Respiratory Medicine 173 (2020) 106160

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Original Research

Parallel gradients in F_{ENO} and in the prevalences of asthma and atopy in adult general populations of Sweden, Finland and Estonia — A Nordic EpiLung study

Paul G. Lassmann-Klee [a,*], Päivi L. Piirilä [a], Ben Brumpton [b,c], Matz Larsson [d], Britt-Marie Sundblad [e], Jaak Põlluste [f,1], Maria Juusela [g], Annamari Rouhos [h], Mari Meren [f,i], Ari Lindqvist [a], Hannu Kankaanranta [j,k,l], Helena Backman [m,n], Arnulf Langhammer [o], Eva Rönmark [m], Bo Lundbäck [l], Anssi R.A. Sovijärvi [a]

[a] Unit of Clinical Physiology, Helsinki University Central Hospital and University of Helsinki, Finland
[b] Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[c] Clinic of Thoracic and Occupational Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[d] Clinical Health Promotion Centre, University of Lund, and Örebro University Hospital, Örebro, Sweden
[e] Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
[f] National Institute for Health Development, Tallinn, Estonia
[g] The Finnish Institute of Lung Health, FILHA, Helsinki, Finland
[h] Department of Pulmonary Medicine, Heart and Lung Center, Helsinki University Central Hospital and University of Helsinki, Finland
[i] The North Estonia Medical Centre, Tallinn, Estonia
[j] Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[k] Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[l] Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[m] Department of Public Health and Clinical Medicine, Division of Sustainable Health, The OLIN Unit, Umeå University, Umeå, Sweden
[n] Department of Health Sciences, Luleå University of Technology, Luleå, Sweden
[o] HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway and Central Norway Regional Health Authority, Trondheim, Norway

ARTICLE INFO

Keywords:
Asthma
F_{ENO}
Atopy
Skin prick test

ABSTRACT

The prevalence of asthma is higher in Sweden and Finland than in neighbouring eastern countries including Estonia. Corresponding difference in bronchial eosinophilic inflammation could be studied by F_{ENO} measurements. We aimed to compare F_{ENO} in adult general populations of Sweden, Finland, and Estonia, to test the plausibility of the west-east disparity hypothesis of allergic diseases.

We conducted clinical interviews (N = 2658) with participants randomly selected from the general populations in Sweden (Stockholm and Örebro), Finland (Helsinki), and Estonia (Narva and Saaremaa), and performed F_{ENO} (n = 1498) and skin prick tests (SPT) in 1997–2003.

The median (interquartile range) of F_{ENO} (ppb) was 15.5 (9.3) in Sweden, 15.4 (13.6) in Finland and 12.5 (9.6) in Estonia. We found the lowest median F_{ENO} values in the Estonian centres Saaremaa 13.1 (9.5) and Narva 11.8 (8.6). In the pooled population, asthma was associated with F_{ENO} ≥25 ppb, odds ratio (OR) 3.91 (95% confidence intervals: 2.29–6.32) after adjusting for SPT result, smoking, gender and study centre. A positive SPT test increased the likelihood of asthma OR 3.19 (2.02–5.11). Compared to Saaremaa, the likelihood of having asthma was higher in Helsinki OR 2.40 (1.04–6.02), Narva OR 2.45 (1.05–6.19), Örebro OR 3.38 (1.59–8.09), and Stockholm OR 5.54 (2.18–14.79).

Abbreviations: CI, 95% confidence interval; F_{ENO}, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in 1 s; IQR, Interquartile range; OR, Odds ratio; SPT, Skin pick test.

* Corresponding author. Unit of Clinical Physiology, Helsinki University Central Hospital, PO Box 340, 00029, HUS/Helsinki, Finland.
E-mail address: paul.klee@fu-berlin.de (P.G. Lassmann-Klee).

[1] Deceased July 2020.

https://doi.org/10.1016/j.rmed.2020.106160
Received 1 June 2020; Received in revised form 18 August 2020; Accepted 15 September 2020
Available online 17 September 2020

There was a higher prevalence of asthma and allergic airway inflammation in adult general populations of Sweden and Finland compared to those of Estonia. Atopy and elevated F_{ENO} level were independently associated with an increased risk of asthma. In conclusion, the findings support the earlier west-east disparity hypothesis of allergic diseases.

1. Introduction

Asthma is an ubiquitous chronic pulmonary disease with a high prevalence mainly in westernised countries, posing an economic burden to public health [1]. A major increase in asthma was observed during the second half of the past century [2], including Scandinavian countries such as Finland [3]. Although this rise seems to have reached a plateau in Finland during the recent years [4], the rise has apparently continued in northern [5] and western Sweden [6]. Additionally, worldwide, the prevalence of asthma still seems to be increasing [7], with hundreds of millions globally afflicted [8]. Neighbouring countries of Finland — Estonia and Russia — have been less affected with asthma [9,10]. In Estonia, a slow increase in asthma prevalence started in the last decades of the past century [11].

Early hypotheses proposed a west–east disparity in allergic diseases, including rhinitis, atopic eczema, and asthma [10,12,13]. Previous studies have shown differences in prevalence, but also in diagnostic criteria [14], as well as differences in exposure and risk factors between countries in eastern and western parts of northern Europe [15]. Researchers in Finland, Sweden and Estonia designed, in the mid-1990s, a multi-centre epidemiological study (FinEsS) to investigate allergic and obstructive respiratory diseases. A key target of the FinEsS study was to find out whether regional differences in the prevalence of asthma were reflected in regional differences of fractional exhaled nitric oxide (F_{ENO}), a biomarker of eosinophilic airway inflammation. We therefore aimed to investigate differences in F_{ENO} in general populations of Sweden (Stockholm and Örebro), Finland (Helsinki), and Estonia (Narva and Saaremaa), and the associations of F_{ENO} with asthma, asthma symptoms, smoking and skin prick test (SPT) findings to common allergens, thus assessing the west-east disparity hypothesis of allergic diseases.

2. Materials and methods

Random samples of general populations in five areas from Sweden, Finland and Estonia answered questionnaires on respiratory symptoms and diseases in 1995–1996, as part of a cross-sectional study. One to five years later, at the turn to the 21st century, random samples from these cohorts were invited to clinical examinations in all participating centres (Fig. 1), including measurements of F_{ENO}, lung function and SPT, and a structured clinical interview on symptoms of respiratory diseases.

