Does Ethnicity Influence Fractional Exhaled Nitric Oxide in Healthy Individuals?

A Systematic Review

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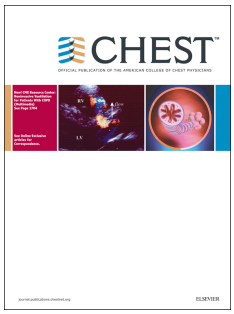

Does ethnicity influence fractional exhaled nitric oxide in healthy individuals? A systematic review

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ABSTRACT

Background

Fractional exhaled nitric oxide (FeNO) is used clinically as a biomarker of eosinophilic airway inflammation. Awareness of the factors influencing FeNO values is important for valid clinical interpretation.

Methods

We undertook a systematic review of PubMed, Cochrane Library, Scopus and Web of Science databases, as well as reference lists of included articles to evaluate whether ethnicity influences FeNO values, and to determine if this influence affects clinical interpretation according to current guidelines. We included all studies that performed online FeNO measurements on at least 25 healthy, non-Caucasian individuals, and examined the effect of ethnicity on FeNO.

Results

From 62 potential studies, 12 studies were included. One study recruited only children (<12 years), six studies recruited children and/or adolescents, four studies recruited adults only, and a single study involved children, adolescents, and adults. In total, 16 different ethnic populations representing 11 ethnicities were studied. Ethnicity was considered a significant influencing factor in ten of the included studies. We found the geometric mean FeNO to be above the normal healthy range in two studies. We also identified five studies in which at least 5% of participants had FeNO results above the age-specific inflammatory ranges.

Conclusion

Ethnicity influences FeNO values and for some ethnic groups this influence likely affects clinical interpretation according to current guidelines. There is a need to establish healthy FeNO reference ranges for specific ethnic groups in order to improve clinical application.

ABBREVIATIONS

ATS American Thoracic Society

ERS European Respiratory Society

FeNO fractional exhaled nitric oxide

ppb parts per billion

INTRODUCTION

Fractional exhaled nitric oxide (FeNO) is regarded as a simple, non-invasive method for assessing eosinophilic airway inflammation.[1-3] Produced by a variety of cells within the lungs, nitric oxide (NO) concentrations are generally low in healthy individuals.[4] However, high concentrations of NO appear to be involved in non-specific host defence mechanisms (particularly Th2-mediated responses), and chronic inflammatory diseases such as asthma.[4,5] The American Thoracic Society (ATS) therefore has recommended using FeNO to aid in the diagnosis and monitoring of eosinophilic airway inflammation and asthma, and for identifying steroid responsive individuals whose chronic respiratory symptoms may be due to airway inflammation.[2]

For FeNO to be reliable as a biomarker, it is important to know factors that influence FeNO values. Currently, it is known that FeNO values are influenced by respiratory infections,[6,7] atopy,[8-10] presence of eosinophils,[11] age,[12,13] gender,[9] height,[13,14] smoking,[13,15] environmental factors,[16,17] and possibly ethnicity.[2,18,19] Current guidelines recommend the use of cut-off values[2] which are presently based solely on age. For example, FeNO levels in adolescents and adults (>12 years old) of over 50 parts per billion (ppb) suggest that eosinophilic inflammation is present and, in symptomatic patients, potential responsiveness to inhaled corticosteroid (ICS) treatment. The corresponding cut-off value in children (< 12 years old) is > 35 ppb.[2] When the individual's FeNO value is in the intermediate range (25-50ppb for adults and 20-35ppb for children), it is recommended that "results should be interpreted cautiously and with reference to the clinical context".[2] Eosinophilic inflammation is considered unlikely with FeNO values< 25 ppb in adults and adolescents or < 20 ppb in children.[2] Notably, factors important in predicted values of other pulmonary

function tests (e.g. sex, height, and ethnicity) were not considered in the recommended cut-off FeNO values.

