Determinants of, and reference equation for, exhaled nitric oxide in the Chinese population

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ABSTRACT Measurement of fractional exhaled nitric oxide concentration (*F*eNO) has been proposed as a useful biomarker for monitoring and management of airway diseases. Limited information is available regarding reference levels of *F*eNO levels in Chinese adults. This study aimed to investigate the reference equation and determinants of *F*eNO in Chinese adults.

1093 (577 males) healthy nonsmoking subjects aged 18–90 years were recruited. *F*eNO was measured online using a chemiluminescence analyser. Other assessments included spirometry, skin prick tests, total serum IgE levels and eosinophil count in peripheral blood.

The geometric mean *F*eNO was 32.6 (95% reference interval (RI) 31.4–33.7) ppb for all subjects. *F*eNO values were higher in males than females (geometric mean (95% RI) 38.3 (36.5–40.2) ppb *versus* 27.1 (25.8–28.5) ppb, $p<0.0001$), and in atopic than nonatopic subjects (34.6 (33.0–36.3) ppb *versus* 29.8 (28.3–31.4) ppb, $p<0.0001$). *F*eNO correlated with age ($r^2=0.23$), height ($r^2=0.20$), IgE level ($r^2=0.18$) and percentage eosinophil count ($r^2=0.18$) (all $p<0.0001$), but not with spirometric parameters. Based on multiple regression modelling, the reference equation of *F*eNO value was:

$\log(FeNO) = 0.781 + 0.104(\text{sex}) + 0.004(\text{age}) + 0.084(\text{atopy}) + 0.003(\text{height in cm})$, where for sex 1=male and 0=female, age is measured in years, for atopy 1=atopic and 0=nonatopic, and height is measured in cm.

The *F*eNO of Chinese adults is higher than that of the Caucasian population, and is affected by age, sex, height and atopic status. This study provides useful references for the interpretation of *F*eNO.

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Exhaled NO fraction in Chinese adults is higher than in Caucasians, and is affected by age, sex, height and atopy http://ow.ly/l5mNR

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Introduction

Noninvasive assessment of airway inflammation has been a popular research topic in recent years. Assessment of biomarkers in exhaled breath, such as fractional exhaled nitric oxide concentration (*F*eNO) or biomolecules in the exhaled breath condensate, is entirely noninvasive and has great potential for serial monitoring of airway inflammation [1]. There is a growing body of literature on *F*eNO measurement. As *F*eNO measurement becomes more important and popular, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have published guidelines for the measurement of *F*eNO [2, 3]. *F*eNO was first demonstrated to be significantly elevated in subjects with asthma two decades ago [4]. Treatment of asthma with inhaled corticosteroids could reduce *F*eNO in asthmatics [5]. *F*eNO correlated with other markers of inflammation such as peripheral blood eosinophil count and eosinophil cationic protein level [6, 7]. Some studies have demonstrated that *F*eNO measurement might be useful for the diagnosis of asthma in adults [8, 9]. *F*eNO measurement has also been investigated in the treatment algorithm for asthma. However, randomised controlled algorithm asthma control trials revealed equivocal benefits when adding *F*eNO measurement to the routine guideline management including spirometry [1, 10].

Correct interpretation of *F*eNO value is important when applying this tool for assessment of airway inflammation. Previous studies on reference values of *F*eNO in the general population were mainly limited to children [11–13]. There are limited data on the reference value of *F*eNO in the adult population [14–18], and there is very limited information on *F*eNO in a healthy, nonsmoking Chinese population. *F*eNO is a promising noninvasive marker for the assessment of airway inflammation, especially for asthma. Understanding *F*eNO in the normal population and factors that may affect its level can improve our understanding of the role of *F*eNO in the clinical management of respiratory diseases. The aim of this study was to establish a reference equation of *F*eNO in a large healthy Chinese adult population.

