Received: 30 November 2020 | Accepted: 15 September 2021

DOI: 10.1111/cea.14019

ORIGINAL ARTICLE

WILEY

Cross-sectional study on exhaled nitric oxide in relation to upper airway inflammatory disorders with regard to asthma and perennial sensitization

Christina Krantz[1] | Simone Accordini[2] | Kjell Alving[1] | Angelo G. Corsico[3,4] | Pascal Demoly[5,6] | Diogenes S. Ferreira[7,8] | Bertil Forsberg[9] | Judith Garcia-Aymerich[10,11,12] | Thorarinn Gislason[13,14] | Joachim Heinrich[15,16,17] | Rain Jõgi[18] | Ane Johannessen[19] | Bénédicte Leynaert[20] | Alessandro Marcon[2] | Jesús Martínez-Moratalla Rovira[21,22] | Elisabet Nerpin[23,24,25] | Dennis Nowak[15,16] | Anna-Carin Olin[26] | Mario Olivieri[27] | Antonio Pereira-Vega[28] | Chantal Raherison-Semjen[29,30] | Francisco Gómez Real[31,32] | Torben Sigsgaard[33] | Guilia Squillacioti[34] | Christer Janson[23] | Andrei Malinovschi[24] | the European Community Respiratory Health Survey III

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[2]Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

[3]Division of Respiratory Diseases, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

[4]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

[5]Département de Pneumologie et Addictologie, Centre Hospitalier Universitaire de Montpellier, Montpellier, France

[6]Hôpital Arnaud de Villeneuve, IDESP, INSERM-Univ Montpellier, Montpellier, France

[7]School of Public Health and Preventive Medicine, Monash University, Melbourne, Vic., Australia

[8]Alergia e Imunologia, Complexo Hospital de Clinicas, Universidade Federal do Parana, Curitiba, Brazil

[9]Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden

[10]ISGlobal, Barcelona, Spain

[11]Universitat Pompeu Fabra (UPF), Barcelona, Spain

[12]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

[13]Department of Sleep, Landspitali_the National University Hospital, Reykjavik, Iceland

[14]Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[15]Institute and Clinic for Occupational, Social and Environmental Medicine, LMU University Clinic, Comprehensive Pneumology Center (CPC), Munich, Germany

[16]German Center for Lung Research (DZL), Gießen, Germany

[17]Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Vic., Australia

[18]Lung Clinic, Tartu University Hospital, Tartu, Estonia

[19]Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[20]Université Paris-Saclay, UVSQ, Univ. Paris-Sud, INSERM, Équipe d'Épidémiologie respiratoire intégrative, CESP, Villejuif, France

[21]Pneumology Service of the University Hospital of Albacete, Albacete, Spain

[22]Faculty of Medicine of Albacete, Castilla-La Mancha University, Albacete, Spain

[23]Department of Medical Sciences, Respiratory Medicine, Allergy and Sleep, Uppsala University, Uppsala, Sweden

[24]Department of Medical Sciences, Clinical Physiology, Uppsala University, Uppsala, Sweden

[25]Department of Medicine, Health and Social Studies, Dalarna University, Falun, Sweden

[26]Section of Occupational and Environmental Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

[27]Unit of Occupational Medicine, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

[28]Pneumology Service, Juan Ramón Jiménez Hospital in Huelva, Huelva, Spain

[29]Univ. Bordeaux, INSERM, Bordeaux, France

[30]Service des Maladies Respiratoires, Pole cardio-thoracique, CHU, Bordeaux, France

[31]Research Unit for Health Surveys (RUHS), Department of Clinical Sciences, University of Bergen, Bergen, Norway

[32]Department of Gynaecology and Obstetrics, Haukeland University Hospital, Bergen, Norway

[33]Department of Public Health, Danish Ramazzini Center, Aarhus University, Aarhus, Denmark

[34]Department of Public Health and Pediatrics, University of Turin, Turin, Italy

Correspondence
Christina Krantz, Uppsala Centre for Cystic Fibrosis, Uppsala University Hospital, Akademiska Sjukhuset, 75185 Uppsala, Sweden.
Email: christina.krantz@kbh.uu.se