2.1. Study populations

In 1995 and 1996, we surveyed 34 951 adults in general populations in Sweden, Finland and Estonia with a postal questionnaire (see flowchart in Fig. 2 and anthropometric and spirometric data in Table 1) sent to individuals randomised in 10-year-age cohorts from the Population Register Centres, taking into account the overall gender distribution in each local population. The postal questionnaire was answered by 27 697 (79% of invited) subjects: 6062 (76%) in Helsinki, 5754 (72%) in Stockholm, 6784 (84%) in Örebro, 4325 (78%) in Narva, and 4808 (89%) in Saaremaa. Among all these, a random sample (stratified by age and gender) of 4944 individuals (18% of those who replied to the postal questionnaires) were invited to a clinical examination. A total of 2658 (54% of invited) volunteers participated: 643 (54%) in Helsinki, 443 (37%) in Stockholm, 719 (60%) in Örebro, 402 (60%) in Narva, and 451 (67%) in Saaremaa. We further randomised these subjects and performed F_{ENO} measurements, and skin prick testing around the turn of the millennium (1997–2003) on 1669 participants. We included for this study a total of 1498 individuals with valid F_{ENO} measurements aged 20–60 years, among whom 92% had valid SPTs.

2.2. Questionnaire and clinical interview

We selected 11 questions from the clinical interview, including those questions with reference to self-reported or diagnosed obstructive respiratory diseases, asthma symptoms, asthma medication, smoking, and self-reported allergic rhinitis or conjunctivitis. The postal questionnaire was based on the OLIN (Obstructive Lung Diseases in Northern Sweden) research project and further on the British Medical Research Council and Tucson questionnaires [3]. The clinical interview was based on the former postal questionnaire, but augmented with detailed questions of symptoms, medication, and possible risk factors for obstructive airway diseases and allergy. Translations of the questionnaire were available in all native languages (Finnish, Swedish, Estonian, and Russian). Independent translations of the questionnaires from Swedish to other languages were produced by bilingual translators who were aware of the objective of the study and had expertise in the study topic.

Fig. 1. Map of the FinEsS research centres in Sweden, Finland and Estonia. Map tiles by Stamen Design, under CC BY 3.0. Data by OpenStreetMap, under ODbL.

2.3. Definitions

The definitions presented below were based on **affirmative answers** to each question.

Asthma: have you ever had asthma?

Asthma diagnosis: Have you been diagnosed with asthma by a physician?

Childhood asthma: Have you had asthma during childhood or had a wheeze during breathing in early childhood?

Chronic obstructive pulmonary disease (COPD) *diagnosis*: Have you been diagnosed with chronic bronchitis or emphysema by a physician?

Current smoker: are you a current smoker?

Allergic rhinitis or conjunctivitis (ARC): Have you or have you had hay fever (allergic rhinitis) or allergic eye inflammation?

Asthma symptoms during the last year: Have you had any asthma symptoms during the last 12 months?

Nightly asthma symptoms last year: Have you ever been woken up during the night or early morning by an attack of shortness of breath with wheezing? If yes, has this happened during the last 12 months?

Asthma medication during the last year: Have you used any asthma medicines during the last 12 months?

Inhaled corticosteroids (ICS) *last year*: Have you used inhaled corticosteroids during the last 12 months (List of national commercial names)?

Short acting β-agonists (SABA) *last year*: Have you used inhaled short acting β-agonists during the last 12 months (List of national commercial names)?

2.4. F_{ENO} measurements

F_{ENO} was measured according to the European Respiratory Society (ERS) guidelines [17], but the expiratory flow rate varied between the study centres. All participating centres employed a chemiluminescence nitric oxide (NO) analyser, Sievers 270B (Boulder, CO, USA). The devices were calibrated daily (two-point calibration). The gas used for inhalation was NO-free synthetic air. The exhalation was visually controlled and flow resistors were used (Hans Rudolph Inc., Shawnee, KS, USA) in order to control the target flow range and to close the soft palate. The expiratory flow rates were: 250 mL/s in Stockholm and Örebro, 50 mL/s in Helsinki, and 100 mL/s in Narva and Saaremaa. The exhalation time was at least 6 s. The mean F_{ENO} obtained for analysis comprised a mean value of three consecutive end-of-exhalation plateau determinations. No nose-clips were used for the manoeuvres, but mouthwashes were performed prior to the measurements: in Helsinki with carbonated water, and in other centres with tap water, in order to reduce oral NO contamination [18,19].

Since the study centres utilised different expiratory flows in F_{ENO} measurements, all F_{ENO} values had to be converted to values with a 50 mL/s flow, the recommended value by the American Thoracic Society (ATS) and ERS [20], for comparison between the study centres. We used a conversion model developed by Lassmann-Klee et al. [21], which accounts for different flow-rates and different mouthwashes.

We selected a F_{ENO} value of ≥25 ppb as an intermediate cut-off value according to ATS and ERS [22,23].

2.5. Skin prick tests

We tested 92% of the participants with SPTs for the following allergens: dog, cat, horse, timothy-grass, birch, mugwort, moulds (*Alternaria alternata*, *Cladosporium herbarum*), and house dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae)*. The testing protocol was previously described elsewhere [24]. All centres, apart from Stockholm, arranged additional testing for storage mites (*Lepidoglyphus destructor*, *Acarus siro*), cow, cockroach (*Blatella germanica*), and latex. We defined a volunteer as atopic, if at least one positive SPT was observed, i.e. a skin reaction of ≥3 mm, after rejecting cases with dermographism [25].

2.6. Spirometry

We used different spirometers in the participating centres: Ohio spirometer (Stockholm), Volugraph 2000 and Vitalograph (Örebro), SensorMedix Vmax22 (Helsinki) and Mijnhardt Vicatest 5 (Narva and Saaremaa). We acquired forced expiratory volume in 1 s (FEV_1) only (Table 1). The highest value of three acceptable FEV_1 values was recorded.