Since the 1990's the ATS/ERS (European Respiratory Society) has recommended that respiratory function reference values should be obtained from representative 'healthy' populations that closely match (age, sex, height, and ethnicity) those presenting in the clinical setting.[20,21] Despite this, there is still little data on 'normal values' in adults and children of non-Caucasian ethnic groups for FeNO. There is strong agreement in the literature[2,13,22] for the need to develop reference ranges for evaluating FeNO values in these groups. However, there is currently no published systematic review on the influence of ethnicity on FeNO values in healthy children and adults.

Thus, we undertook a systematic review of published literature to explore ethnicity as a potential factor influencing FeNO values in healthy adults and children of non-Caucasian ethnic groups. In this review, ethnicity refers to a group of people who identify with each other based on common ancestral, social, cultural, or national experiences including languages, art, religious symbols, and physical appearance.[23,24] Our primary objective was to evaluate if ethnicity influenced FeNO levels in studies of healthy cohorts. Given the importance of cut-offs, we also evaluated if an ethnic influence affected the clinical interpretation according to current guidelines.[2]

METHODS

Search Strategy

Studies were identified by searching the PubMed, Cochrane Library, Scopus and Web of Science databases with the search text: (exhaled nitric oxide or FeNO or eNO) and (race or ethnic or non-Caucasian) and (normal or healthy or well or asymptomatic). Latest searches were performed in December 2016 and there were no language exclusions. Abstracts, reviews, and comments were not included. Reference lists of relevant articles were also searched.

Eligibility Criteria

Studies were included in the review if they (i) recruited healthy, non-Caucasian individuals; (ii) explored race or ethnicity as a factor influencing FeNO measurements; (iii) performed FeNO measurements in line with international recommendations; and (iv) identified the type of NO analyser used.

Studies were excluded if they (i) recruited < 25 healthy non-Caucasian subjects; (ii) included individuals with chromosomal or other genetic conditions; or (iii) performed offline FeNO measurements.

Study Selection and Data Extraction

Two authors (TB and MM) independently reviewed the searches. Potentially relevant studies were identified from titles, abstracts, and/or descriptions and then retrieved for full review. We also conducted searches of bibliographies to identify additional studies. The

authors then independently selected trials for inclusion from the full text using specific criteria. A third person (AC) was available to adjudicate any disagreement.

Data was extracted in duplicate from each study and included: study location and population source, number of participants and age range, medical history, smoking status/history, analyser used, exclusion criteria, statistical model used, factors examined and found significant, and measured FeNO levels. The source of clinical information was noted if available. For example, it was noted whether atopy was recorded via clinical history only, self-reported on questionnaires or via formal laboratory testing (immunoglobulin E (IgE)).

Statistical Analysis

Where possible, the geometric mean and the standard deviation of FeNO were obtained for each population. Assuming that FeNO is log-normally distributed, we estimated the 5^{th} and 95^{th} percentiles for each population making use of the relationship between the standard deviation (SD) on the original scale, the standard deviation on the log scale (sigma) and the geometric mean, i.e. SD^2 = (exp(sigma^2) - 1)*exp(2*log(geomean)+sigma^2). All statistical analysis was performed by a statistician (MC) with Stata13 software.[25]

RESULTS

The search identified 62 potential studies (26 in PubMed, 1 in Cochrane, 20 in Scopus and 15 in Web of Science). After title and abstract screening, 11 publications were retrieved for full text review. Two studies were further excluded as they did not contain sufficient FeNO data

to comment on. Screening of reference lists identified three studies to be included in the review. This resulted in 12 articles for inclusion. Reasons for paper exclusions are shown in figure 1.

Study Characteristics

Of the 12 studies, one (8%) study only recruited children (<12 years), one (8%) study only recruited adolescents (12-18 years), five (42%) studies included children and adolescents (12-18 years) as a grouped sample, four (33%) studies focused solely on adults, and one study (8%) included all ages. There were 16 different ethnic populations (children or adults) studied representing 11 ethnicities (Hispanic, African-American, African-Canadian, North-African Arab, Pacific Islander/Maori, Japanese, Korean, Chinese, Taiwanese, South-Asian (in England), and Asian-Canadian). All participants were selected from schools or the general population.