Funding information
Sociedad Espanola de Neumologia y Cirygia Torácia (SEPAR 1001/2010); Centro de Exalencia Severo Ochoa 2019-2023 (CEX2018-000806-S); Servicio Andaluz de Salud; Swedish Research Council for Health, Working Life and Social Research; Västerbotten County Council ALF grant; CERCA program; ResMed Foundation, California, USA; Orkuveita Reykjavíkur (Geothermal plant); University of Icelnd Research Fund; German Research Foundation MA 711/6-1; German Reasearch Foundation NO 262/7-1; Agence Nationale de la Santé, Région Ile de France, domaine d'intérêt majeur; German Research Foundation HE 3294/01-1; Westerm Norway Regional Health Authorities grant no 911631; Norwegian Research Council grant no 214123; Cariverona foundation; Vegagerdin (The Icelandic Road Administration); Talecris Biotherapeutics GmbH; Abott Diagnostics; Freiwillige Akademische Gesellschaft; The Lung Leagues of the cantons Basel Stadt/Basel, Landschaft, Geneva, Ticino, Valais, and Zurich; SUVA; Ministère de la Santé, Programme Hospitalier de Recherche Clinique 187 (PHRC) national 2010; European Commission 018996 (GABRIEL); Wellcome Trust WT 084703MA; the canton governments of Aargan, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais and Zurich; Swiss Lung League; Federal Office for Public Health; Federal Office of Roads and Transport; Swiss National Science Foundation (grants no 4026-028099); Federal Office for Forest, Environment and Landscape; Comité Scientifique AGIRadom 2011; Estonian Ministry of Education (grant code SF0180060s09); Estonian Research Council Personal Research Grant no 562; National Health & Medical Research Council Australia; Research Foundation Flanders (grant code G.0.0410.08.N.10); Medical Research Council (Grant Number 92091); Medical Research Council, Grant/Award Number: 92091; National Health & Medical Research Council; Research Foundation Flanders (FWO); Estonia, Grant/Award Number: Tartu and SF0180060s09; Estonian Ministry of Education; Estonian Research Council Personal Research, Grant/Award Number: 562; Ministère de la Santé, Programme Hospitalier de Recherche Clinique (PHRC); INSERM U897 Université Bordeaux Segalen; German Research Foundation, Grant/Award Number: 3294/10-1; Hamburg—German Research Foundation, Grant/Award Number: 711/6-1 and 262/7-1; The Landspítali University Hospital Research Fund; University of Iceland Research Fund; ResMed Foundation; Italian Ministry of Health; Chiesi Farmaceutici SpA; Cariverona Foundation; Education Ministry (MIUR); Norwegian Research Council, Grant/Award Number: 214123; Western Norway Regional Health Authorities, Grant/Award Number: 911631; Bergen Medical Research Foundation; Fondo de Investigación Sanitaria, Grant/Award Number: PS09/02457, PS09/00716, PS, 09/01511, PS09/02185 and PS09/03190; Servicio Andaluz de Salud, Sociedad Española de Neumología y Cirurgía Torácica, Grant/Award Number: 1001/2010; Fondo de Investigación Sanitaria, Grant/Award Number: PS09/02457; Barcelona—Fondo de Investigación Sanitaria, Grant/Award Number: PS09/00716; Galdakao—Fondo de Investigación Sanitaria, Grant/Award Number: 09/01511; Fondo de Investigación Sanitaria, Grant/Award Number: PS09/02185; Servicio Andaluz de Salud; "Centro de Excelencia Severo Ochoa 2019-2023" Program, Grant/Award Number: CEX2018-000806-S; Generalitat de Catalunya through the CERCA Program; Swedish Heart and Lung Foundation; Swedish Asthma and Allergy Association; Swedish Association against Lung and Heart Disease; Swedish Research Council for Health, Working Life and Welfare (FORTE); Swedish Council for Working Life and Social Research; Västerbotten County Council ALF; Swiss National Science Foundation, Grant/Award Number: 33CSCO, -134276/1, 33CSCO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532 and 4026-028099; UBS Wealth Foundation; Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission, Grant/Award Number: 018996; Wellcome Trust, Grant/Award Number: 084703MA; National Institute for Health Research through the Primary Care Research Network

Abstract

Background: Fractional exhaled nitric oxide (FeNO) is a well-known marker of type-2 inflammation. FeNO is elevated in asthma and allergic rhinitis, with IgE sensitization as a major determinant.

