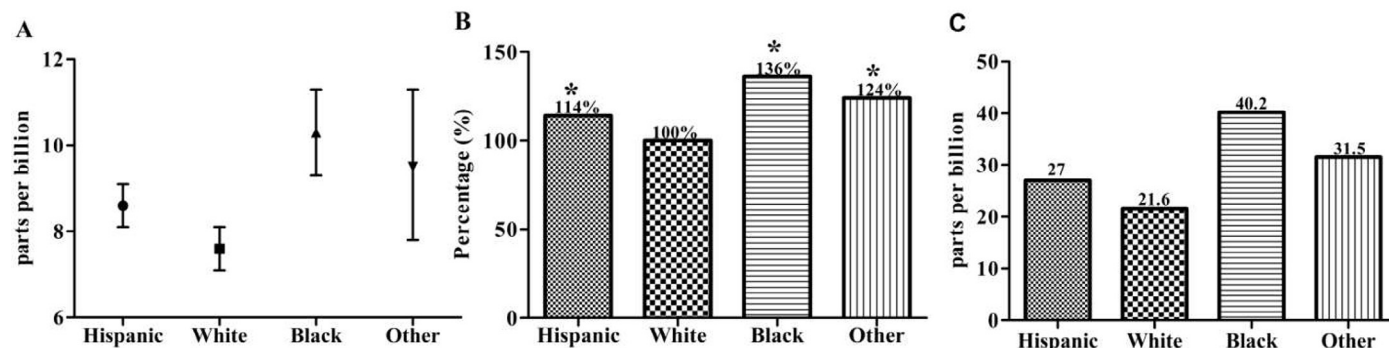


Figure 2. Fractional exhaled nitric oxide (FeNO) values in normal children (6–11 years old) in 4 racial and ethnic groups (Hispanic, white, black, and other). (A) Geometric mean value and 95% confidence interval (CI). (B) Relative percentage of geometric mean of other groups compared with the white group. (C) The 95th percentile of FeNO value. Percentile and mean data were weighted to represent the US population. **P* < .05.

FENO value in abnormal children

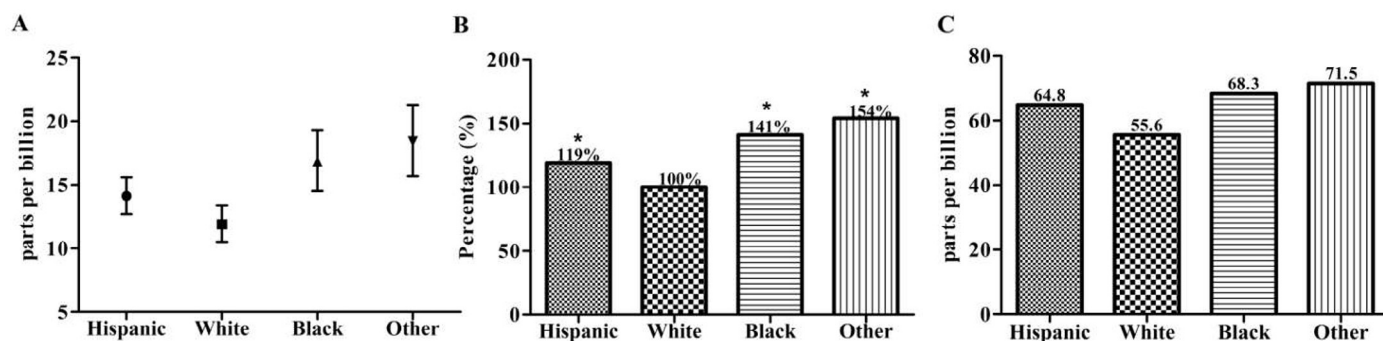


Figure 3. Fractional exhaled nitric oxide (FeNO) values in abnormal children (6–11 years) in 4 racial and ethnic groups (Hispanic, white, black, and other). (A) Geometric mean value and 95% confidence interval (CI). (B) Relative percentage of geometric mean of other groups compared with the white group. (C) The 95th percentile of FeNO value. Percentile and mean data were weighted to represent the US population. * $P < .05$.

we found the widest 95% CI was due to mixed samples in the NHANES regarding the race or ethnicity differentiation. However, compared with the white population, the black and other populations consistently had significantly higher FeNO values, ranging from 24% to 54% in children and 9% to 29% in adults.