Methods

Subject recruitment

This was a cross-sectional observational study in which *F*eNO was measured in healthy Chinese adults in Hong Kong. Subjects were recruited by advertisements posted at the Chinese University of Hong Kong, Prince of Wales Hospital (Hong Kong, China) and newspapers. Subjects aged between 18 and 90 years who had expressed interest in this study were stratified into different age groups and randomly selected to participate in the study so that each age group of both sexes would have a similar number of subjects. All subjects were not current smokers. Previous smokers must have stopped smoking for at least 1 year with a smoking history of $<$10 pack-years. Subjects with a history of chronic respiratory diseases like asthma, chronic obstructive pulmonary disease, bronchiectasis, previous lung surgeries, chronic cough and sputum and wheeze over the past year were excluded. The study was approved by the ethics committee of the Chinese University of Hong Kong (approval number: CRE-2006.438) and informed consent was obtained from each subject.

FeNO measurement

*F*eNO was measured in the morning (between 09:00 h and 11:00 h) before spirometry. *F*eNO was measured online using a chemiluminescence analyser (NOA 280i; Sievers Instruments, Boulder, CO, USA) according to ATS/ERS recommendations [2]. Subjects were in the sitting position (with no nose clip); they exhaled to residual volume, inserted a mouth piece, inhaled to total lung capacity, and then exhaled for 10 s at a constant flow rate of 50 mL·s^{-1}. The measurement was repeated until three *F*eNO values varied $<$10% or two values varied $<$5%. The mean *F*eNO (in ppb) was then recorded. All subjects had to refrain from strenuous physical activity or exercise for $\geqslant$30 min prior to *F*eNO measurement. In addition, subjects avoided eating for 1 h and caffeine ingestion for 6 h before the test. Subjects were not tested within 4 weeks of an upper or lower respiratory tract infection.

Spirometry

Spirometry (pre- and post-bronchodilator) was performed using the MicroLab 3300 spirometer (CareFusion, Basingstoke, UK), according to the ATS standards [19].

Skin prick test

Allergen skin prick test was performed on the volar aspect of forearm using a panel of eight common aeroallergens according to standard methods [20]. A wheal size 3 mm larger than negative control 15 min after skin prick was considered a positive test. Allergens including *Dermatophagoides pteronyssinus* and *D. farinae*, house dust, cockroach, *Cladosporidium*, Bermuda grass, cat fur and dog hair (ALK-Albelló, Hørsholm, Denmark) were used.

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Blood test

Peripheral blood was taken for measurement of eosinophil count and total IgE level.

Statistical analysis

Data were categorised and analysed using the Statistical Package for Social Sciences (SPSS) for Windows release 17.0 (SPSS Inc., Chicago, IL, USA). *F*eNO values were log-transformed before analysis. *F*eNO is presented as geometric mean and 95% reference interval (RI) (RI was calculated by exponentiating the reference limit obtained from the log-transformed data) and median with interquartile range, as appropriate. The associations between *F*eNO and anthropometric measurements, spirometric variables and atopic status were assessed by multivariate linear regression and Spearman correlations. The reference equation was computed by multiple linear regression modelling. From the predictors selected *a priori*, the variables for the final regression model were chosen using backward stepwise regression analysis. The upper 95% cut-off limits were calculated from the regression model based on the whole population, taking into account age, sex, height and atopic status of the subjects using mid-class values in the group. All comparisons were made two-sided, and p-values <0.05 were considered significant.

Results

In total 1113 subjects were recruited for this study. Among these subjects, 1093 (98.2%) were able to perform satisfactory *F*eNO measurement (*i.e.* able to maintain the flow rate or produce reproducible results) and were included in the final analyses. Among those 20 subjects (six males and 14 females) who could not perform satisfactory *F*eNO measurement, nine (45%) and four (20%) were aged >60 and >70 years, respectively. In the 1093 subjects with satisfactory *F*eNO measurement, 24 (2.2%) had bronchodilator reversibility in the spirometry examination, and only two subjects (0.2%) had post-bronchodilator forced expiratory volume in 1 s <80% predicted normal. The demographic characteristics of the subjects are shown in table 1.