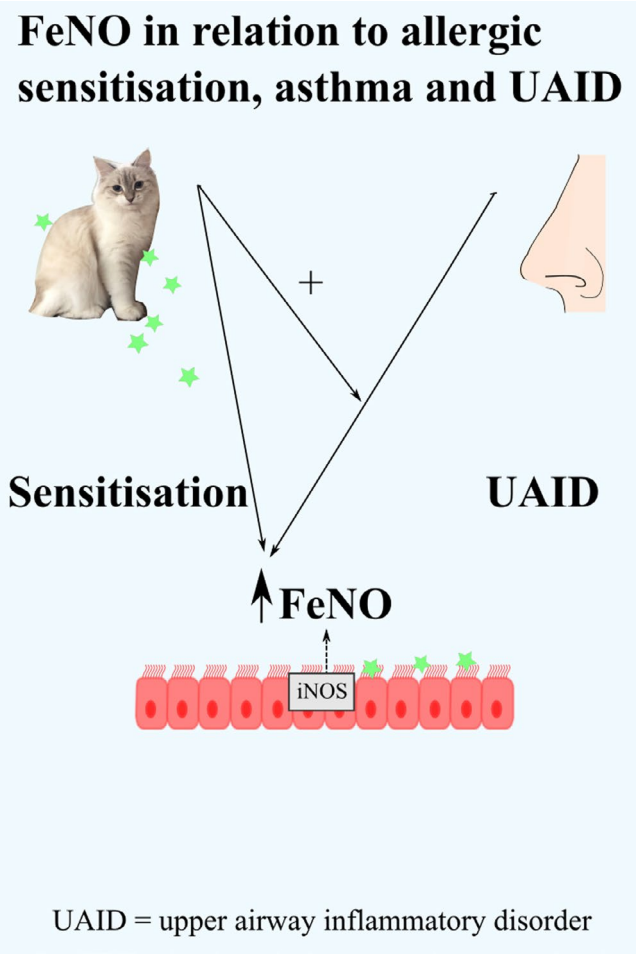
Objective: We aimed to see whether there was an independent association between upper airway inflammatory disorders (UAID) and FeNO, after adjustment for asthma and sensitization, in a multi-centre population-based study.

Methods: A total of 741 subjects with current asthma and 4155 non-asthmatic subjects participating in the second follow-up of the European Community Respiratory Health Survey (ECRHS III) underwent FeNO measurements. Sensitization status was based on measurement of IgE against airborne allergens; information on asthma, UAID and medication was collected through interview-led questionnaires. Independent associations between UAID and FeNO were assessed in adjusted multivariate regression models and test for interaction with perennial sensitization and asthma on the relation between UAID and FeNO were made.

Results: UAID were associated with higher FeNO after adjusting for perennial sensitization, asthma and other confounders: with 4.4 (0.9–7.9) % higher FeNO in relation to current rhinitis and 4.8 (0.7–9.2) % higher FeNO in relation to rhinoconjunctivitis. A significant interaction with perennial sensitization was found in the relationship between current rhinitis and FeNO ($p = .03$) and between rhinoconjunctivitis and FeNO ($p = .03$). After stratification by asthma and perennial sensitization, the association between current rhinitis and FeNO remained in non-asthmatic subjects with perennial sensitization, with 12.1 (0.2–25.5) % higher FeNO in subjects with current rhinitis than in those without.

Conclusions & Clinical Relevance: Current rhinitis and rhinoconjunctivitis was associated with higher FeNO, with an interaction with perennial sensitization. This further highlights the concept of united airway disease, with correlations between symptoms and inflammation in the upper and lower airways and that sensitization needs to be accounted for in the relation between FeNO and rhinitis.

KEYWORDS
asthma, exhaled nitric oxide, FeNO, nasal polyposis, population-based, rhinitis



GRAPHICAL ABSTRACT
Upper airway inflammatory diseases, current rhinitis and rhinoconjunctivitis, are associated with higher FeNO at a population level. There is an interaction with perennial IgE sensitisation on these associations.

