



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

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