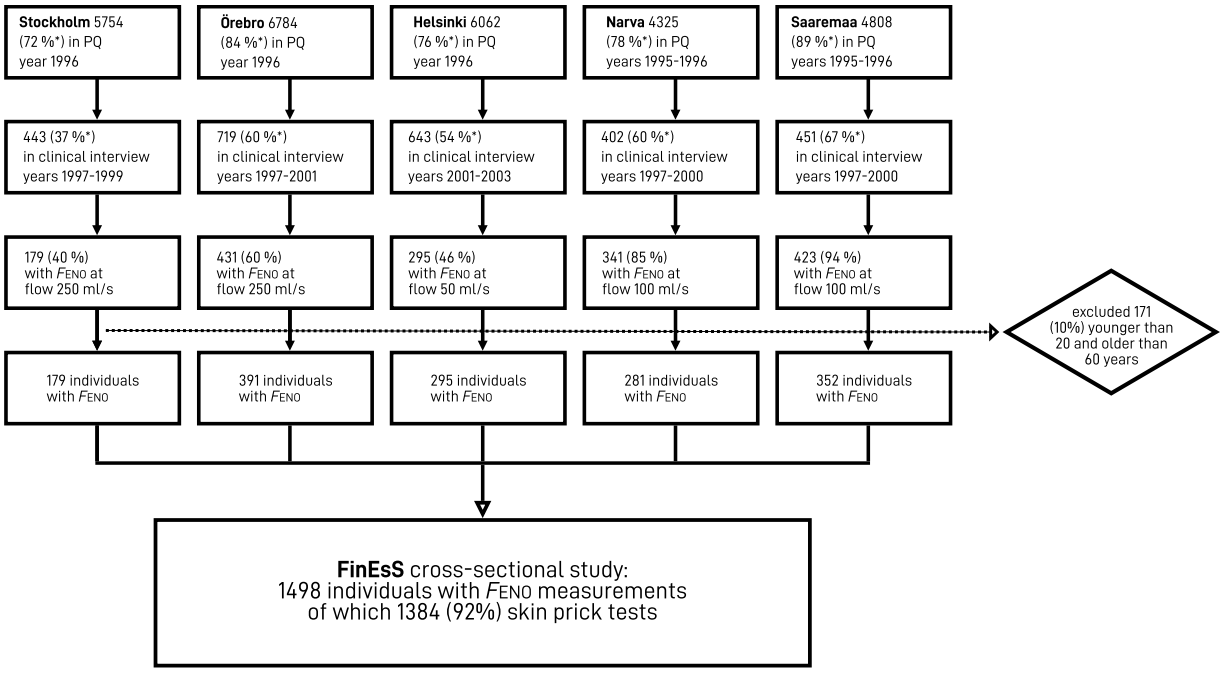

Fig. 2. Flowchart of population selection in Finland, Sweden and Estonia (FinEsS). Presented as *n*, (%*) percentage of invited, or (%) percentage of total. Postal questionnaire (PQ), fractional exhaled nitric oxide (F_{ENO}).

2.7. Statistics

All statistical tests were performed in *R* [26]. Due to a non-normal distribution of F_{ENO} in the general population, we tested the differences between the centres and countries with a Kruskal–Wallis test, with a post-hoc Dunn's test for multiple comparison and Holm's adjustment.

F_{ENO} distributions in two-group variables were compared with a Wilcoxon–Mann–Whitney–Test for independent groups.

We calculated raw odds ratios (OR) with a two-by-two table, the 95% confidence intervals (CI) using the method number ten by Newcombe [27] and corresponding *p* values with Pearson's χ^2 test with Yates' continuity correction. The adjusted ORs were calculated by binary logistic regression. Within the binary logistic regression, we tested the multiple parameters of the study centre variable with Wald χ^2 statistics. The best fitting models were selected by using the Akaike information criterion (AIC).

We calculated a minimum sample size of $n = 1232$ for a binary logistic regression when considering an odds ratio of 1.5 for an event and a prevalence of 4%, according to Hsieh et al. [28].

2.8. Ethics

The study was approved by the Ethics Committee of Department of Medicine of Helsinki University Hospital, the Tallinn Ethics Committee in Estonia and the Swedish Ethical Review Authority. All individuals filled in a written informed consent form attached to the structured interview.

3. Results

Totally, 1498 persons were included in the analyses from five centres. Age, height, weight, BMI, and FEV_1 results were similar in the study centres (Table 1).

3.1. Prevalence of symptoms and diagnoses

The diagnoses, respiratory symptoms, and median F_{ENO} varied significantly between the areas (Table 2). The population in Stockholm had a high prevalence of asthma (13%), asthma diagnosis (11%), asthma symptoms last year (13%) and asthma drug use (ICS 9%, SABA 10%), while the population in Saaremaa had the lowest prevalences of asthma (3%), asthma diagnosis (2%), asthma symptoms, and asthma drug use. We found the highest prevalence of COPD diagnosis (18%) and current smokers (41%) in the population of Narva. The studied sample from Helsinki had the highest prevalence of allergic rhinitis or conjunctivitis (ARC) (40%) and atopy (49%).

3.2. Fractional exhaled nitric oxide: F_{ENO}

The median (interquartile range (IQR)) F_{ENO} was 14.0 (10.5) ppb in the pooled sample, and 15.5 (9.3) in Sweden, 15.4 (13.6) in Finland and 12.5 (9.6) in Estonia (Kruskal–Wallis test, $p < 0.001$). The post-hoc analysis showed differences in median F_{ENO} between Estonia and the other countries ($p < 0.001$). Median F_{ENO} varied significantly between the centres ($p < 0.001$) (Fig. 3). We found lower median F_{ENO} ($p < 0.001$) values in Estonian centres, with differences between Narva and Helsinki ($p < 0.001$), Narva and Stockholm ($p = 0.001$), and Narva and Örebro ($p < 0.001$); and as well as significant differences between Saaremaa and Helsinki ($p = 0.002$), and Saaremaa and Örebro ($p < 0.001$).

3.3. Between country comparisons for asthma

The likelihood of having asthma was higher in Sweden and Finland than in Estonia, with crude *OR 2.39(1.48-3.85)* and *2.0(1.12-3.58),* respectively. Comparing Sweden with Finland, we found similar likelihood of having asthma, crude *OR 1.19(0.71-2.0)*.

3.4. F_{ENO} and asthma

We found that self-reported asthma was associated with F_{ENO} ≥25 ppb, *OR 3.91(2.39-6.32)*, after adjusting for SPT result, smoking, gender and study centre in a binary logistic regression model (Fig. 4) (Model can be found in the Appendix). Within this same model, we found that the overall effect of the study centre in general ($p < 0.01$) was a significant factor associated with asthma. Analysing the differences between the study centres within the model, we found that compared to Saaremaa, the likelihood of having asthma was higher in Helsinki *OR 2.40(1.04-6.02)*, Narva *OR 2.45(1.05-6.19)*, Örebro *OR 3.38(1.59-8.09)*, and Stockholm *OR 5.54(2.18-14.79)*. Within the model, asthma was associated with a positive SPT result, *OR 3.19(2.02-5.11)*, but not with smoking *OR 0.87(0.50-1.46)* or gender *OR 0.81(0.51-1.27),* in the whole population.