1 | INTRODUCTION

Asthma is a common respiratory disease with a prevalence in adults of over 4% worldwide and a large variation of prevalence between countries.[1,2] Comorbidity with allergic rhinitis (AR) is common in asthma, and AR has an impact on asthma control and severity.[3,4] There is also evidence that AR to a certain extent is part of the same entity as asthma, with bronchial hyperreactivity, signs of small airway impairment[5,6] and lower airway inflammation (with increased sputum eosinophils) seen in patients with AR.[7,8] There is ample evidence of a united airway disease linking upper airway symptoms in asthma to structural and inflammatory changes in the lower airways of patients with AR.[9] In epidemiological analyses of more than 15,000 participants, both hypothesis-driven and hypothesis-free approaches showed that multimorbidity of asthma, rhinitis and eczema occurred more frequently than expected by chance and that sensitization as a mechanism explained only a small part of this multimorbidity.[10,11]

Atopic asthma is the most common subgroup of asthma and is associated with type-2 inflammation.[12] Type-2 inflammation is also seen in non-atopic eosinophil asthma, where group 2 innate lymphoid cell (ILC2) plays an important role in the inflammation.[13] Exhaled nitric oxide (NO) is a well-established marker of type-2 inflammation leading to activation of inducible NO synthase in the airway epithelium.[14] Fractional exhaled NO (FeNO) is a non-invasive method of measuring NO production in the lower airways, which is elevated in subjects with asthma,[15] with higher levels in subjects with allergic asthma than in subjects with non-allergic asthma.[16] In subjects with allergic asthma, both FeNO and inducible NO synthase expression are higher than in healthy controls and FeNO increases further after allergen provocation.[17] FeNO levels can be reduced by treatment with inhaled corticosteroids (ICS),[18] and FeNO has been proposed as a complementary tool for diagnosis and treatment management in asthma.[19]

FeNO levels are influenced by constitutional factors like age, gender and height.[20] Current smoking reduces FeNO levels,[20] while Immunoglobulin E (IgE) sensitization is related to increased levels of FeNO in both subjects with asthma[21] and healthy controls.[16] Moreover, the type and degree of sensitization are important, with perennial sensitization[22] and multiple sensitization[23] related to larger increases in FeNO. Within the framework of united airway disease, FeNO has been reported to be increased in subjects with AR without asthma in relation to healthy controls[24,25] and higher FeNO levels have been seen in asthmatic subjects with concomitant AR than in asthmatic subjects without AR.[25,26]

In subjects with asthma, chronic rhinosinusitis (CRS) with nasal polyps has been shown to have an impact on health-related quality of life,[27] structural lung changes and asthma exacerbations.[28] FeNO is higher in patients with asthma and concomitant nasal polyps than in those without nasal polyps[29,30] and has been shown to be reduced upon surgical treatment of the nasal polyps.[31] Furthermore, presence of nasal polyps in subjects with CRS is related to higher FeNO levels.[32]

KEY MESSAGES

- Current rhinitis and rhinoconjunctivitis are associated with higher FeNO at a population level.
- There is an interaction with perennial IgE sensitization on these associations.
- In non-asthmatic subjects with perennial sensitization, current rhinitis and rhinoconjunctivitis are related to higher FeNO.

Most of the studies on FeNO in relation to allergic rhinitis or nasal polyps, with or without asthma, have been done on selected samples, without adjustment for the type of allergic sensitization. The aim of this study was to assess whether there was an independent association between upper airway inflammatory disorders (UAID) (ie rhinitis, rhinoconjunctivitis, CRS or nasal polyposis) and FeNO in subjects from a large multi-centre, cross-sectional population-based study, with regard to interaction with IgE sensitization and asthma. Our hypothesis was that there was an independent association between UAID and FeNO in both subjects with asthma and non-asthmatic subjects, with an interaction with sensitization.

2 | METHODS

2.1 | Study sample

We carried out a cross-sectional analysis of the data, collected between the years 2010 and 2013 at 25 centres across 11 countries in Europe and in Australia, as part of the second follow-up of the European Community Respiratory Health Survey (ECRHS III).

