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Exhaled nitric oxide and influencing factors in a random population sample

Stefan Karrasch [a,e,*], Kathrin Ernst [a], Jürgen Behr [c], Joachim Heinrich [b], Rudolf M. Huber [d], Dennis Nowak [e], H.-Erich Wichmann [b,h,i], Sebastian E. Baumeister [b,g], Christa Meisinger [b], Karl-Heinz Ladwig [b], Rolf Holle [f], Rudolf A. Jörres [e], Holger Schulz [a], for the KORA Study Group[j]

[a] Comprehensive Pneumology Center, Institute of Lung Biology and Disease, Helmholtz Zentrum München, Munich, Germany
[b] Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany
[c] Division of Pulmonary Diseases, Department of Internal Medicine I, Grosshadern, LMU, Munich, Germany
[d] Division of Respiratory Medicine, Department of Medicine, Innenstadt, LMU, Munich, Germany
[e] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, LMU, Munich, Germany
[f] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, Munich, Germany
[g] Institute for Community Medicine, University of Greifswald, Greifswald, Germany
[h] Institute of Medical Data Management, Biometrics and Epidemiology, LMU, Munich, Germany
[i] Klinikum Grosshadern, LMU, Munich, Germany

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Summary
The aim of the current study was to determine the impact and interaction of important influencing factors on the fraction of exhaled nitric oxide (FeNO).

FeNO was measured in a population-based sample of 1250 middle-aged subjects from the KORA F4 cohort (Augsburg, Germany). Analysis of covariance models was performed including the factors age, height, FVC, FEV_1, sex, current smoking status, recent respiratory tract infection, and respiratory allergy.

Geometric mean (SD as factor; 95% confidence interval as factor) FeNO was 13.9 (1.9; 1.033) ppb. FeNO significantly depended on age, height, smoking, infection and allergy. Smoking reduced FeNO by 21%, while infection and allergy led to increases by 9 and 11%, respectively. Increases in age by

* Corresponding author. Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, LMU, Ziemssenstr. 1, D-80336 Munich, Germany. Tel.: +49 89 5160 7655; fax: +49 89 5160 3957.
E-mail address: stefan.karrasch@med.uni-muenchen.de (S. Karrasch).
URL: http://arbmed.klinikum.uni-muenchen.de/.
[j] The KORA study group consists of H.-E. Wichmann (speaker), R. Holle, J. John, T. Illig, C. Meisinger, A. Peters, and their coworkers, who are responsible for the design and conduct of the KORA studies.

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10 years and in height by 10 cm were associated with increases of FeNO by 15 and 10%, respectively. Non-smokers demonstrated independent multiplicative superposition of factors affecting FeNO while the effect of allergy was virtually eliminated in smokers without infection.

We conclude that in middle-aged non-smokers the effects of infection, age and height can be easily taken into account and do not significantly disturb the effect of respiratory tract allergies on FeNO. In current smokers, however, effects were heterogeneous and information on smoking intensity seems to be useful for better adjustment.

Introduction

Since the discovery that the fraction of exhaled NO (FeNO) is increased in patients with asthma,[1] much work has been done to establish FeNO as a noninvasive marker of bronchial inflammation and a useful readout particularly in allergic asthma.[2] Naturally, the diagnostic applicability of FeNO depends on the availability of reference values that adequately take into account the major factors affecting FeNO. Within the last years a number of publications have provided such reference values on the basis of population samples of adults or children.[3–8]

Although the available data do not fully agree on the panel of factors influencing FeNO, important factors besides atopy have clearly been identified, including age, height, sex, smoking and respiratory tract infection.[4,9–12] Regarding practical implications the question arises to which extent these factors numerically affect FeNO and whether some of them are even capable of extinguishing the information on airway allergic inflammation carried by FeNO. A recent study[13] demonstrated that major factors such as smoking and respiratory tract infection were associated with changes in FeNO according to a law of independent superposition, which allowed taking account of these factors in a simple manner. However, the population studied predominantly comprised young subjects, with a mean age of 34 years. As differences in the cumulative exposure to noxious substances including cigarette smoke and possible subsequent alteration of the respiratory epithelium may be more pronounced with increasing age the question arises whether the superposition of effects also applies in subjects of higher age and whether it is comparable, both qualitatively and quantitatively, to that found in younger subjects.