The studies differed greatly in the type and extent of information obtained. The sample size of the ethnic populations ranged from 31[26] to 1798.[27] Atopy was assessed objectively in seven (58%) studies using skin prick test and/or IgE levels. Three (25%) studies relied on questionnaire data only, while two (17%) studies sought no information regarding atopy. Respiratory history and/or current health were assessed by respiratory examination in two (17%) studies, spirometry and clinical examination and/or questionnaire in four (33%) studies and questionnaires alone in three (25%) studies. Smoking status was collected for all of the included studies.

There was a variety of approaches used in the studies to statistically examine potential determinants of FeNO values. Multiple linear regression (MLR) was the predominant analysis method used (n=9, 75%). Exclusion criteria used in the studies varied and included known respiratory disease/illness diagnosis (n=11, 92%); presence of other chronic diseases, asthma and/or atopy (n=6, 50%); premature birth (n=3, 25%); and smoking history (n=2, 17%). The characteristics of the included studies are outlined in table 1.[19,26-36]

Table 1: Description of studies included in review

Study/Year	Ethnic group (Location)	Total Sample Size	Age Range (n=)	Medical History; Other Data	Analyser Used	Exclusion Criteria	Statistical Model	Factors Influencing* FeNO
Baptist et al. 2015[28]	African-American (USA)	128	7-18 (72)	Questionnaire (atopy, history); skin prick test, spirometry	NIOX MINO	Respiratory disease (other than asthma), cardiac conditions	MLR, logistic regression	Ethnicity, atopy, spirometry results, asthma
Brody et al. 2013[27]	African-American (USA) Hispanic (USA)	4718 (combined)	6-11 (216) 12-19 (224) 20-79 (489) 6-11 (446) 12-19 (356) 20-79 (996)	Clinical history, respiratory exam	NIOX MINO	Asthma, respiratory symptoms or disease	Univariate and multiple regression (logFeNO)	Ethnicity, age, height, time of testing, ECP
Ko et al. 2013[29]	Chinese (China)	1113	18-90 (1093)	IgE, skin prick test	Sievers NOA280i	Respiratory disease	MLR (logFeNO)	Ethnicity, sex, age, height, skin test atopy, IgE, ECP
Rouatbi et al. 2012[30]	North African Arab (Tunisia)	354	6-16 (211)	Questionnaire (atopy, history), clinical history	Medisoft HypAir	Respiratory disease, atopic conditions, premature birth, other chronic conditions	Univariate and multiple regression	Ethnicity, spirometry results
Yao et al. 2012[31]	Taiwanese (Taiwan)	1717	5-18 (693)	IgE, respiratory exam	EcoMedics CLD88sp	Respiratory disease, atopic conditions, premature birth, other chronic conditions	Univariate and multivariate analysis (logFeNO)	Ethnicity, age, height, BSA, spirometry results, IgE, ambient NO, atopy, time of testing, drinking water
Sonnappa et al. 2011[26]	South-Asian (England)	68	4-7 (31)	Clinical history, respiratory exam; skin prick test, spirometry	EcoMedics CLD88sp	Respiratory disease, atopic conditions, premature birth, other chronic conditions	Univariate, MLR	Ethnicity, skin test atopy

Matsunaga et al. 2010[32]	Japanese (Japan)	240	18-74 (197)	Questionnaire (atopy)	NIOX MINO	Respiratory disease, atopic conditions, smoking	Regression tree based model (logFeNO)	Nil
Kim et al. 2010[33]	Korean (Korean)	263	20-68 (166)	Questionnaire (atopy, history); skin prick test, spirometry	Sievers NOA280i	Smoking, asthma, respiratory illness, recent airway infection	MLR	Ethnicity, sex, atopy,
Levesque et al. 2008[34]	African-American (USA)	994	18-40 (895)	Questionnaire (respiratory); IgE, CRP	Sievers NOA280i	Asthma, respiratory symptoms or disease, other chronic conditions	Univariate, MLR (logFeNO)	Ethnicity, sex, current URI symptoms, IgE, ECP
Kovesi et al. 2008[35]	African-Canadian (Canada) Asian-Canadian (Canada)	2298 (combined)	9-13 (32) 9-13 (70)	Questionnaire (ARI); Spirometry	EcoMedics CLD88sp	Respiratory illness, asthma, other chronic diseases	Univariate and multivariate analysis (logFeNO)	Ethnicity, age, height
Edwards et al. 2005[36]	Pacific Island/Maori (New Zealand)	164	5-17 (76)	Questionnaire (atopy, history); IgE, skin prick test	Model LR 2000	Respiratory disease	Logistic and linear regression	Nil
Wong et al. 2005[19]	Chinese (China)	531	12-18 (258)	Questionnaire (atopy)	NIOX MINO	Nil	Student t-test, Spearman's rank correlation (logFeNO)	Ethnicity, sex