The ECRHS is a population-based multi-centre study of asthma and allergy performed mainly in European countries and following a standardized protocol. The first postal survey was sent to randomly selected young adults (age 20–44 years) in the early 1990s. Among the responders, both a random sample and a sample of subjects reporting respiratory symptoms were invited to participate in additional examinations at their respective study centres. These groups have later been invited to follow-up studies (ECRHS II and ECRHS III) in 2000–2002 and 2010–2013 respectively. Further information about the ECRHS can be found on the homepage of the study (www.ecrhs.org), as well as in previously published articles.[1,33,34]

Of the 5,824 participants in ECRHS III, 126 were excluded due to self-reported emphysema or chronic obstructive pulmonary disease (COPD), and 526 were excluded due to a lack of FeNO measurements (Figure 1). The group that lacked FeNO measurements did not differ in prevalence of self-reported asthma, current rhinitis or rhinosinusitis from subjects with FeNO measurements, but they were older and had a higher percentage of females, as well as more prevalence of severe rhinitis, symptoms of CRS and nasal steroid treatment (Online Table 1). The remaining participants were divided into subjects with self-reported asthma (with a positive answer to

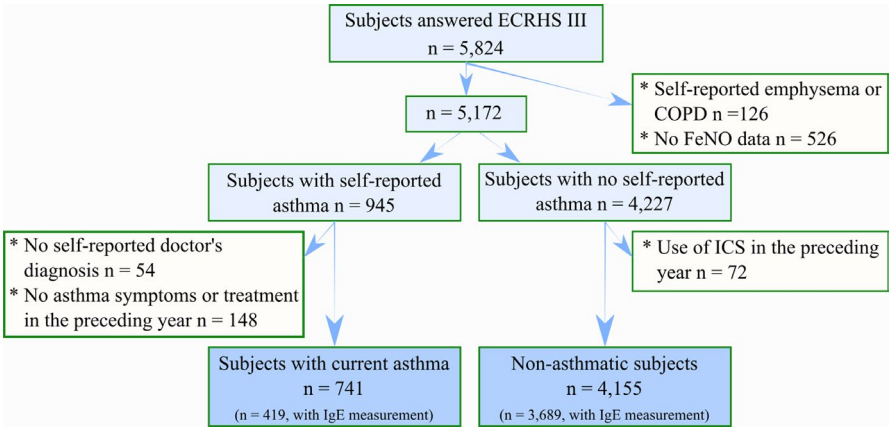


FIGURE 1 Flow chart of subject selection for this study

TABLE 1 Characteristics of subjects with current asthma and non-asthmatic controls. Data presented as means ± standard deviations for continuous variables and as numbers (%) for categorical variables

	Current asthma (n = 741)	Non-asthmatic subjects (n = 4155)	p value
Female	439 (59.2%)	2065 (49.7%)	<.001
Age (years)	54.0 (± 7.1)	54.2 (± 7.1)	.4
Height (cm)	169.0 (± 9.8)	170.4 (± 9.6)	<.001
Weight (kg)	79.5 (± 16.8)	78.8 (± 16.4)	.3
BMI (kg/m^2)	27.8 (± 5.5)	27.1 (± 4.8)	<.001
Smoking habits			
Never smoker	363 (49.1%)	1796 (43.4%)	.002
Ex-smoker	277(37.5%)	1570 (37.9%)	
Current smoker	99 (13.4%)	774 (18.7%)	
Sensitization to perennial allergens	170 (40.6%)	490 (13.3%)	<.001
Current rhinitis	496 (67.3%)	1513 (36.6%)	<.001
Rhinoconjunctivitis	390 (52.9%)	757 (18.3%)	<.001
Persistent rhinitis	163 (22.1%)	448 (10.9%)	.2[1]
Severe rhinitis	146 (19.8%)	235 (5.7%)	<.001[2]
Symptoms of CRS	69 (9.4%)	117 (2.8%)	<.001
CRS	71 (9.6%)	213 (5.2%)	<.001
Nasal polyposis	103 (14.0%)	252 (6.2%)	<.001
Nasal steroid use	208 (28.2%)	356 (8.6%)	<.001
ICS use			
Chronic	207 (27.9%)	0 (0%)	n.a.
Intermittent	127 (17.1%)		
None	407 (54.9%)		
Regular LTRA use	18 (2.4%)	0 (0%)	n.a.