The geometric mean *F*eNO was 32.6 (95% RI 31.4–33.7) ppb. The range of *F*eNO was 4.2–315 ppb. *F*eNO value was higher in males than females (geometric mean (95% RI) 38.3 (36.5–40.2) ppb *versus* 27.1 (25.8–28.5) ppb, $p<0.0001$) and higher among atopic when compared with nonatopic subjects (34.6 (33.0–36.3) ppb *versus* 29.8 (28.3–31.4) ppb, $p<0.0001$). *F*eNO correlated with age ($r^2=0.23$, $p<0.0001$), height ($r^2=0.20$, $p<0.0001$), IgE level ($r^2=0.18$, $p<0.0001$) and percentage eosinophil count ($r^2=0.18$, $p<0.0001$). However, *F*eNO had no correlation with spirometric parameters. We entered parameters that had significant correlations with *F*eNO into a multivariate linear regression model, and found that sex, age, height, atopic status, serum IgE level and blood percentage eosinophil count were independently associated with *F*eNO value (table 2).

By putting the demographic parameters, including age, sex and height, together with atopic status by skin prick test, into a multiple linear regression modelling, the reference equation of *F*eNO in our Chinese adults is as follows:

$$\log(F\text{eNO}) = 0.781 + 0.104(\text{sex}) + 0.004(\text{age}) + 0.084(\text{atopy}) + 0.003(\text{height})$$

where for sex 1=male and 0=female, age is measured in years, for atopy 1=atopic and 0=nonatopic and height is measured in cm. The intercept value was 0.78, r^2 was 0.144 and residual SD was 0.24.

Using this reference equation, we calculated the upper 95% cut-off limits for *F*eNO, according to height and age (using the mid-class values). The data are presented in table 3 and the corresponding graphic presentation is shown in figure 1 for both atopic and nonatopic subjects.

Discussion

This has been the first large scale study assessing the *F*eNO value in the Chinese adult population. We have developed a reference equation for prediction of *F*eNO value in this population. We have shown that sex, age, height and atopic status by skin prick tests were determinants of *F*eNO.

Reference ranges for *F*eNO measured in accordance with the current ATS/ERS standards have been reported previously in children [11–13, 17]. There were studies that assessed the reference equations of *F*eNO in healthy adults and, among these studies [14–18], only one involved healthy nonsmoking adults as in our study [14]. Many studies involved subjects who were current smokers or ex-smokers, with airway diseases or respiratory tract infections [15, 16, 18, 21, 22]. For example, a study from Germany included current smokers, asthma subjects and subjects with respiratory tract infections (in 24.3%, 3.8% and 20.2%, respectively, among the 897 subjects) [15]. Other large-scale studies from Sweden [21] and Germany [18] measured *F*eNO values in >2000 and >1000 subjects, respectively. In these studies, subjects with physician-diagnosed asthma or those on inhaled steroids [21], or smokers or patients with

TABLE 1 Demographics of the subjects

	Mean ± SD	Median (interquartile range)	n (%)
Age years			
All	47.3 ± 16.6	48 (27.0)	1093 (100)
18–30			216 (19.8)
31–40			190 (17.4)
41–50			188 (17.2)
51–60			208 (19.0)
61–70			196 (17.9)
71–90			95 (8.7)
Sex			
Male			516 (47.2)
Female			577 (52.8)
Height cm	162.5 ± 8.8	163.0 (13.0)	
BMI kg·m^{-2}	24.0 ± 3.7	23.6 (5.1)	
Atopy			
Positive			645 (59.0)
Negative			444 (40.6)
Pre-bronchodilator FEV_1 L	2.76 ± 0.77	2.72 (1.09)	
Pre-bronchodilator FVC L	3.12 ± 0.85	3.04 (1.21)	
Pre-bronchodilator FEV_1/FVC ratio %	88.72 ± 6.27	89.29 (7.39)	
Pre-bronchodilator FEV_1 % predicted	104.42 ± 14.18	104.72 (122.29)	
Pre-bronchodilator FVC % predicted	95.49 ± 13.68	96.15 (94.61)	
Post-bronchodilator FEV_1 L	2.82 ± 0.77	2.77 (1.07)	
Post-bronchodilator FVC L	3.15 ± 0.84	3.06 (1.19)	
Post-bronchodilator FEV_1/FVC ratio %	89.78 ± 6.23	90.19 (7.61)	
Post-bronchodilator FEV_1 % predicted	106.79 ± 13.87	107.15 (123.65)	
Post-bronchodilator FVC % predicted	96.57 ± 13.04	97.31 (96.90)	
Total IgE kIU·L^{-1}	151.6 ± 393.4	48.0 (122.0)	
Eosinophil count %	2.8 ± 2.1	2.0 (3.0)	
Eosinophil count ×10^9·L^{-1}	0.188 ± 0.196	0.100 (1.300)	

BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

respiratory infections were included [18]. A very recent study from the USA reported the F_{ENO} value in >13 000 subjects aged 6–80 years [16]. This study involved children, adults, smokers, subjects with asthma and subjects on asthma medications. Subjects with self-reported asthma or wheezing, or who had prescriptions for asthma/wheezing in the past 12 months, were excluded when normal values and thresholds were calculated. Since the prediction model equations in this study were derived for age groups of 6–11 years and 12–80 years, teenagers <18 years of age were also included in the older age group [16].

When compared with the Caucasian population, adult Chinese subjects had a higher geometric mean F_{ENO} value. Table 4 summarises the comparison of F_{ENO} of normal adults without known lung diseases between different populations. Compared with the study performed in Sweden by OLIN *et al.* [14] with 1131 subjects,

TABLE 2 Multivariate linear regression of factors associated with fractional exhaled nitric oxide concentration (F_{ENO}) value in healthy subjects

	β coefficients (95% CI)	Ratio of mean F_{ENO} (95% CI)	p-value
Sex	**0.085 (0.044–0.127)**	**1.216 (1.107–1.340)**	**<0.001**
Age per year	0.004 (0.003–0.005)	1.009 (1.007–1.012)	<0.001
Atopic status by skin test	0.039 (0.005–0.072)	1.094 (1.012–1.181)	0.023
Height per cm	0.003 (0.001–0.005)	1.007 (1.002–1.012)	0.014
Log IgE per kIU·L^{-1}	0.051 (0.025–0.076)	1.125 (1.059–1.191)	<0.001
Eosinophil percentage per %	0.016 (0.009–0.023)	1.038 (1.021–1.054)	<0.001

n=1093.

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TABLE 3 95% upper limits of fractional exhaled nitric oxide concentration (*F*eNO) (ppb) according to classes of height, age, sex and atopy calculated as mid-class values among 1093 healthy subjects

	Age years											
	18–30		31–40		41–50		51–60		61–70		71–90	
Male												
Atopy	+	-	+	-	+	-	+	-	+	-	+	-
Height cm												
<150	28.5	23.5	31.9	26.3	34.9	28.8	38.3	31.6	40.0	34.7	48.3	39.9
150–159.9	30.3	25.0	33.9	28.0	37.2	30.7	40.8	33.6	44.7	36.9	51.4	42.4
160–169.9	32.3	26.6	36.1	29.8	39.6	32.6	43.4	35.8	47.6	39.3	54.7	45.1
170–179.9	34.3	28.3	38.4	31.7	42.1	34.7	46.2	38.1	50.6	41.8	58.2	48.0
⩾180	36.5	30.1	40.8	33.7	44.8	36.9	49.1	40.5	53.9	44.5	61.9	51.1
Female												
Atopy	+	-	+	-	+	-	+	-	+	-	+	-
Height cm												
<150	22.5	18.5	25.1	20.7	27.5	22.7	30.2	24.9	33.1	27.3	38.0	31.4
150–159.9	23.9	19.7	26.7	22.0	29.3	24.2	32.1	26.5	35.2	29.1	40.5	33.4
160–169.9	25.4	21.0	28.4	23.4	31.2	25.7	34.2	28.2	37.5	30.9	43.1	35.5
170–179.9	27.0	22.3	30.2	24.9	33.1	27.3	36.4	30.0	39.9	32.9	45.8	37.8
⩾180	28.8	23.7	32.1	26.5	35.3	29.1	38.7	31.9	42.4	35.0	48.7	40.2