Further, we found the ATS cutoff points for children (<20 ppb indicates unlikely allergic airway diseases and >35 ppb indicates likely allergic airway diseases) were well fitted with white, Hispanic, and other races and ethnicities. However, for black normal children, the 35-ppb cutoff point is questionable and could cause

FENO value in normal adults

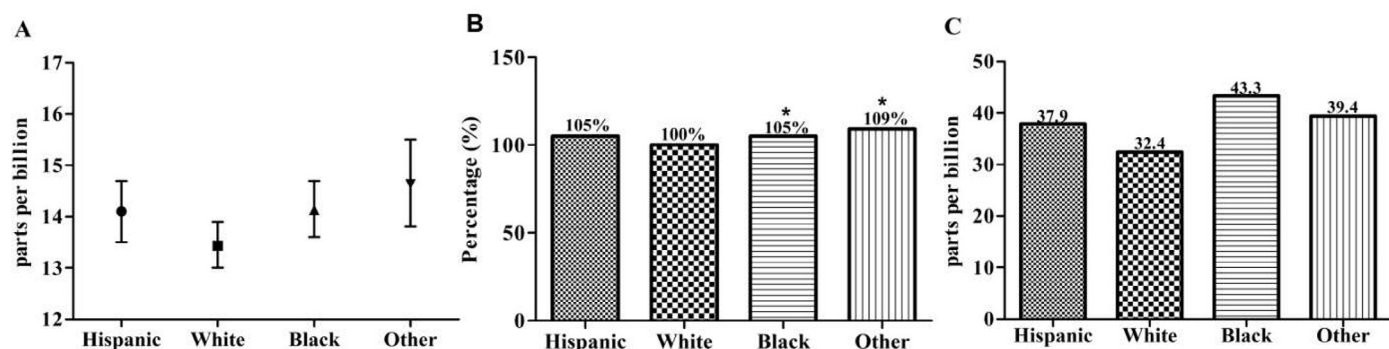


Figure 4. Fractional exhaled nitric oxide (FeNO) values in normal adults (12–80 years) in 4 racial and ethnic groups (Hispanic, white, black, and other). (A) Geometric mean value and 95% confidence interval (CI). (B) Relative percentage of geometric mean of other groups compared with the white group. (C) The 95th percentile of FeNO value. Percentile and mean data were weighted to represent the US population. * $P < .05$.