(n=) value in Age Range column represents the final size of each ethnic population tested after exclusion criteria was applied to the total sample size.

ARI: acute respiratory infection: **BSA:** body surface area; **CRP:** C-reactive protein; **ECP:** eosinophil cationic protein; **FeNO:** fractional exhaled nitric oxide; **IgE:** immunoglobulin E; **MLR:** multiple linear regression; **NO:** nitric oxide; **URI:** upper respiratory infection; **USA:** United States of America; ***:** influencing or having significant association.

The influence of ethnicity of FeNO levels

FeNO results were predominately reported as either the arithmetic (n=6, 50%) or geometric (n=5, 42%) means. One study (8%) reported the median FeNO result. The influence of ethnicity on FeNO reported by the studies was determined by comparing results i) directly with Caucasian participants recruited at the same time[19,26,27,35,36] or ii) indirectly using previously published Caucasian studies[9,14,37] chosen by the study (table 2). Ethnicity was considered a significant determinant of FeNO values in ten of the 12 studies (83%). Nine (75%) studies found their healthy (non-Caucasian) ethnic groups to have increased FeNO levels when compared to Caucasian results. Only the study of North African Arab children[30] found that measured FeNO values for their group were decreased compared to Caucasian data. The studies conducted by Matsunaga *et al.*[32] and Edwards *et al*.[36] found no difference between their populations (Japanese and New Zealand Pacific Islander/Maori respectively) and comparable to Caucasian results. There was however a large variation in the differences observed, table 2. For example, in Kovesi *et al's.*[35] study the arithmetic mean FeNO level was 12.7 ppb in Caucasian children, whereas African-Canadian children had higher levels at 17.4 ppb, and Asian-Canadian children had even higher levels at 22.8 ppb. Findings were similar for adults, where Ko *et al.*[29] measured geometric mean FeNO levels of 16.6 ppb in Caucasians and 32.6 ppb in Taiwanese adults.

Other factors that significantly influence FeNO levels

Atopic status (as defined by skin prick test) was found to be a significant factor in five (42%) studies while height, age, and sex were significant in four (33%) studies each. Other significant factors identified included spirometry values, IgE, and ECP levels in three (25%)

studies each; time of testing in two studies (17%); body surface area (BSA), drinking of water prior to testing, and ambient NO in one (8%) study each.

Table 2: FeNO result variation of ethnic populations against Caucasian data

Study	Mean (ppb)			Comparative Study (pbb)		Difference Observed (ppb)
Baptist et al. 2015[28]	African-American		19.3†	Not specified		N/A
Brody et al. 2013[27]	African-American	6-11 yr	10.7‡	Caucasian* (n=1748)	7.6	+3.1
		12-19 yr	14.7‡		11.2	+3.5
		20-79 yr	13.9‡		14.1	-0.2
	Hispanic	6-11 yr	8.6‡		7.6	+1
		12-19 yr	12.1‡		11.2	+0.9
		20-79 yr	13.6‡		14.1	-0.5
Ko et al. 2013[29]	Chinese		32.6‡	Olin et al. 2006[14]	16.6	+16
Rouatbi et al. 2012[30]	North African Arab		5·0†	Malmberg et al. 2003[37]	11.9	-6.9
Yao et al. 2012[31]	Taiwanese		13.7‡	Malmberg et al. 2003[37]	11.9	+1.8
Sonnappa et al. 2011[26]	South-Asian		6.3†	Caucasian* (n=37)	4.6	+1.7
Matsunaga et al. 2010[32]	Japanese		15.4‡	Travers et al. 2007[9]	17.9	-2.5
Kim et al. 2010[33]	Korean		30.7‡	Olin et al. 2006[14]	16.6	+14.1
Levesque et al. 2008[34]	African-American		20.4‡	Travers et al. 2007[9]	17.9	+2.5
Kovesi et al. 2008[35]	African-American		17.4†	Caucasian* (n=559)	12.7	+4.7
	Asian-Canadian		22.8†			+10.1
Edwards et al. 2005[36]	Pacific Islander		6.3§	European* (n=58)	5.1	+1.2
Wong et al. 2005[19]	Chinese		19.9†	Caucasian* (n=33)	12.7	+7.2