In the total pooled sample, the mean F_{ENO} was higher in participants with asthma (27 ppb) than without asthma (16 ppb) ($p < 0.001$), see Table 3. When stratifying for current smoking status, the mean F_{ENO} was higher in non-smokers, than in smokers ($p < 0.01$), both in asthmatics and in non-asthmatics. Further stratification revealed a higher mean F_{ENO} in atopic asthmatic individuals, than in non-asthmatics ($p < 0.001$) with atopy. Analogously, non-atopic asthmatic individuals had a higher mean F_{ENO} compared to non-asthmatics ($p = 0.016$) without atopy.

3.5. F_{ENO} ≥25 ppb

In the pooled sample, individuals with F_{ENO} ≥25 ppb were more likely to have atopy, self-reported asthma, physician diagnosed asthma, and allergic rhinitis (Table 4). Participants with F_{ENO} ≥25 ppb were more likely to report asthma symptoms, nightly symptoms, ICS use, and SABA use, in the previous year. Current smokers were more likely to have a F_{ENO} result <25 ppb. A result of F_{ENO} ≥25 ppb was not associated with COPD diagnosis or childhood asthma.

The prevalence of F_{ENO} ≥25 ppb in the pooled sample was 14.6%, with 14.7% in Sweden, 21.4% in Finland, and 11.2% in Estonia. In the centres, the prevalence of F_{ENO} ≥25 ppb was 10.6% in Stockholm, 16.6% in Örebro, 21.4% in Helsinki, 11.4% in Narva, and 11.1% in Saaremaa.

The ORs (95% CIs) for F_{ENO} ≥25 ppb, compared to Finland, were

Table 1
Anthropometric data and forced expiratory volume in 1 s (FEV1) in adult general populations of Stockholm, Örebro, Helsinki, Narva, and Saaremaa.

		Total	Stockholm	Örebro	Helsinki	Narva	Saaremaa
	n	1498	179	391	295	281	352
Gender	f/m	824/674	99/80	199/192	174/121	162/119	190/162
	%	55/45	55/45	51/49	59/41	58/42	54/46
Age (years)	mean (sd)	40.9 (10.9)	39.3 (10.0)	42.1 (10.8)	40.9 (10.2)	40.2 (11.6)	41.0 (11.4)
Height (cm)	mean (sd)	171.1 (9.3)	172.9 (9.6)	172.2 (9.2)	170.0 (9.3)	168.6 (8.7)	171.7 (9.3)
Weight (kg)	mean (sd)	75.3 (14.7)	72.7 (13.5)	75.5 (13.8)	75.2 (16.2)	73.7 (13.5)	77.6 (15.7)
BMI(kg/m^2)	mean (sd)	25.7 (4.5)	24.2 (3.5)	25.4 (3.9)	26.0 (5.0)	25.9 (4.4)	26.3 (5.0)
FEV_1 (L)	mean (sd)	3.4 (0.9)	3.7 (0.8)	3.2 (0.8)	3.3 (0.9)	3.4 (0.9)	3.6 (0.9)

f = female, m = male, sd = standard deviation.

Table 2
Median F_{ENO} (interquartile range (IQR)) and prevalence of asthma, respiratory symptoms within the last year, and atopy in Stockholm, Örebro, Helsinki, Narva, and Saaremaa.

		Stockholm	Örebro	Helsinki	Narva	Saaremaa	p
F_{ENO} median (IQR)		14.4 (8.0)	**15.7(10.1)**	15.4 (13.6)	11.8 (8.6)	13.1 (9.5)	<0.001†
		%	%	%	%	%	
Ever asthma	Yes	**12.8**	8.5	9.1	6.3	2.9	<0.001
Asthma by MD	Yes	**11.4**	7.8	7.2	5.4	2.3	<0.001
Asthma in childhood	Yes	8	**8.6**	7.3	1.8	6.4	<0.01
Asthma symptoms	Yes	**13.4**	9.2	12.5	6.1	2.6	<0.001
Nightly symptoms	Yes	**7.3**	4.9	1	6.4	4.3	<0.01
Asthma medication	Yes	**12.3**	6.9	9.2	4.6	2.3	<0.001
ICS used	Yes	**8.9**	4.1	5.1	1.1	0.6	<0.001
Saba used	Yes	**10.1**	5.9	4.4	3.6	2.3	<0.01
Atopy	Positive	21.2	33.5	**48.5**	37.7	25.8	<0.001
Allergic rhinitis	Yes	33	39.4	**40**	32.4	17.6	<0.001
Current smoking	Yes	37.2	22	37	**40.5**	34.1	<0.001
COPD by MD	Yes	2.9	1.31	2.8	**17.8**	9.2	<0.001

MD = medical doctor, COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroid, SABA = short-acting β_2-agonist, bolded numbers represent the highest prevalence †p values calculated with Kruskal-Wallis test for the differences in $F_{ENO,}$ for the others Pearson's χ^2 test for the interviews' answers and atopy (skin prick tests).

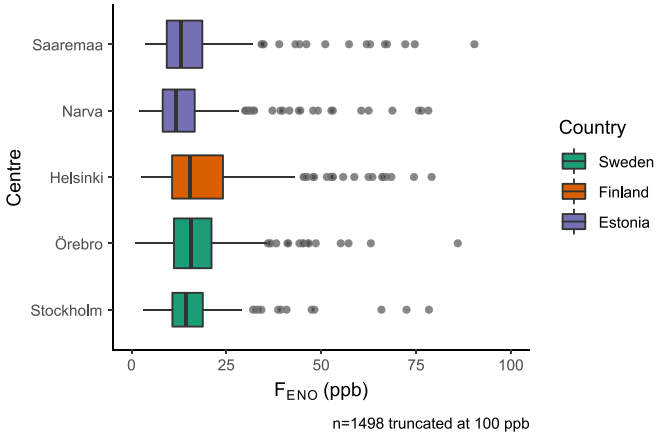

Fig. 3. Boxplot with fractional exhaled nitric oxide (F_{ENO}) values of general adult populations from the participating centres: Helsinki ($n = 295$), Stockholm ($n = 179$), Örebro ($n = 391$), Narva ($n = 281$), and Saaremaa ($n = 352$) grouped by countries.