FENO value in abnormal adults

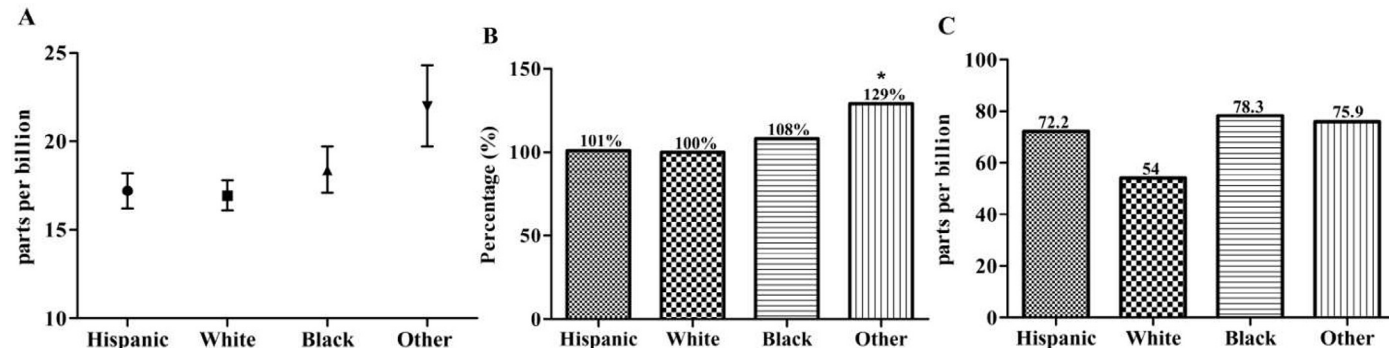


Figure 5. Fractional exhaled nitric oxide (FeNO) values in abnormal adults (12–80 years) in 4 racial and ethnic groups (Hispanic, white, black, and other). (A) Geometric mean value and 95% confidence interval (CI). (B) Relative percentage of geometric mean of other groups compared with the white group. (C) The 95th percentile of FeNO value. Percentile and mean data were weighted to represent the US population. * $P < .05$.

unnecessary treatment. Our data support the current ATS cutoff points for adults (<25 ppb for unlikely allergic airway diseases and >50 ppb for likely allergic airway diseases). For the healthy, normal population, the 95th percentile of FeNO values in Hispanic, white, black, and other races and ethnicities was significantly below the 50-ppb cutoff point.

We acknowledge several limitations of our study. First, when defining the “abnormal” groups, not all chronic respiratory disorders and other chronic nonrespiratory disorders that can affect FeNO values were included because of data unavailability. Second, FeNO measurements in the NHANES were not in full accordance with current standards (the test should be performed ≥ 3 times to achieve results within a 5% difference).^{1,23} However, it is unlikely the results were affected by FeNO measurements because of the large sample in this study. Third, the mechanisms behind the different FeNO values in different racial and ethnic groups are unclear because of the survey nature of the NHANES. Multiple factors can interact to contribute differences in FeNO values. First, the environment (especially high altitude) was shown to affect FeNO values significantly in studies focusing on Tibetans.³⁶ Interestingly, those differences of FeNO values were significant not only for adults who had always lived at high altitude but also for Tibetan compared with non-Tibetan newborn infants.³⁷ Second, different traditional diets between races and ethnic groups can play an important role in the regulation of FeNO production.^{38,39} Third, genetic variations in NO synthase and arginase have been shown to influence exhaled NO levels in children.⁴⁰

In the general US population, children from all other races and children of Hispanic origin have significantly higher FeNO values than non-Hispanic white children. For adults, except those of Hispanic origin, all other racial and ethnic groups have significantly higher FeNO values than non-Hispanic whites. Although significant differences in FeNO values for different racial and ethnic groups are present, a current cutoff point of 50 ppb is sufficient to separate healthy from asthmatic populations in adults. However, for black children, we suggest increasing the cutoff point from 35 to 40 ppb to avoid unnecessary diagnosis and treatment.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.janai.2017.11.021>.

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Supplementary Data

Methods

Sampling Design in the NHANES

The NHANES has a long history; it has been in existence since 1960 and has surveyed more than 190,000 people. The NHANES was born from the National Health Survey Act in 1956. This law authorized a survey to provide current statistical data on the amount, distribution, and effects of illness and disability in the United States. The sampling process could be simplified as 4 stages. In stage 1, all counties in the United States are divided into 15 groups based on their characteristics. One county is selected from each large group, and together they form the 15 counties in the NHANES for each year. In stage 2, within each county, smaller groups (with a large number of households in each group) are formed, and 20 to 24 of these small groups are selected. In stage 3, all the houses or apartments within those selected small groups are identified, and a sample of approximately 30 households is selected within each group. In stage 4, NHANES interviewers go to each selected household and ask for information (age, race, and sex) on all persons in the household. For a detailed sampling design, see https://wwwn.cdc.gov/nchs/data/series/sr02_160.pdf.

“Smoker” Definition

The Smoking Cigarette Use dataset in the NHANES provides data on cigarette use; history of use, age at initiation, current use, past 30-day prevalence, amount, cigarette brand, and other related details are included. For adults at least 20 years of age, questions were asked in the home by trained interviewers using the Computer-Assisted Personal Interviewing (CAPI) system. For youth 12 to 19 years old, the questions were asked at the Mobile Examination Center (MEC) during the MEC interview using the Audio Computer-Assisted Self-Interviewing (ACASI) system, in English and Spanish only.