The comparative studies were either previously published Caucasian studies chosen by the study, or Caucasian participants recruited at the same time as the ethnic group.*

n=: number of Caucasian participants recruited; **ppb:** parts per billion; **†:** arithmetic mean; **‡:** geometric mean; **§:** median

Clinical implications based on current reference ranges

To better understand potential differences between the ethnic groups, we estimated the 5th and 95th percentiles for all studies involving children (figure 2) and adults (figure 3). As mentioned, five of the paediatric studies included both children (<12 years) and adolescents (12-18 years) and did not report separate values for these age groupings. Therefore these results could not be readily interpreted according to the current interpretation guidelines[2] which group children (<12 years) separately to a combined adolescent (>12 years) and adult group. As seen in figures 2 and 3, the geometric means of ten of the non-Caucasian populations (adults and children) were placed within the normal/healthy cut-off range. The geometric mean values for Chinese[29] and Korean adults however fell into the intermediate range. After estimating the 95th percentile of FeNO, we found 5% of recruited participants in three studies (Hispanic children and adults,[27] African-American adults,[27] and Japanese adults) to have FeNO results in the age-specific intermediate range. Interestingly, we found a further five studies (African-American children,[27] African-American adults,[34] Korean adults, and Chinese adults[19,29]) where >5% of the population had FeNO results in the age-specific inflammatory range.

DISCUSSION

Given the growing importance of FeNO as a diagnostic[38] and monitoring tool[2], we undertook a systematic review to determine the influence (if any) of ethnicity on FeNO results and the consequent impacts on clinical interpretation. We identified 12 relevant studies, of which 10 found ethnicity to influence FeNO levels in healthy children and/or adults. The studies represented 16 populations from eleven ethnicities. While the geometric means of FeNO for 10 of the non-Caucasian populations were within the normal/healthy FeNO range as recommended by the ATS,[2] the FeNO means in two populations were outside the normal/healthy range. Furthermore, we found five studies (figures 2 and 3) where greater than 5% of the study's sampled population had FeNO levels in the inflammatory range despite these individuals being healthy and free of atopy. In these individuals, their FeNO results indicate the presence of eosinophilic airway inflammation i.e. abnormal. Thus, our systematic review's findings may be of clinical significance when interpreting the presence or absence of inflammation during the evaluation of individual patients as well as in research studies.

This is the first systematic review to focus specifically on the influence of ethnicity on FeNO values. A recent systematic review[13] that explored FeNO normal/reference values and possible influencing factors (such as age, sex, height, weight, smoking status, race and atopy) only identified three studies where ethnicity influenced FeNO values on non-Caucasian populations. Two of these studies are included in our review, and the third was not included due to recruitment of patients with asthma and allergic conditions. However, this paper also reported higher FeNO values for Asian-Canadian and African-Canadian

children when compared to Caucasian participants.[39] This review did not comment on the differences observed in FeNO results between the different ethnic groups.

We identified two populations[29,33] with geometric means of FeNO values in the intermediate range of Caucasian data. Furthermore, by calculating the 95th percentile, we also identified three populations[27,32] with >5% of values in the intermediate range and five populations[19,27,29,33,34] with >5% of values in the inflammatory range of current ATS guidelines[2] which is based predominantly on Caucasian data. Additionally, four[28,31,35,36] of the five studies (figure 2) that reported combined values from different age groups, had 95th percentiles higher than the normal healthy cut-off ranges[2] for both children and adults.