CRS = chronic rhinosinusitis, nasal steroid use = any use of intranasal steroid during the preceding 12 months, ICS = inhaled corticosteroids, chronic = continuous use during the preceding 3 months, intermittent = any but not continuous use during the preceding 12 months, none = no use during the preceding 12 months, LTRA = leukotriene receptor antagonist, n.a. = non-applicable. p value[1] = persistent vs intermittent rhinitis, p value[2] = moderate to severe vs mild rhinitis. Sensitization based on n = 419 subjects with current asthma, and n = 3689 non-asthmatic controls. In 17 cases (2 individuals with current asthma and 15 non-asthmatic subjects), the question on smoking was not answered.

the question 'Have you ever had asthma'; n = 945) or those without (with a negative answer to the same question; n = 4227). In the self-reported asthma group, 54 individuals were omitted due to no doctor's diagnosis of asthma and 148 subjects due to absence of asthma symptoms or treatment in the year preceding the study. In the non-asthmatic group, 72 individuals were omitted due to the use of inhaled bronchial corticosteroids during the preceding year. This yielded 741 subjects with current asthma and 4,155 non-asthmatic

subjects (Figure 1). The 148 subjects with self-reported doctor's diagnosis of asthma, but without treatment or symptoms the preceding year (Figure 1), did not differ in gender, age, height or perennial sensitization from subjects with current asthma, but had lower weight, BMI and reported less UAID and nasal steroid treatment than those with current asthma(Online Table 2). They also differed significantly in FeNO from both current asthma and non-asthmatic subjects (Online supplement).

2.2 | Questionnaire and definitions of asthma, rhinitis, smoking habits and medication

All participants answered a detailed, interview-led questionnaire containing questions on respiratory symptoms from the upper and lower airways, self-reported diagnosis of asthma, COPD, emphysema, CRS or nasal polyposis, use of oral, inhaled or nasal medication during the preceding year, allergies and smoking habits. For a few subjects, there are missing data regarding smoking and upper airway disorders; these are reported in the results section.

Current asthma was defined as self-reported doctor-diagnosed asthma and at least one respiratory symptom (self-reported asthma attack, wheezing, nocturnal chest tightness, attacks of shortness of breath at night, after strenuous exercise or at rest) during the preceding 12 months and/or use of asthma medication during the same period.

Current rhinitis was defined as sneezing, or blocked or runny nose without concomitant cold or influenza during the preceding year. Rhinoconjunctivitis was defined as current rhinitis with concomitant itchy or runny eyes. We further divided rhinitis based on persistency and severity. Persistent rhinitis was defined as nasal problems more than 4 days in one week and more than 4 weeks in a row in the preceding 12 months. Intermittent rhinitis was defined as having current rhinitis but not fulfilling the criteria for persistent rhinitis. Severity of rhinitis was grouped based on the extent to which each nasal symptom (runny nose, blocked nose, itchy nose and attacks of sneezing) had affected daily activities and sleep (1. not a problem, 2. a slight problem, but not bothersome, 3. a bothersome problem, but without effect on daily activities or sleep, 4. a problem that affects some activities or sleep). Moderate to severe rhinitis was defined as having at least one of the nasal symptoms affect some activities or sleep. Mild rhinitis was defined as current rhinitis not fulfilling the criterion for moderate to severe rhinitis.[3]

CRS and nasal polyposis were defined as self-reported doctor's diagnosis of the respective conditions. Symptoms of CRS were defined as blocked nose combined with at least one other symptom (discoloured secretion from the nose, pain or pressure in the forehead, nose or eyes, or loss of smell) for more than 12 weeks during the preceding 12 months.[3]

A smoker was defined as someone who had smoked at least one cigarette per day or one cigar a week for at least one year, or at least 20 packs of cigarettes or 360 g of tobacco in their lifetime. Subjects were defined as never smokers if they had never smoked or had smoked less than the amount stated above. Smokers were further

TABLE 2 FeNO levels (ppb) in relation to sensitization and upper airway inflammatory symptoms in subjects with current asthma and non-asthmatic subjects