Based on these considerations the present study identified the relevant factors influencing FeNO in a large population-based sample of middle-aged subjects.

Material and methods

Study population

Data are based on the KORA F4 study (2006–2008), a follow-up study of the KORA S4 survey conducted in 1999–2001. The KORA S4 study population was recruited from the region of Augsburg in the South of Germany. The study design, sampling method, and data collection have been described in detail elsewhere.[14] Briefly, in the KORA S4 survey of the 6640 men and women aged 25–74 years that were randomly selected from population registries, 4261 participated in the baseline examination, out of which 3080 (72%) also took part in the follow-up examination conducted between 2006–08. Persons were considered ineligible for follow-up if they had died during follow-up, moved too far outside the study area, or were lost to follow-up. The current study was restricted to 1250 subjects aged between 41 and 63 years without intake of inhaled or systemic corticosteroids ($n = 32$) or missing values on any of the analytical variables. All study participants gave written informed consent and the study was approved by the ethics committee of the Bavarian Medical Association (Table 1).

Assessments

Body weight and height were determined by standardized anthropometry, spirometry was performed using ATS/ERS recommendations[15] by a pneumotachograph-type spirometer (Masterscreen, Cardinal Health, Würzburg, Germany). At least two acceptable and reproducible measurements were required. The spirometer was calibrated at least daily using a 1L-calibration pump.

FeNO was determined from controlled expirations at a flow rate of 50 mL/s in accordance with ATS/ERS recommendations[16] (NIOX 2.0, Aerocrine, Sweden). At least three

Table 1 Descriptive data of the study cohort.

	Women	Men
n (%)	656 (52.5)	594 (47.5)
Age (range), y	51.5 ± 5.6 (41–63)	51.7 ± 5.9 (41–63)
Height, cm	163.6 ± 6.2	176.9 ± 6.3
Weight, kg	71.5 ± 14.1	87.7 ± 15.0
FVC, L (%pred)	3.64 ± 0.62 (120.6 ± 15.8)	5.03 ± 0.80 (112.0 ± 13.8)
FEV_1, L, (%pred)	2.84 ± 0.51 (110.7 ± 16.9)	3.89 ± 0.71 (107.9 ± 16.4)
Current smokers, *n* (%)	140 (21.3)	152 (25.6)
Respiratory tract infection, *n* (%)	110 (16.8)	79 (13.3)
Respiratory allergy, *n* (%)	86 (13.1)	70 (11.8)

Absolute numbers and percentages, or mean values and standard deviations are given.

Table 2 Parameter estimates from the full ANCOVA model including interactions ($R^2 = 0.20$).

	Parameter (log_{10})	SEM (log_{10})	p-value	−95%CI (log_{10})	+95%CI (log_{10})	Factor on FeNO	Δ% of FeNO
Intercept	0.06243	0.22065	0.777275	−0.37045	0.49531	−	−
Sex (male)	−0.01297	0.01117	0.246020	−0.00895	0.03488	0.971	−3%
Age per 10 years	0.06152	0.01260	0.000001	0.03680	0.08624	1.152	+15%
Height per 10 cm	0.04495	0.01150	0.000098	0.02239	0.06751	1.109	+11%
Respiratory allergy	0.04326	0.01050	0.000040	0.02266	0.06386	1.105	+11%
Smoking	−0.10276	0.01105	<0.000001	−0.12444	−0.08108	0.789	−21%
Respiratory infection	0.04811	0.01097	0.000013	0.02659	0.06964	1.117	+12%
Sex (male) × Smoking	−0.01968	0.00824	0.017026	−0.03584	−0.00352	0.956	−4%
Infection × Smoking	0.02431	0.01098	0.026932	0.00278	0.04584	1.058	+6%

acceptable and reproducible maneuvers were required. Final FeNO values were calculated as arithmetic mean of these values. The NO analyzer was calibrated every two weeks using a certified calibration gas (Linde, Germany) according to the manufacturer's recommendations. Ambient air pressure, temperature, humidity and ambient NO levels were recorded for each measurement.