Using STATA software, we also estimated the proportion of participants from each study that would be classified as having elevated results (above the inflammatory cut-off values) based off the current ATS[2] guidelines (table 3). These patients would be classified as having abnormal results and would likely prompt further treatment and/or investigation. Based on these results we then estimated the number of participants from each study that may be misclassified (either normal or abnormal results) according to current ATS[2] guidelines. For the studies involving children, the Asian-Canadian[35] and African-American[28,35] populations had the highest proportion of participants with results in the inflammatory range. Similarly for adults, studies involving Chinese,[29] Korean[33] and African-American[34] participants had the highest proportion of participants with results in the inflammatory range.

The proportion of participants possibly misdiagnosed is therefore high in these populations (greater than 10% in some studies[29,35]) suggesting that current Caucasian cut-off ranges[2]

may be too low for accurate use in some ethnic groups. These observations highlight the need for further studies in non-Caucasian populations to determine if Caucasian-based cut-off reference ranges are clinically applicable for detecting the presence of eosinophilic inflammation.

Table 3: Clinical implications for interpretation based on current ATS guidelines[2]

	Estimated % of study participants above the ATS defined inflammatory range (≥ 35ppb for child studies, ≥ 50ppb for adult studies)	Estimated % of study participants that may be misclassified according to current guidelines	Estimated % of study participants greater than the 95th percentile that may be normal
Child studies			
South-Asian [26]	0.2%	4.8% ‡	96%
Hispanic [27]	1.3%	3.7% ‡	74%
African-American [27]	4.7%	0.3% ‡	6%
" [28]	10.1%	5.1% †	0% §
" [35]	11.1%	6.1% †	0% §
Asian-Canadian [35]	17.3%	12.3%†	0% §
Taiwanese [31]	7.7%	2.7% †	0% §
Pacific-Islander [36]	2%	3% ‡	60%
North-African [30]	-	-	-
Adult studies			
Hispanic [27a]	2.1%	2.9% ‡	58%
" [27b]	3.4%	1.6% ‡	32%
African-American [27a]	1.9%	3.1% ‡	62%
" [27b]	2.3%	2.7% ‡	54%
" [34]	10.8%	5.8% †	0% §
East-Asian [29]	20%	15% †	0% §
" [33]	10.9%	5.9% †	0% §
" [19]	6.1%	1.1% †	0% §
" [32]	0.3%	4.7% ‡	94%

All results were estimated using STATA software. For all studies results show (i) proportion of participants above the ATS defined inflammatory range, (ii) proportion of participants that may be misclassified according to current guidelines, and (iii) proportion of participants with FeNO results greater than the study defined 95th percentile that may be normal.

†: proportion of participants classified as inflammatory but may be normal

‡: proportion of participants classified as normal but may be inflammatory

§: 95th percentiles are already in the respective inflammatory ranges and therefore participants with FeNO values greater than this are considered abnormal

FeNO values of healthy individuals in a number of ethnic groups appear to be higher than Caucasian values. The mechanism by which ethnicity influences FeNO levels of healthy children and adults are still largely unknown. It is possible that there are differences between ethnic groups in the activity of NO synthase (the enzyme essential for NO

production) and in allele frequencies of the NO synthase genes.[40-42] Other contributing factors may include complex interactions between genetic and biological, and/or environmental factors i.e. diet, second hand smoking, air pollution, and socioeconomic status.[16,17,34,43] None of these potential factors have been adequately tested in either Caucasian or non-Caucasian populations and preliminary results are inconsistent and require further investigation.

Current ATS guidelines[2] only recommend FeNO cut-off ranges to be adjusted for age despite evidence showing other potential factors that may influence results. Clinicians are expected to follow these guidelines when treating patients (Caucasian or non-Caucasian) without consideration of ethnicity, atopy status, diet, geographical location, and other socio-economic factors. The importance of our findings relate to the implications of using the recommended ATS cut-offs[2] when evaluating patients clinically or in research studies. For example, the United Kingdom based National Institute for Health and Care Excellence (NICE) recommended that "FeNO testing is used to help diagnose asthma in adults and children when the diagnosis is unclear". Also, a recent systematic review on the use of FeNO for diagnosing asthma did not consider ethnic factors and suggested that a cut-off of >50 ppb guarantees sufficient positive predictive value for ruling in the presence of asthma.[38] Given that this value is less than the 95th percentile for healthy people in eight populations (figures 2 and 3), use of such cut-offs without any ethnic consideration may result in the over treatment of patients with corticosteroids that could result in side-effects without any benefit. We therefore consider that it is appropriate to investigate how applicable the current Caucasian based FeNO cut-off ranges are to other ethnic populations.