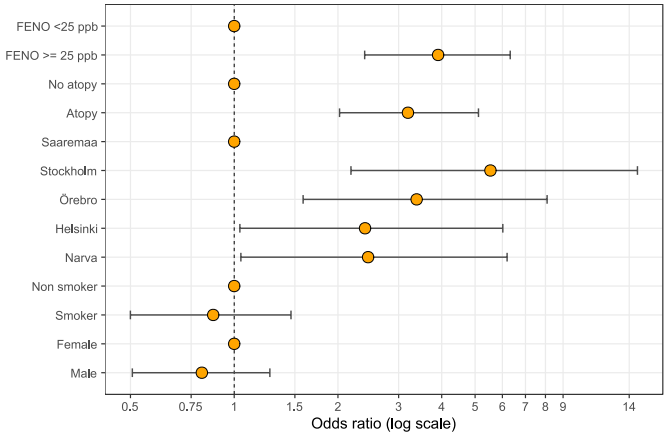

Fig. 4. Binary logistic regression model with asthma as outcome and F_{ENO} ≥25 ppb, participating centre, gender, smoking, and atopy as predictors. Presented as odds ratio (OR) with 95% confidence intervals. Reference groups: F_{ENO} <25 ppb, no atopy, Saaremaa, non-smoker and female.

0.60 (0.41–0.89) in Sweden and 0.48 (0.33–0.72) in Estonia, and adjusted for positive SPT 1.52 (1.11–2.07), smoking 0.33 (0.22–0.49), and male gender 1.36 (1–1.85). Similarly, compared to Helsinki, the adjusted OR for F_{ENO} ≥25 ppb was 0.42 (0.21–0.81) in Stockholm, 0.65 (0.43–0.98) in Örebro, 0.53 (0.32–0.84) in Narva and 0.45 (0.28–0.71) in Saaremaa.

4. Discussion

We observed a west–east gradient of F_{ENO} levels and prevalences of asthma and asthma symptoms in the studied populations from Sweden, Finland and Estonia. In the pooled samples, we found a higher median F_{ENO} in Sweden and Finland compared to Estonia. The Estonian centres had a lower median F_{ENO} compared to Swedish and Finnish centres. The Estonian populations and the pooled Estonian sample also had lower adjusted ORs for asthma.

Previous investigations on these Nordic populations hypothesised diagnostic differences and labelling of asthma as potential explanations for the lower prevalence of asthma and its symptoms in Estonia [14], as well as possible low physician diagnosis rates [11]. Nevertheless, we found significantly different F_{ENO} levels in the regions studied, supporting the view, that there is a real disparity in asthma prevalences between the studied centres, reflecting differences in allergic airway diseases. The reasons for the west–east gradient in F_{ENO} and asthma prevalence may be based, for example, on differences in genetic, geographical, environmental, occupational and socio-economical risk factors and lifestyle, and on protective factors, like rural living. A previous comparison between Uppsala in Sweden and Tartu in Estonia found a lower prevalence of atopy, and a lower prevalence of pollen-associated asthma symptoms in Estonia than in Sweden [29]. However, a previous FinEsS study found, apart from similar prevalence of sensitisation in Sweden, Finland and Estonia, a deviant sensitisation pattern: storage mites and cockroach were major sensitisers in Estonia [30], while sensitisation in Finland and Sweden was mainly attributable to pollen and furry animals [24,31]. Moreover, marked differences in the sensitisation levels have been found between North Karelia in Finland and the Republic of Karelia in Russia, with higher asthma prevalence in Finnish Karelia [32]. Remarkably, another study in Uppsala and Tartu found lower mean eosinophilic cationic protein (ECP) blood levels, a biomarker of eosinophilic inflammation, in Tartu [33], further endorsing the findings of the present study. Farm living was previously found to reduce the risk for allergy and asthma development [6,34,[35]], and this could partly explain the lower asthma risk in Saaremaa, an Estonian island with a high degree of rurality. On the other hand, Narva is a highly industrialised and air-polluted area next to the

Table 3
Fractional exhaled nitric oxide (F_{ENO}) mean (SD) stratified by smoking and atopic status in participants with or without asthma.

		Asthmatics (n = 103)				Non asthmatics (n = 1329)			
F_{ENO} (ppb)	mean (sd)	27 (29)				16.3 (11)			
		current non smoker		current smoker		current non smoker		current smoker	
	n (%)	80 (73%)		23 (22%)		903 (68%)		422 (32%)	
F_{ENO} (ppb)	mean (sd)	29.8 (31.6)		17.1 (12.9)		18 (11.6)		12.8 (8.8)	
F_{ENO} ≥25 ppb	%	32 (40%)		4 (17%)		142 (16%)		26 (6%)	
		atopic	non-atopic	atopic	non-atopic	atopic	non-atopic	atopic	non-atopic
		Σn = 67		Σn = 21		Σn = 841		Σn = 393	
	n (%)	42 (63%)	25 (37%)	13 (62%)	8 (38%)	271 (32%)	570 (68%)	130 (33%)	263 (67%)
F_{ENO} (ppb)	mean (sd)	31.5 (37.3)	30.9 (22.5)	21.7 (14.9)	11.3 (7.1)	19.9 (14.2)	17 (9.8)	13.3 (11.4)	12.4 (7.4)
F_{ENO} ≥25 ppb	n (%)	17 (41%)	13 (52%)	3 (10%)	1 (13%)	53 (20%)	80 (14%)	10 (7.7%)	15 (6%)

Data shown as n (%) or mean (standard deviation).

Table 4
Univariate crude odds ratio (with 95% confidence intervals) in the pooled sample for F_{ENO} ≥25 ppb and diagnosis, respiratory symptoms and medication within last year, and current smoking.

		Odds ratio	Confidence Intervals	p
Ever asthma	Yes	3.71	2.40–5.74	<0.001
Asthma by MD	Yes	2.78	1.74–4.44	<0.001
Asthma in childhood	Yes	1.35	0.78–2.33	0.358
Asthma symptoms	Yes	3.1	2.06–4.68	<0.001
Nightly symptoms	Yes	2.04	1.15–3.60	0.02
Asthma medication	Yes	3.22	2.05–5.05	<0.001
ICS used	Yes	2.48	1.34–4.60	0.005
Saba used	Yes	3.40	2.04–5.65	<0.001
Atopy	Positive	1.62	1.20–2.19	0.002
Allergic rhinitis	Yes	2.11	1.58–2.83	<0.001
COPD by MD	Yes	1.09	0.61–1.92	0.897
Current smoking	Yes	0.33	0.23–0.49	<0.001

MD = medical doctor, COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroid, SABA = short-acting β_2-agonist.