“Smoker” in the present study was defined as participants who answered “yes” to the question, “Have you smoked at least 100 cigarettes in your entire life?”

“Household Smoker” Definition

The Smoking and Tobacco Use–Household Smokers section of the Family Questionnaire in the NHANES provides information on exposure to secondhand smoke. After an initial screening question asking whether any household member smoked any tobacco products inside the home, information about the total number of smokers, total number of cigarette smokers, and total number of cigarettes smoked was obtained.

“Household smoker” in the present study was defined as participants who answered “yes” to the question, “Does anyone who lives here smoke cigarettes, cigars, or pipes anywhere inside this home?”

Interview Setting and Group Criteria for Race and Ethnicity

The family and sample person demographic questionnaires were asked, in the home, by trained interviewers using the CAPI system. The respondent selected the language of interview (English or Spanish) or requested that an interpreter be used. Hand cards, showing response choices or information that survey participants needed to answer the questions, were used for some questions. The hand cards were printed in English, Spanish, Mandarin Chinese (traditional and simplified), Korean, and Vietnamese. The

interviewer directed the respondent to the appropriate hand card during the interview. When necessary, the interviewer further assisted the respondent by reading the response choices listed on the hand cards.

Persons at least 16 years of age and emancipated minors were interviewed directly. A proxy provided information for survey participants who were younger than 16 and for participants who could not answer the questions themselves.

The Standards for the Classification of Federal Data on Race and Ethnicity issued by the Office of Management and Budget in 1997 (https://nces.ed.gov/programs/handbook/data/pdf/Appendix_A.pdf) were used to determine race and ethnicity in the present study. First, all participants were asked about their Hispanic origin. Respondents who self-identified as “Mexican American” and “other Hispanic” were included in the Hispanic group regardless of their other racial identities. Second, all other non-Hispanic participants would be categorized based on their self-reported race: white, black, and other.

FeNO Measurement

Fractional exhaled NO was measured using the Aerocrine NIOX MINO (Aerocrine AB, Solna, Sweden), a portable, hand-held NO analyzer approved by the Food and Drug Administration in 2008. This device relies on an electrochemical sensor to detect exhaled NO levels and provides measurements from 5 to 300 ppb in whole numbers. Testing was conducted with participants sitting in front of a mirror so they could see display prompts on the NO analyzer screen. While holding the device, participants were asked to empty their lungs, to place their mouth on the disposable analyzer’s filter mouthpiece, and to fill their lungs to capacity with NO-free air. Then, participants were asked to blow out all the air at a constant pressure while exhaled NO from the bronchial tree was measured. The NIOX MINO has a dynamic flow restrictor to stabilize flow rate at 50 mL/s. The device automatically provides auditory and visual cues to assist in performing the test correctly. The health technicians also coached participants to maintain the air flow at a slow, fixed, steady rate. The standard exhalation time, as specified by the manufacturer, was 10 seconds for participants who were at least 130 cm tall and 6 seconds for those no taller than 130 cm. The Respiratory Health ENO Procedures Manual provides a detailed description of the examination procedure (https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/Respiratory_Health_ENO_Procedures_Manual.pdf).

The test result, an integer between 5 and 300 ppb, was displayed on the screen of the device 140 seconds after a valid test was completed. Codes indicating a result above or below the range of the device detection limit and error codes also were displayed on the screen. It was common for current smokers to have to repeat FeNO levels below the limit of detection. Results indicating a value above the limit of detection were unusual, and subsequent measurements were often within the normal range of the test device. The NHANES protocol required 2 FeNO measurements that were reproducible, in accordance with testing procedures recommended by the manufacturer and similar to those published by the ATC and the European Respiratory Society. If either or both of the first 2 valid FeNO measurements were below 30 ppb and the measurements were within 2 ppb of each other or if both measurements were over 30 ppb and within 10% of each other, then the test was considered reproducible and complete.