Information on the presence of current respiratory tract infection (during the last 3 weeks), respiratory allergy (i.e. physician-diagnosed asthma or symptoms of respiratory allergy including hay fever within the last 3 days) as well as current smoking status were assessed by a standardized questionnaire.

Data analysis

Subjects currently using inhaled or oral corticosteroids were excluded because of the effect of these drugs on FeNO values. The data of the remaining sample ($n = 1250$) were used for analysis. For data description arithmetic mean values and standard deviations (SD) were used or geometric mean values and standard deviations in case of FeNO values. Geometric SD was expressed as a factor for multiplication with the geometric mean.

Statistical analysis was performed by linear models based on analysis of covariance (ANCOVA) using log-transformed FeNO values as the dependent variable. The factors included in the analysis comprised age, height, FVC, FEV_1 as continuous variables, and sex, current smoking status, respiratory tract infection and respiratory allergy as categorical variables. Initially these main factors were used without interactions and then the whole set of pairwise interactions between those factors that were statistically significant was added. The panel of interactions was then reduced by excluding non-significant interactions in a stepwise manner according to their p-value. The procedure followed was similar to that used in a previous study[13] in order to achieve comparability between the results. Statistical significance was assumed for $p < 0.05$. Analyses were performed using the commercially available software STATISTICA® (StatSoft Inc, USA).

Results

The geometric mean (SD as factor; 95% confidence interval as factor) FeNO value in the whole population ($n = 1250$) was 13.9 (1.9; 1.033) ppb. In the presence of respiratory allergy (12.5%) FeNO was 16.5 (2.1; 1.129) ppb, and in the absence 13.6 (1.8; 1.036) ppb. Current smokers (23.4 %) showed geometric mean (SD; 95% CI) FeNO of 9.0 (1.9; 1.075) ppb, and current non-smokers of 15.9 (1.8; 1.037) ppb. After respiratory tract infection (15.1%) values were 15.3 (1.9; 1.100) ppb, and in the absence of infection 13.7 (1.9; 1.038) ppb.

According to the final ANCOVA of log_{10}FeNO model including second-order interactions, FeNO was dependent on height, age, the presence of respiratory allergy, respiratory tract infection and smoking status ($p < 0.0005$ each). The analysis of interactions revealed all of them as not being significantly different from zero, except for an interaction between sex and smoking, as well as between infection and smoking. The parameters of this additive regression model are shown in Table 2. This table also

Table 3 Parameter estimates from the ANCOVA model including smoking intensity ($R^2 = 0.21$).

		Parameter (log_{10})	SEM (log_{10})	p-value	−95%CI (log_{10})	+95%CI (log_{10})	Factor on FeNO	Δ% of FeNO
Intercept		−0.00723	0.15245	0.962188	−0.30632	0.29186	−	−
Age per 10 years		0.06071	0.01219	0.000001	0.03679	0.08464	1.150	+15%
Height per 10 cm		0.04366	0.00763	<0.000001	0.02870	0.05863	1.106	+11%
Respiratory allergy		0.04625	0.01037	0.000009	0.02590	0.06660	1.112	+11%
Cigarettes smoked per day	$0< n \leq 10$	0.00965	0.02136	0.651371	−0.03225	0.05156	1.022	+2%
	$10< n \leq 20$	−0.07758	0.02022	0.000131	−0.11725	−0.03791	0.836	−16%
	$20< n$	−0.14101	0.02994	0.000003	−0.19975	−0.08227	0.723	−28%
Respiratory infection		0.03693	0.00962	0.000130	0.01805	0.05581	1.089	+9%

Table 4 Parameter estimates from the ANCOVA model without interactions ($R^2 = 0.19$).

	Parameter (log_{10})	SEM (log_{10})	*p*-value	−95%CI (log_{10})	+95%CI (log_{10})	Factor on FeNO	Δ% of FeNO
Intercept	0.08891	0.15447	0.565011	−0.21414	0.39195	–	–
Age per 10 years	0.06096	0.01239	0.000001	0.03665	0.08528	1.151	+15%
Height per 10 cm	0.04315	0.00774	<0.000001	0.02797	0.05833	1.104	+10%
Respiratory allergy	0.04406	0.01053	0.000031	0.02341	0.06472	1.107	+11%
Smoking	−0.11912	0.00834	<0.000001	−0.13549	−0.10276	0.760	−24%
Respiratory infection	0.03678	0.00976	0.000173	0.01763	0.05592	1.088	+9%

includes re-transformed parameters which correspond to multiplicative factors with regard to FeNO as well as the respective alteration in percent.