Russian border, with an ethnic Russian majority [9], and high prevalences of smoking (40.5%) and COPD (17.8%). A recent study analysing the air concentrations of fine particles, benzene, and phenol, showed a similar prevalence of self-reported asthma in Narva, as in our present study [36]. The environmental factors, smoking and occupational conditions could partly explain the low median F_{ENO}, since our analyses revealed a slightly higher likelihood of asthma in Narva compared to Saaremaa.

Previous studies observed a decrease of F_{ENO} levels by current smoking [37–39], and others have also suggested a similar effect by past smoking [39,40]. An experimental study in lung epithelial cells discovered a possible mechanism for the effect of cigarette smoke on F_{ENO} production, down-regulation of an inducible nitric oxide synthase enzyme (iNOS) [41]. Our stratified analyses corroborate the lower F_{ENO} levels in smokers, independently of asthma or atopy.

As expected, a F_{ENO} level ≥25 ppb was strongly associated with asthma in the pooled population. Likewise, a positive SPT result was associated with asthma. A previous study from an Icelandic population, in which F_{ENO} ≥25 ppb was positively associated with asthma and a positive SPT, found a similar prevalence of F_{ENO} ≥25 ppb as in our Finnish population [42].

Previously, atopy and smoking were found to be associated with F_{ENO} in Scandinavian populations [42–44]. Nevertheless, a previous investigation in Helsinki could not find differences of F_{ENO} between SPT negative and SPT positive healthy asymptomatic non-smokers [45]. Thus, elevated F_{ENO} in atopic subjects indicates an allergic airway disorder. In concordance with a large study of F_{ENO} in Scandinavia [44], we showed here that atopic subjects frequently have elevated F_{ENO} levels regardless of smoking.

This is, as far as we know, the largest multi-centre study on F_{ENO} in populations of Northern European countries, including skin prick testing and a structured interview. The study reflects the era after the Estonian Restoration of Independence and the end of the Soviet occupation during the 1990's, which apart from its historical importance, marks a change in lifestyle, occupational and socio-economical conditions. At the same time, Finland and Sweden were already immersed in a westernised lifestyle with a higher socio-economical status. This background gives unique possibilities to study the differences in the prevalences of asthma and atopy and to find out differences in F_{ENO} levels. Previously, an increase in atopic sensitisation was found after the German Reunification in schoolchildren in former East Germany during the 1990's [2].

One strength of the study is, that self-reported parameters were compared with measured F_{ENO} and skin-prick test data. Weaknesses of the present study could be, apart from employing self-reported parameters, a possible selection bias through multiple inclusion steps and the differences in expiratory flows in the original F_{ENO} measurements. Nevertheless, we employed similar F_{ENO} devices and applied a validated conversion model to standardise F_{ENO} to the recommended expiratory flow of 50 mL/s [21] to obtain comparable values. The standardised F_{ENO} values are similar to those obtained in large general populations studies [46] and also by applying a reference equation to our pooled population [47]. The F_{ENO} value obtained in Örebro in the present study is in harmony with the values found in a general population study from Gothenburg in Sweden [44], which employed the recommended expiratory flow of 50 mL/s.

In conclusion, the median F_{ENO} was lower in the general adult populations in Estonia, than in Sweden or Finland. We found that F_{ENO} followed a west-east gradient, parallel with the differences in asthma prevalence in the studied centres and a higher likelihood of asthma in western populations. The findings support the earlier west-east disparity hypothesis of allergic diseases. We also showed here that atopy and increased F_{ENO} values (≥25 ppb) were independently positively associated with asthma, confirming earlier studies.

Author contributions

BL and AS conceived and designed the research. ML, MM, AS, and B-MS supervised the experiments. PLK analysed the data and wrote the manuscript, under the tutelage of PLP and AS. All authors read and approved the manuscript.

Acknowledgments

We thank staff members from the Skin and Allergy Hospital and the Laboratory of Clinical Physiology at the Meilahti Hospital, and Alyce Whipp, MPH for the language revision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106160.

Funding

This work was supported by: Foundation of the Finnish Anti-Tuberculosis Association, Finland; The Research Foundation of the Pulmonary Diseases, Finland; Tampere Tuberculosis Foundation: Eero Hämäläinen, Finland; Väinö and Laina Kivi Foundation, Finland; Ida Montin Foundation, Finland; Estonian Science Foundation, Estonia; Nummela Sanatorium Foundation, Finland; the University of Helsinki, Finland; and the Nordic Council of Ministers: NordForsk (Nordic Epi-Lung Study), Norway.

References

[1] T. To, S. Stanojevic, G. Moores, A.S. Gershon, E.D. Bateman, A.A. Cruz, L.-P. Boulet, Global asthma prevalence in adults: findings from the cross-sectional world health survey, BMC Publ. Health 12 (2012) 204, https://doi.org/10.1186/1471-2458-12-204.

[2] E. von Mutius, S.K. Weiland, C. Fritzsch, H. Duhme, U. Keil, Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany, Lancet 351 (1998) 862–866, https://doi.org/10.1016/S0140-6736(97)10100-3.

[3] P. Pallasaho, B. Lundbäck, S.L. Läspä, E. Jönsson, J. Kotaniemi, A.R.A. Sovijärvi, L. A. Laitinen, Increasing prevalence of asthma but not of chronic bronchitis in Finland? Report from the FinEsS-Helsinki study, Respir. Med. 93 (1999) 798–809, https://doi.org/10.1016/S0954-6111(99)90265-2.

[4] H. Hisinger-Mölkänen, P. Pallasaho, T. Haahtela, A. Lindqvist, A. Sovijärvi, P. Piirilä, The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland, Respir. Med. 155 (2019) 121–126, https://doi.org/10.1016/j.rmed.2019.07.014.

[5] H. Backman, P. Räisänen, L. Hedman, C. Stridsman, M. Andersson, A. Lindberg, B. Lundbäck, E. Rönmark, Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys, Clin. Exp. Allergy 47 (1426), https://doi.org/10.1111/cea.12963, 1435, n.d.

[6] E. Borna, B.I. Nwaru, A. Bjerg, R. Mincheva, M. Rådinger, B. Lundbäck, L. Ekerljung, Changes in the prevalence of asthma and respiratory symptoms in western Sweden between 2008 and 2016, Allergy 74 (2019) 1703–1715, https://doi.org/10.1111/all.13840.