Our findings suggest that, in the presented non-Caucasian groups, it may be incorrect to use the current ATS cut-off values to interpret the presence of inflammation and that doing so could lead to inappropriate diagnosis of disease and negatively impact treatment plans. Future studies should also be mindful of the current age differentiating cut-off points as recommended by the ATS[2] when analysing and reporting results.

Limitations

This systematic review is limited to 12 studies and only includes 11 ethnic groups. Asian and African ethnicities were the best represented non-Caucasian groups. The differences between the studies in terms of methodology and reporting of results affected our ability to make direct comparisons between the studies. For uniformity, all FeNO results were compared with current ATS guidelines.[2] Despite our efforts it was not possible to examine the effect on interpretation for five paediatric studies as the data was not reported separately as per ATS guideline[2] age groupings. Also, our estimated 95th percentile assumes that FeNO data are log-normally distributed. If however the reported data is positively skewed, then our estimate will be an underestimate. Also, there were insufficient studies for us to take into account the possible effect of FeNO analysers used.

CONCLUSION

This is the first systematic review to explore ethnicity as an influencing factor on FeNO. We have shown that ethnicity does influence FeNO levels. The effect of ethnicity was found to be small in some groups with no impact on clinical interpretation. However in other groups (African- and Asian-Canadian, African-American, Taiwanese, Korean and Chinese) ethnicity may potentially have clinical significance. In these groups, >5% of normal healthy children

and adults without atopy had FeNO values above the 'normal' Caucasian range, thus making it inappropriate to use the current Caucasian ATS cut-off values for clinical interpretation on these ethnic groups. Establishing normal, intermediate and inflammatory ranges for FeNO levels for non-Caucasian ethnicities is crucial to ensuring that the presence of inflammation can be adequately defined. This will ensure that FeNO measurements are clinically beneficial.

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TB and MM contributed to reviewing articles for inclusion and interpretation of results. Where necessary, AC resolved any conflict regarding inclusion. TB contributed to preparation of the manuscript as well as the design of figures and tables. AC and MM provided guidance throughout this process and major editing of first drafts. MC performed all statistical analysis and generated graphs. AC, MC, HP, LR, DH, MB and MM edited this review. All authors agreed on the final version before submission.

FIGURE LEGENDS

Figure 1: **PRISMA flow chart of included/excluded articles for FeNO systematic review**

Figure 2: **Distribution of FeNO (geometric mean and estimated 5th and 95th percentiles) for non-Caucasian samples of children (<12 years)**

Figure 2:

Numbers on graph refer to reference number within the review. Vertical lines (at 20 and 35 ppb) shown for three studies display clinical cut-off points based on the current ATS guidelines for children (<12years old) where ≤20ppb is considered normal, 21-34ppb considered intermediate, and ≥35ppb considered inflammation present.[2] Remaining studies reported combined values for children (<12 years) and adolescents (12-18 years old) and therefore cannot be interpreted using current interpretation guidelines. The size of the marker of the geometric mean (■) is proportional to the sample size. Figure shows that more than 5% of healthy children in two studies had FeNO results above the normal healthy range.

Figure 3: **Distribution of FeNO (geometric mean and estimated 5th and 95th percentiles) for non-Caucasian samples of adults (>12 years)**

Figure 3:

a; 12-19 years: b; >20 years

Numbers on graph refer to reference number within the review. Vertical lines (at 25 and 50 ppb) show clinical cut-off points based on the current ATS guidelines where ≤25ppb is considered normal, 26-49ppb considered intermediate, and ≥50 ppb considered

■

inflammation to be present.[2] The size of the marker of the geometric mean ( ) is proportional to the sample size. Figure shows that more than 5% of healthy adults in all of the studies had FeNO results above the normal healthy range.