	Current asthma ($n = 741$)	*p* value	Non-asthmatic subjects ($n = 4155$)	*p* value	*p* value interaction
Perennial sensitization					
No	18.1 (16.7–19.7)	<.001	16.0 (15.7–16.3)	<.001	.06
Yes	24.4 (21.9–27.3)		19.2 (18.2–20.4)		
Current rhinitis					
No	19.5 (17.9–21.2)	.02	16.1 (15.7–16.4)	<.001	.18
Yes	22.1 (20.7–23.5)		17.0 (16.6–17.5)		
Rhinoconjunctivitis					
No	20.3 (18.9–21.9)	.1	16.1 (15.8–16.4)	<.001	.6
Yes	22.0 (20.5–23.6)		17.8 (17.1–18.6)		
CRS symptoms					
No	21.2 (20.2–22.4)	.6	16.4 (16.1–16.7)	.7	.5
Yes	20.4 (16.9–24.6)		16.7 (15.1–18.5)		
CRS diagnosis					
No	21.3 (20.2–22.5)	.4	16.4 (16.1–16.7)	.4	.2
Yes	19.8 (16.6–23.5)		16.9 (15.7–18.3)		
Nasal polyposis					
No	20.7 (19.6–21.9)	.04	16.4 (16.1–16.7)	.9	.04
Yes	24.2 (21.2–27.5)		16.6 (15.5–17.7)		

Results presented as geometric means (95% confidence intervals). FeNO, Fractional exhaled nitric oxide; CRS, chronic rhinosinusitis, *p* value interaction relates to the interaction between current asthma and the relation of each variable and log FeNO.

divided into current or ex-smokers based on their smoking habits during the month preceding the study.

Nasal steroid use was defined as any self-reported use of nasal spray containing corticosteroids during the preceding 12 months. Regular use of leukotriene receptor antagonist (LTRA) was defined as continuous use of LTRA during the preceding 3 months. Use of ICS was divided into regular, intermittent or no use based on reported use during the preceding year: regular if the participant had used ICS continuously during the three months preceding the study, intermittent if ICS had been used, but not continuously, and none if the participant reported no use of ICS in the 12 months preceding the study.

2.3 | Anthropometry

Weight and height of all participants were measured by trained health technicians, and body mass index (BMI) was calculated.

2.4 | Exhaled nitric oxide

FeNO was measured using an electrochemical analyser (NIOX MINO; Aerocrine AB) at a flow rate of 50 ml/s. The participants were instructed to refrain from eating, drinking, smoking or strenuous exercise during the hour before the measurement. Measurements were performed in accordance with ATS guidelines[35] with the exception that only single measurements were made. NIOX MINO detects FeNO values from 5 to 300 ppb. No value above 207 ppb was measured. A total of 15 subjects (10 subjects without asthma and 5 with current asthma) had levels 'below 5 ppb' (no actual value) and those subjects were assigned an arbitrary FeNO value of 3.5 ppb (5 divided by √2).

2.5 | IgE sensitization

Blood samples for IgE analyses were drawn at all centres. Blood samples were not obtained in 788 study participants (322 individuals with current asthma and 466 non-asthmatic subjects). The IgE analyses were performed at a single central laboratory (AMC Amsterdam) using the ImmunoCAP system (Thermo Fisher Scientific). Measurements were made of specific IgE against *Dermatophagoides pteronyssinus* (house dust mite), timothy grass and cat. These three sensitizations are the most prevalent in adults within the countries included in the study, even though the variance between countries are high.[36,37] Participants were defined as sensitized towards an individual allergen if the concentration of IgE against that specific allergen was ≥0.35 kU_A/L. As the number of participants with only grass sensitization was low (n = 35 (8%), in subjects with current asthma and n = 253 (7%) in non-asthmatic subjects), we grouped sensitization into two groups—perennial sensitization (cat- and/or house dust mite-sensitized) or no perennial sensitization (no sensitization or sensitization only towards timothy grass)—for stratified and multivariate analyses.