+: positive; -: negative.

our geometric mean *F*eNO was much higher (32.6 ppb *versus* 16.6 ppb). This ethnic difference was consistent with our previous observation in paediatric subjects involving 258 local and 33 Caucasian students with a mean age of 14 years in Hong Kong. We found that their mean *F*eNO was 25.3, 15.8, 14.9 and 10.1 ppb for Chinese boys, Chinese girls, Caucasian boys and Caucasian girls, respectively [28]. Another large-scale paediatric study in Canada involving 656 school children aged 9–12 years also found that Asian-Canadian subjects had a higher *F*eNO value than white subjects and the African-Canadian subjects [12]. Furthermore, a study involving 62 children in the UK found that *F*eNO was significantly higher, after correcting for atopic status, by an average of 36% in South Asians when compared to the white subjects [29]. A recent study from Taiwan involving 681 Asian children aged 5–18 years found that the geometric mean *F*eNO and the upper 95% CI were 13.7 and 29.7 ppb, respectively, and this was also higher when compared with the Caucasian population [30]. In fact, other smaller-scale studies involving Chinese and Korean adults also showed a similar level of *F*eNO value to our study (table 4) [25–27]. A study involving 895 African-Americans noted that the mean *F*eNO for males and females were 27 ± 26 ppb and 18 ± 18 ppb, respectively [31]. The *F*eNO value of this group of African-American subjects appeared to be greater than the Caucasian population but less than that of the Asian population. As this study involved asthma subjects and subjects with respiratory tract infection (current/past week), it is thus difficult to compare their results

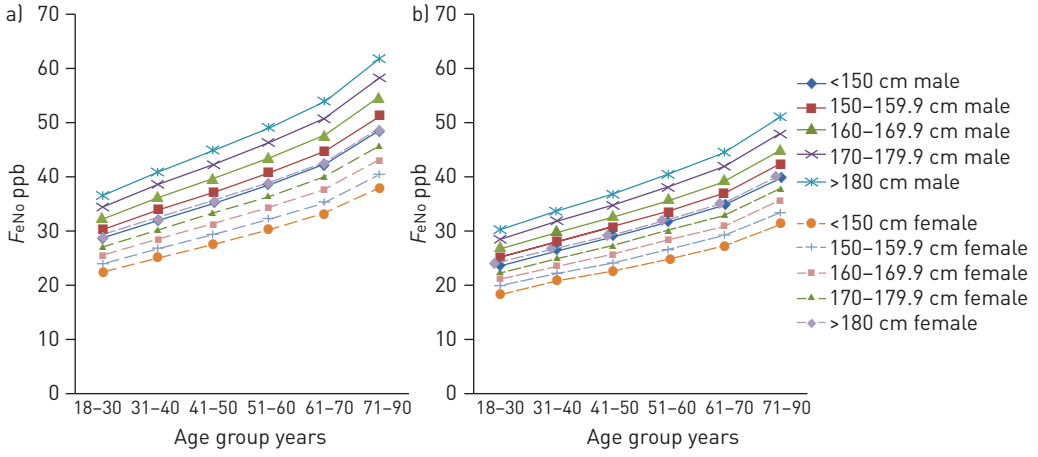

FIGURE 1 95% upper limits of fractional exhaled nitric oxide concentration (*F*eNO) according to age and height in a) atopic subjects and b) nonatopic subjects.