[7] B. Lundbäck, H. Backman, J. Lötvall, E. Rönmark, Is asthma prevalence still increasing? Expet Rev. Respir. Med. 10 (2016) 39–51, https://doi.org/10.1586/17476348.2016.1114417.

[8] GBD 2016 disease and injury incidence and prevalence collaborators, global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet 390 (2017) 1211–1259, https://doi.org/10.1016/S0140-6736(17)32154-2.

[9] L. Jannus-Pruljan, M. Meren, J. Pölluste, H.-M. Loit, J. Kiviloog, A. Baburin, B. Lundbäck, Postal survey on asthma, chronic bronchitis and respiratory symptoms among adult Estonians and non-Estonians (FinEsS-study), Eur. J. Publ. Health 14 (2004) 114–119, https://doi.org/10.1093/eurpub/14.2.114.

[10] B. Bjorksten, D. Dumitrascu, T. Foucard, N. Khetsuriani, R. Khaitov, M. Leja, G. Lis, J. Pekkanen, A. Priftanji, M.A. Riikjarv, Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe, Eur. Respir. J. 12 (1998) 432–437.

[11] M. Meren, A. Raukas-Kivioja, L. Jannus-Pruljan, H.-M. Loit, E. Rönmark, B. Lundbäck, Low prevalence of asthma in westernizing countries—myth or reality? Prevalence of asthma in Estonia—a report from the “FinEsS” study, J. Asthma 42 (2005) 357–365, https://doi.org/10.1081/JAS-62985.

[12] E. von Mutius, F.D. Martinez, C. Fritzsch, T. Nicolai, G. Roell, H.H. Thiemann, Prevalence of asthma and atopy in two areas of West and East Germany, Am. J. Respir. Crit. Care Med. 149 (2 Pt 1) (1994) 358–364, https://doi.org/10.1164/ajrccm.149.2.8306030.

[13] L. Bråbäck, A. Breborowicz, K. Julge, A. Knutsson, M.A. Riikjärv, M. Vasar, B. Björkstén, Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area, Arch. Dis. Child. 72 (1995) 487–493.

[14] P. Pallasaho, M. Meren, A. Raukas-Kivioja, E. Rönmark, Different labelling of obstructive airway diseases in Estonia, Finland, and Sweden, Eur. J. Epidemiol. 20 (2005) 975–983, https://doi.org/10.1007/s10654-005-4117-6.

[15] T. Haahtela, T. Laatikainen, H. Alenius, P. Auvinen, N. Fyhrquist, I. Hanski, L. von Hertzen, P. Jousilahti, T.U. Kosunen, O. Markelova, M.J. Mäkelä, V. Pantelejev, M. Uhanov, E. Zilber, E. Vartiainen, Hunt for the origin of allergy – comparing the Finnish and Russian Karelia, Clin. Exp. Allergy 45 (2015) 891–901, https://doi.org/10.1111/cea.12527.

[17] S. Kharitonov, K. Alving, P.J. Barnes, Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force, Eur. Respir. J. 10 (1997) 1683–1693.

[18] P.G. Lassmann-Klee, T. Lindholm, M. Metsälä, L. Halonen, A.R.A. Sovijärvi, P. Piirilä, Reduction of FENO by tap water and carbonated water mouthwashes: magnitude and time course, Scand. J. Clin. Lab. Invest. 78 (2018) 153–156, https://doi.org/10.1080/00365513.2017.1419574.

[19] P.G. Lassmann-Klee, L. Lehtimäki, T. Lindholm, L.P. Malmberg, A.R.A. Sovijärvi, P. Piirilä, Influence of mouthwashes on extended exhaled nitric oxide (FENO) analysis, Scand. J. Clin. Lab. Invest. 78 (2018) 450–455, https://doi.org/10.1080/00365513.2018.1497802.

[20] ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, Am. J. Respir. Crit. Care Med. 171 (2005) 912–930, https://doi.org/10.1164/rccm.200406-710ST.

[21] P.G. Lassmann-Klee, L. Lehtimäki, T. Lindholm, L.P. Malmberg, A.R.A. Sovijärvi, P. L. Piirilä, Converting FENO by different flows to standard flow FENO, Clin. Physiol. Funct. Imag. 39 (2019) 315–321, https://doi.org/10.1111/cpf.12574.

[22] R.A. Dweik, P.B. Boggs, S.C. Erzurum, C.G. Irvin, M.W. Leigh, J.O. Lundberg, A.-C. Olin, A.L. Plummer, D.R. Taylor, An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications, Am. J. Respir. Crit. Care Med. 184 (2011) 602–615, https://doi.org/10.1164/rccm.9120-11ST.

[23] I. Horváth, P.J. Barnes, S. Loukides, P.J. Sterk, M. Högman, A.-C. Olin, A. Amann, B. Antus, E. Baraldi, A. Bikov, A.W. Boots, L.D. Bos, P. Brinkman, C. Bucca, G. E. Carpagnano, M. Corradi, S. Cristescu, J.C. de Jongste, A.-T. Dinh-Xuan, E. Dompeling, N. Fens, S. Fowler, J.M. Hohlfeld, O. Holz, Q. Jöbsis, K.V.D. Kant, H. H. Knobel, K. Kostikas, L. Lehtimäki, J.O. Lundberg, P. Montuschi, A.V. Muylem, G. Pennazza, P. Reinhold, F.L.M. Ricciardolo, P. Rosias, M. Santonico, M.P. van der Schee, F.-J. van Schooten, A. Spanevello, T. Tonia, T.J. Vink, A European Respiratory Society technical standard: exhaled biomarkers in lung disease, Eur. Respir. J. 49 (2017) 1600965, https://doi.org/10.1183/13993003.00965-2016.

[24] P. Pallasaho, E. Rönmark, T. Haahtela, A.R.A. Sovijärvi, B. Lundbäck, Degree and clinical relevance of sensitization to common allergens among adults: a population study in Helsinki, Finland, Clin. Exp. Allergy 36 (2006) 503–509, https://doi.org/10.1111/j.1365-2222.2006.02460.x.

[25] L. Heinzerling, A. Mari, K.-C. Bergmann, M. Bresciani, G. Burbach, U. Darsow, S. Durham, W. Fokkens, M. Gjomarkaj, T. Haahtela, A.T. Bom, S. Wöhrl, H. Maibach, R. Lockey, The skin prick test – European standards, Clin. Transl. Allergy 3 (2013) 3, https://doi.org/10.1186/2045-7022-3-3.