If smoking intensity (i.e. self-reported number of cigarettes smoked per day) was used instead of the binary smoking variable, the interactions between smoking and sex as well as between smoking and infection disappeared. The other factors were virtually unaffected by this. The results of this analysis are shown in Table 3.

Finally, Table 4 shows the model obtained with the binary smoking variable when interactions were omitted. The estimates of the reduced model (Table 4) were well within the 95% confidence limits of the full model (Table 2). The corresponding formula for the calculation of FeNO by the model without interactions is:

$$\mathrm{FeNO[ppb]} = 13.405 \times 1.151^{(\mathrm{age[y]}-50)/10} \times 1.104^{(\mathrm{height[cm]}-170)/10} \times 1.107^{allergy} \times 0.760^{smoking} \times 1.088^{infection}$$

(Here, the variables *allergy*, *smoking* and *infection* are set to 1 if the respective factor is present, otherwise they are set to zero.)

Fig. 1 shows the geometric mean values and SD of FeNO for the different combinations of binary categories and illustrates the independent superposition of the binary factors as well as the deviation from this finding in smokers with or without respiratory allergy. Similarly, the positive correlation between FeNO and age is shown in Fig. 2, after adjusting for allergy, infection, smoking and height. Regarding its effect on FeNO, a difference of 5 cm in height was approximately equivalent to an age difference of 3 years.

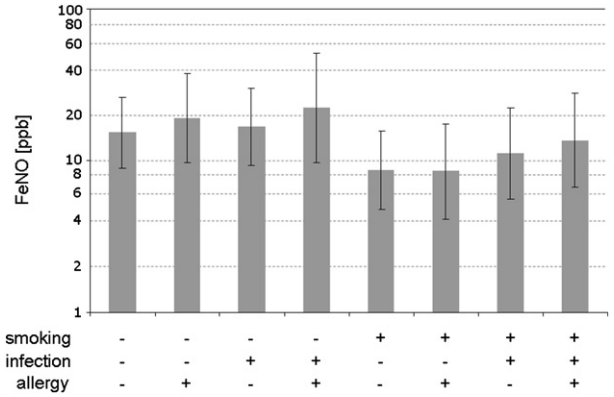

Figure 1 FeNO values in the study population (geometric mean ÷ SD).

Moreover, the parameter estimates of the reduced model without interactions were used to compute predicted values of FeNO. As an example, Table 5 shows the results as a function of binary categories for a range of different values of height for the age category of 50 years.

Discussion

The present study evaluated the relationship between FeNO values and major influencing factors in a randomly selected population-based cohort of adults of age 41–63 years. Age, height, respiratory tract infection, smoking and respiratory allergy had a statistically significant effect on FeNO. Significant interactions were found between sex and smoking as well as respiratory tract infection and smoking, however, the impact of these interactions was considered negligible.

The pattern of effects on FeNO was similar to that found in a previous study in young adults (mean age 34 years) and the present analysis was designed to compare the patterns between the two populations of different age range. In the subjects of younger age (34.5 ± 13.0 y) there was no effect of age on FeNO, however a significant relationship with sex.[13] This relationship was not eliminated by presence of height as a significant predictor. In the present study, sex only became significantly associated with FeNO when height was omitted from the model (data not shown), similar to findings reported previously.[7] It is not clear which factors underly this difference in the pattern of predictors. The frequencies of smoking, respiratory allergies and respiratory tract infections were similar in both studies. However, the sample described

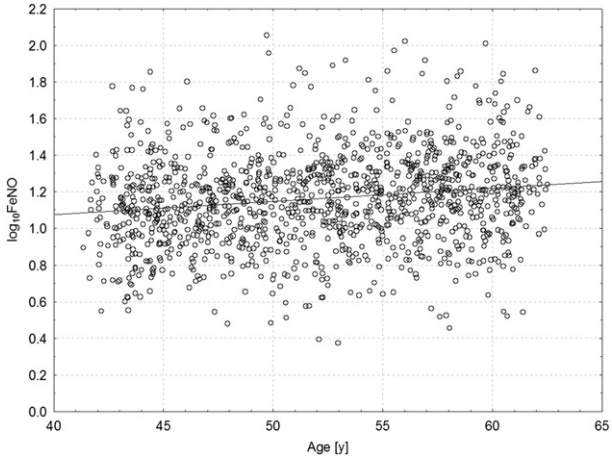

Figure 2 Relationship between log_{10}FeNO and age after adjustment for allergy, infection, smoking and height.