TABLE 4 Comparison of fractional exhaled nitric oxide concentration (F_{ENO}) in healthy adults in published studies

Study	Year	Characteristics of the subjects	Instrument	F_{ENO} value
Travers *et al.* [23]	2007	New Zealand n=193 (93 male and 100 female) Age 56.3±12.9 years 19 (9.8%) subjects were current smokers 46 (23.8%) subjects were atopic	NIOX system; Aerocrine AB, Solna, Sweden	Geometric mean 17.9 (90% CI 7.8–41.1) ppb, without adjustment for sex, atopy and smoking status
Olivieri *et al.* [24]	2006	Italy n=204 (102 male and 102 female) Age 36.1±9.9 years All nonsmokers Atopy not specified	CLD88; Ecomedics, Dürnten, Switzerland	Actual mean 11.7±5.0 ppb for males; 9.9±4.3 ppb for females
Olin *et al.* [14]	2007	Sweden n=1131 (558 male, 573 female) All never-smokers Age 50.3±13.81 years 286 (25.3%) had atopy	NIOX system	Geometric mean 16.6 (95% RI 5.87–47.14) ppb for the whole population Atopic subjects 18.8 (95% RI 6.03–58.74) ppb; nonatopic subjects 16.0 (95% RI 5.91–58.76) ppb Males 18.5 (95% RI 16.67–51.13) ppb; females 14.9 (95% RI 5.36–41.52) ppb
Chng *et al.* [25]	2005	Singapore 45 normal subjects (34 with atopy and 11 with no atopy) Sex distribution not stated Mean (range) age 19.6 (18–27) years Smoking status unknown	NIOX system	Median (range) 38.4 (16.7–49.3) ppb for atopic subjects; 15.7 (11.5–21.7) ppb for nonatopic subjects
Kim *et al.* [26]	2010	Korea n=166 (80 male and 86 female) 80 (48.1%) subjects had atopy Age 33.2±12.1 years and 32.2±7.9 years for males and females, respectively (range 20–86 years) All non-smokers	NO analyser 280i; Sievers Instruments, Boulder, CO, USA	Mean F_{ENO} of male and female subjects were 35.7±13.2 ppb and 26.0±14.2 ppb, respectively Mean F_{ENO} of atopic males 37.3±12.1 ppb; nonatopic males 33.9±14.3 ppb; atopic females 28.6±17.7 ppb; and nonatopic females 24.1±10.6 ppb
Tsang *et al.* [27]	2001	Hong Kong n=120 (59 male and 61 female) All non-smokers Age of males 48.2±16.8 years; females 47.2±15.0 years Atopy not specified	Sievers NO analyser	Actual mean for males 34.5±25.7 ppb; females 23.1±14.7 ppb
Current study	2012	Hong Kong n=1093 (516 male and 577 female) All nonsmokers Age 47.3±16.6 years 645 (59.0%) subjects had atopy	NO analyser 280i	Geometric mean 32.6 (95% RI 31.4–33.7) ppb for all subjects Males 38.3 (95% RI 36.5–40.2) ppb; females 27.1 (25.8–28.5) ppb Atopic subjects 34.6 (95% RI 33.0–36.3) ppb; nonatopic subjects 29.8 (28.3–31.4) ppb

Data are presented as mean±SD, unless otherwise stated. Only publications involving healthy adults with no known respiratory disease were selected. All instruments used a flow rate of flow rate of 50 $mL \cdot s^{-1}$.

directly with "healthy" subjects of other populations or ethnicity [31]. Another large US study involving Hispanic, white, black and subjects of other ethnicities also found that using white subjects as reference, other ethnic groups had higher F_{ENO} value. However, the composition of the other ethnic groups was unspecified in this study [16]. There is also some smaller-scale study of F_{ENO} value in normal healthy subjects of other populations [32].