[26] R. Core Team, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2018. https://www.R-project.org/.

[27] R.G. Newcombe, Interval estimation for the difference between independent proportions: comparison of eleven methods, Stat. Med. 17 (1998) 873–890, https://doi.org/10.1002/(sici)1097-0258 (19980430)17:8<873::aid-sim779>3.0.co;2-i.

[28] F.Y. Hsieh, D.A. Bloch, M.D. Larsen, A simple method of sample size calculation for linear and logistic regression, Stat. Med. 17 (1998) 1623–1634.

[29] R. Jõgi, C. Janson, E. Björnsson, G. Boman, B. Björkstén, Atopy and allergic disorders among adults in Tartu, Estonia compared with Uppsala, Sweden, Clin. Exp. Allergy 28 (1998) 1072–1080, https://doi.org/10.1046/j.1365-2222.1998.00366.x.

[30] A. Raukas-Kivioja, E.-S. Raukas, M. Meren, H.-M. Loit, E. Rönmark, B. Lundbäck, Allergic sensitization to common airborne allergens among adults in Estonia, Int. Arch. Allergy Immunol. 142 (2007) 247–254, https://doi.org/10.1159/000097027.

[31] K. Warm, A. Lindberg, B. Lundbäck, E. Rönmark, Increase in sensitization to common airborne allergens among adults – two population-based studies 15 years apart, Allergy Asthma Clin, Immunol. 9 (2013) 20, https://doi.org/10.1186/1710-1492-9-20.

[32] E. Vartiainen, T. Petäys, T. Haahtela, P. Jousilahti, J. Pekkanen, Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia, J. Allergy Clin. Immunol. 109 (2002) 643–648, https://doi.org/10.1067/mai.2002.123307.

[33] R. Jõgi, B. Björkstén, G. Boman, C. Janson, Serum eosinophil cationic protein (S-ECP) in a population with low prevalence of atopy, Respir. Med. 96 (2002) 525–529, https://doi.org/10.1053/rmed.2002.1320.

[34] B.N. Lambrecht, H. Hammad, The immunology of the allergy epidemic and the hygiene hypothesis, Nat. Immunol. 18 (2017) 1076–1083, https://doi.org/10.1038/ni.3829.

[35] G. Wennergren, L. Ekerljung, B. Alm, J. Eriksson, J. Lötvall, B. Lundbäck, Asthma in late adolescence – farm childhood is protective and the prevalence increase has levelled off, Pediatr. Allergy Immunol. 21 (2010) 806–813, https://doi.org/10.1111/j.1399-3038.2010.01057.x.

[36] H. Orru, J. Idavain, M. Pindus, K. Orru, K. Kesanurm, A. Lang, J. Tomasova, Residents’ self-reported health effects and annoyance in relation to air pollution exposure in an industrial area in eastern-Estonia, Int. J. Environ. Res. Publ. Health 15 (2018) 252, https://doi.org/10.3390/ijerph15020252.

[37] D.R. Taylor, P. Mandhane, J.M. Greene, R.J. Hancox, S. Filsell, C.R. McLachlan, A. J. Williamson, J.O. Cowan, A.D. Smith, M.R. Sears, Factors affecting exhaled nitric oxide measurements: the effect of sex, Respir. Res. 8 (2007) 82, https://doi.org/10.1186/1465-9921-8-82.

[38] K. Kostikas, A.I. Papaioannou, K. Tanou, A. Koutsokera, M. Papala, K. I. Gourgoulianis, Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season, Chest 133 (2008) 906–913, https://doi.org/10.1378/chest.07-1561.

[39] M. Juusela, P. Pallasaho, E. Rönmark, S. Sarna, A. Sovijärvi, B. Lundbäck, Dose-dependent association of smoking and bronchial hyperresponsiveness, Eur. Respir. J. 42 (2013) 1503–1512, https://doi.org/10.1183/09031936.00073712.

[40] C.P. McSharry, I.C. McKay, R. Chaudhuri, E. Livingston, I. Fraser, N.C. Thomson, Short and long-term effects of cigarette smoking independently influence exhaled nitric oxide concentration in asthma, J. Allergy Clin. Immunol. 116 (2005) 88–93, https://doi.org/10.1016/j.jaci.2005.03.025.

[41] J.C. Hoyt, R.A. Robbins, M. Habib, D.R. Springall, L.D.K. Buttery, J.M. Polak, P. J. Barnes, Cigarette smoke decreases inducible nitric oxide synthase in lung

epithelial cells, Exp. Lung Res. 29 (2003) 17–28, https://doi.org/10.1080/01902140303759.
[42] A.K. Thorhallsdottir, D. Gislason, A. Malinovschi, M. Clausen, T. Gislason, C. Janson, B. Benediktsdottir, Exhaled nitric oxide in a middle-aged Icelandic population cohort, J. Breath Res. 10 (2016), 046015, https://doi.org/10.1088/1752-7155/10/4/046015.
[43] Y. Çolak, S. Afzal, B.G. Nordestgaard, J.L. Marott, P. Lange, Combined value of exhaled nitric oxide and blood eosinophils in chronic airway disease: the Copenhagen General Population Study, Eur. Respir. J. 52 (2018) 1800616, https://doi.org/10.1183/13993003.00616-2018.
[44] A.-C. Olin, A. Rosengren, D.S. Thelle, L. Lissner, B. Bake, K. Torén, Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample, Chest 130 (2006) 1319–1325, https://doi.org/10.1378/chest.130.5.1319.
[45] A. Rouhos, A. Kainu, J. Karjalainen, A. Lindqvist, P. Piirilä, S. Sarna, T. Haahtela, A.R.A. Sovijärvi, Atopic sensitization to common allergens without symptoms or signs of airway disorders does not increase exhaled nitric oxide, Clin. Res. J. 2 (2008) 141–148, https://doi.org/10.1111/j.1752-699X.2007.00045.x.
[46] T. Jacinto, A. Malinovschi, C. Janson, J. Fonseca, K. Alving, Evolution of exhaled nitric oxide levels throughout development and aging of healthy humans, J. Breath Res. 9 (2015), 036005, https://doi.org/10.1088/1752-7155/9/3/036005.
[47] A.-C. Olin, B. Bake, K. Torén, Fraction of exhaled nitric oxide at 50 mL/s: reference values for adult lifelong never-smokers, Chest 131 (2007) 1852–1856, https://doi.org/10.1378/chest.06-2928.