Table 5 Predicted FeNO values at the age of 50 y.

Smoking	−	−	−	−	+	+	+	+
Infection	−	−	+	+	−	−	+	+
Allergy	−	+	−	+	−	+	−	+
Height [cm]								
150	11.0	12.2	12.0	13.2	8.4	9.2	9.1	10.1
160	12.1	13.4	13.2	14.6	9.2	10.2	10.0	11.1
170	13.4	14.8	14.6	16.1	10.2	11.3	11.1	12.3
180	14.8	16.4	16.1	17.8	11.3	12.5	12.2	13.6
190	16.4	18.1	17.8	19.7	12.4	13.8	13.5	15.0

by Dressel et al.[13] had been drawn from an outpatient clinic that was responsible for preventive follow-up measurements in a broad range of occupationals, whereas the second sample was derived from a population-based setting. It is worth to be mentioned that the magnitude of coefficients regarding height, allergy, infection and smoking was very similar in both studies. Therefore we consider it likely that the data reflect true differences in the pattern of factors influencing FeNO in different age ranges.

In contrast to the data by Dressel et al.,[13] however, a significant influence of age was found in our, partly overlapping, age group. There have been conflicting reports regarding the association between FeNO and age[17,18]. Potentially, this relationship is only detectable at very young ages and in advanced age, whereas it might be negligible during young adulthood. Possible explanations for an increase of FeNO with age could include diet[19], latent respiratory inflammation or an increase in peripheral (alveolar) NO.[20] Irrespective of this we find that in particular the adjustment for smoking and for height can be performed in clinical practice in a simple manner as reported previously.

The evidence for a significant independent effect of sex on FeNO values is inconsistent.[11] In our cohort, no significant impact of sex was found after adjustment for other factors, especially height. In view of the age range of the present population sample, one explanation for this observation might be a change in the hormonal status with increasing age as a relationship between estrogen/progesterone levels and exhaled NO has recently been described.[21] Furthermore, changes of FeNO in association with premenstrual asthma have been found[22]; in fact, estrogen can activate the endothelial NO synthase in human bronchiolar epithelial cells in vitro[23]. However, if the analysis in our cohort was limited to premenopausal women as compared to men, the impact of sex still remained non-significant.

The adjusted level of FeNO values in the present data set was comparable to results described in previous studies,[5,12] however, other authors reported higher values.[8,13,18] Beyond differences in the populations, the use of different NO analyzers may account for this difference even if they were calibrated regularly using certified calibration gases and expiratory flow rate as an important determinant to FeNO values was carefully checked to be 50 mL/s when the target mouth pressures were achieved.

Despite studies that have reported comparability of NO chemiluminescence analyzers,[24] the differences between the mean values reported in various study populations by different researchers have to be kept in mind.[25] There might be further differences in readings between handheld analyzers and chemiluminescence analyzers, as indicated by recalibration factors being different from one.[26] This situation might bear some similarity to that of bronchial inhalation challenges. Experience shows that many clinicians use slightly different protocols and nebulizers despite the claim for standardization. This leads to difficulties in comparing provocative concentrations between different clinicians, but the categorization regarding bronchial hyperresponsiveness might not be as critically dependent on the use of different protocols, as far as critical threshold are appropriately adjusted. These considerations indicate that one still has to be cautious when referring to absolute FeNO values. Despite this, our current and previous data indicate that the adjustment for major influencing factors *per se* acts similar and thus might be considered as an implementable set of factors for clinical use.

We conclude that FeNO was affected by infection, age and height in a random selected study population. These factors can easily be taken into account and do not significantly disturb the association of FeNO with respiratory tract allergies. In current smokers, however, information on smoking intensity seems to be useful for better adjustment.

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Conflict of interest statement

None declared.

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