Our study found that male subjects had a higher F_{ENO} value than female subjects and atopy was associated with higher F_{ENO} value. In addition, height and age were both positively associated with the F_{ENO} level. Furthermore, these factors all had independent association with the F_{ENO} value as multivariate analysis with adjustment of the other factors found a statistically significant association. Age and height were important factors for F_{ENO} in children [12, 13]. The effect of age and height affecting F_{ENO} in adults is less

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consistent, with studies showing conflicting results [14, 15]. Concerning the effect of sex on *F*eNO, our study noted a major difference between sexes, similar to the results reported by TRAVERS *et al.* [23] and TAYLOR *et al.* [33]. However, this was not observed in the study by OLIN *et al.* [14]. There is also a controversial relationship between *F*eNO and atopy. Some studies have suggested that atopy, such as the number of positive skin prick tests and total IgE level, may affect *F*eNO value [34, 35], whereas other studies suggested that *F*eNO value was not influenced by atopy [36]. Concerning the upper limit of normal of the *F*eNO value, our study found that the upper limits of *F*eNO value ranged from 19 to 62 ppb, depending on age, sex, height and atopic status. There was only one study that assessed the *F*eNO value in a large population of healthy adults, and that found that the upper limits of *F*eNO ranged from 24.0 to 54.0 ppb, depending on age, height and atopy [14]. When comparing this Swedish study with our study, apart from the difference in ethnicity, their subjects were older, taller and had less atopy. Difference in body build and height can affect lung volume and this may also account for the variations of *F*eNO value among different populations.

Apart from the demographic factors of the subjects (such as age and ethnicity), other factors may also affect *F*eNO level. A previous study found that exhaled NO measurements in healthy subjects and patients with airways disease differed according to the type of analyser used [37]. Their study compared three brands of machines (Ecomedics (Dürnten, Switzerland), NIOX (Aerocrine AB, Solna, Sweden) and Logan Research Ltd (Rochester, UK)). Sievers, the brand of machine used in this study, was not assessed. It was thus not certain whether the difference in the *F*eNO level in our population when compared to other studies would be attributable to machine difference. This factor might not be very significant as all current machines should follow the ATS/ERS guidelines [2, 3] for calibration and maintenance. Conversely, a study from Singapore using the NIOX machine in testing 45 first-year Asian medical students and another study from Korea involving 166 adults aged 20–80 years using the same Sievers machine as in this study [26], found similar *F*eNO values to our study [25].

We speculated that differences in environmental exposures or genetic polymorphisms of high-producing nitric oxide synthase genotypes would be related to the *F*eNO level in different populations. The production of endogenous nitric oxide from L-arginine is dependent on the enzyme NO synthase (NOS). All NOS isoenzymes convert L-arginine to L-citrulline, with the generation of NO. Three isoforms of NOS are known. *NOS1* and *NOS3* are both constitutively expressed in the human airway, whereas *NOS2* is inducible by inflammation [38]. It is possible that differences in genetic background may affect the activity of NOS enzymes resulting in differences in NO production. A population-based study of young adult twins revealed that variation in *F*eNO was explained by genetic and nonshared environmental effects [39]. A previous study noted that the NOS3 missense sequence variant in the endothelial NOS gene (G894T) was associated with *F*eNO in an American cohort of subjects with asthma. The TT genotype had a significantly higher *F*eNO than the GT genotype [40]. An inhibitor of iNOS was noted to produce marked inhibition of *F*eNO in both normal and asthmatic subjects [41]. Further studies are needed to assess the genetic contributions of *F*eNO value in different ethnicities. Apart from genetic factors, environmental factors such as air pollution, allergens and diet may also affect the *F*eNO level, but we have not assessed these factors in this study [42–45].

This study had some limitations. *F*eNO was measured on just one occasion for the subjects and repeatability was not tested. In addition, we recruited volunteers to join the study and the subjects were not randomly recruited from a large population or community. The percentage of atopic subjects in this study was on the high side and this might be due to selection bias.

In summary, we have shown that sex, age, atopic status and height were determinants of *F*eNO value in a large population of Chinese subjects. *F*eNO value in the Chinese subjects appeared to be higher than that of the Caucasian population. In this population, the upper limits of *F*eNO ranged from 19 to 62 ppb, depending on their age, sex, height and atopic status. Further studies are needed to explore the genetic and other determinants of *F*eNO. This study provides useful population-based reference values for the accurate interpretation of *F*eNO levels in the Chinese population.

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