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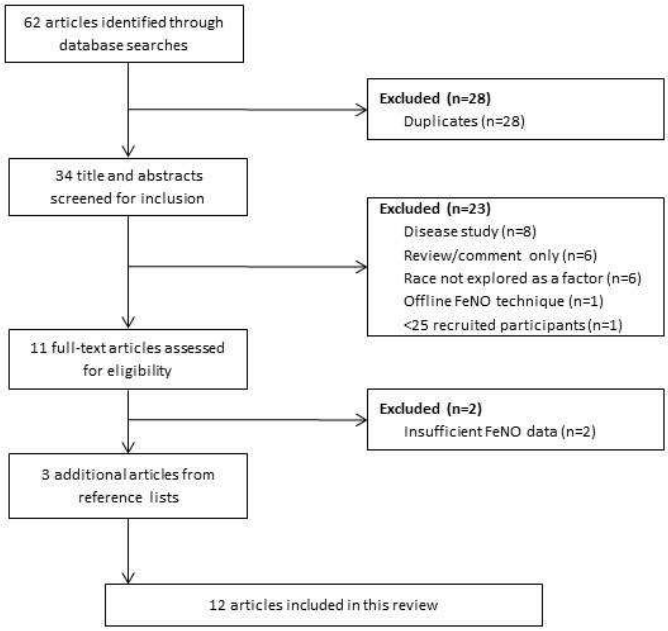

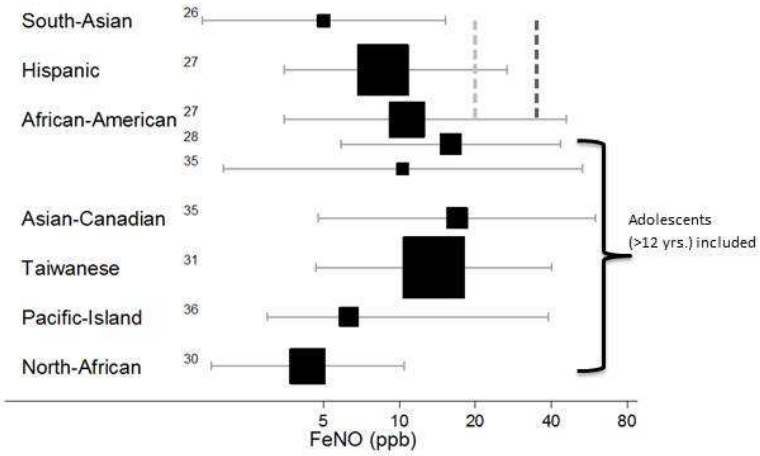
South-Asian
26
Hispanic
27
African-American
27
28
35
Asian-Canadian
35
Taiwanese
31
Pacific-Island
36
North-African
30
Adolescents
(>12 yrs.) included
5
10
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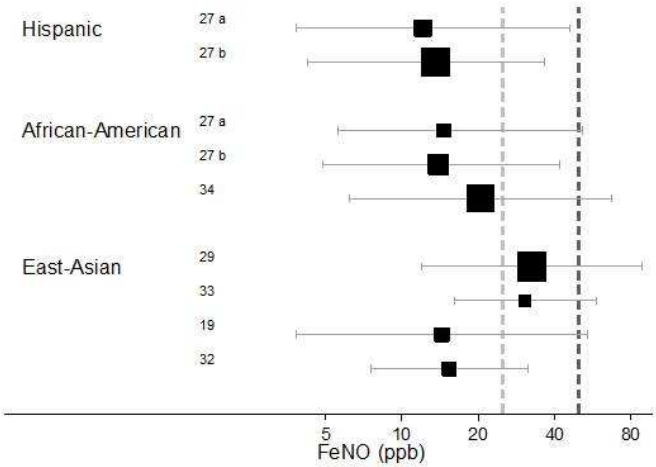
40
80
FeNO (ppb)


Hispanic
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FeNO (ppb)