2.6 | Statistical methods

STATA 15.1 (StataCorp) was used for all statistical analyses. The results are presented as numbers and percentages for categorical variables, means with standard deviations for continuous variables with normal distribution, and geometric means with 95% confidence intervals for variables with a right-skewed distribution (ie FeNO). For variables with a right-skewed distribution, logarithmic transformation was performed before statistical testing. Differences in log FeNO levels in relation to categorical variables, such as gender, smoking habits, UAID and perennial sensitization, were tested separately for participants with current asthma and non-asthmatic subjects, using t tests for dichotomous variables or one-way ANOVA (adjusted for multiple testing) in multiple strata (ie severity and persistency of rhinitis, ICS use and smoking habits), and tests for interactions with asthma were made. To assess whether there was an independent relationship between UAID and FeNO, both subjects with current asthma and non-asthmatic subjects were further stratified by perennial sensitization and the same tests were used to evaluate differences in FeNO levels in relation to UAID in the stratified groups. Interaction analysis between sensitization and UAID with FeNO as outcome was also performed.

To further evaluate the independent association of upper airway disorders with FeNO, multiple linear regression analyses were performed on the groups stratified by current asthma and perennial sensitization, as well as on the entire study population, with adjustments for gender, age, height, weight, smoking status, centre and treatment for rhinitis and asthma, with log-transformed FeNO as outcome. The UAID that had a relationship to FeNO in the univariate analysis (ie current rhinitis, rhinoconjunctivitis and nasal polyps) were tested individually in these multiple linear regression models, as they are related to each other. The results from the analyses, for example β coefficient with 95% confidence interval, were than back-transformed and presented as % difference in FeNO $(((10^{\beta}-1) \times 100)$ with 95% confidence interval $((10^{CI}-1)X100))$ in relation to the reference group. A test for interactions with perennial sensitization was added individually to all models; the model including all study subjects also had a test for interactions with asthma added.

A p value of <.05 was considered statistically significant.

2.7 | Ethics

Approval for the study was obtained at each participating centre from the regional committee for medical research ethics, in accordance with national legislation (Australia: Human Research Ethics Committee of Alfred Hospital—Nr - CF11/1818 – 2011001012, Belgium:-Adviescommissie Medische Ethiek UZA-UA (CME). Nr: 11/41/288—UA, Denmark: Regionshuset Viborg, De Videnskabsetiske Komiteer—Nr: 20110106, Estonia:—Research Ethics Committee of the University of Tartu, Estland. Nr: 209T-17, France:—Comite de protection des personnes, Sud V Est Nr: 2011-A00013-38, Germany:—Ethik-Kommission der Bayerischen Landesarztekammer.

Nr: 10015, Iceland:— National Biotecs Committe of Iceland (NBCI) Nr: VSNb2011090016/03.11, Italy:—Verona—Comitato Etico per la sperimentazione, Azienda Ospedaliera Universitaria Integrata Verona. Nr: N. Prog 1393, Turin—Ethics Committee of the Local Health Authority TO2 of Turin. Nr: 569/09/08, Meeting of June 10th 2008, Norway:—Universitetet i Bergen, Regional komité for medisinsk og helsefaglig forskningsetikk, Vest-Norge (REK Vest) Nr: 2010/759, Sweden:—Ethics Committee at the Medical Faculty, Uppsala University Nr: 1999/313 and 2010/068, Spain:—Barcelona—Comité Ético de Investigación Clínica del Instituto Municipal de Asistencia Sanitaria, Barcelona, Spain), Nr PS09/00716 and 2009/3500/I, Galdakao— Comité Éticode Investigacióndel Hospital de Galdakao, Spain Nr: 20101104, Huelva—Comisión de Investigación del Hospital Juan Ramón Jiménez de Huelva Nr: 20090417, Oviedo—Comité Ético de Investigación Clínica Regional, Hospital Universitario Central de Asturias, Nr: 20110415, Albacete—Comité de Ética e Investigación de Complejo Hospitalario de Albacete, Nr: 04/09, England : NRES Committee London—Stanmore REC Reference 11/LO/0965, IRAS number 70769.). All participants gave informed consent prior to inclusion in the study.

3 | RESULTS

A total of 741 participants with current asthma and 4,155 non-asthmatic subjects were included in the study. The baseline characteristics of both groups are given in Table 1. There was a higher proportion of females in the group with asthma than in the group without asthma. Age and weight were similar between groups, but the group with asthma had higher BMI and lesser height than the non-asthmatic group. The proportion of current smokers was lower among subjects with current asthma than those without asthma. The proportion of participants sensitized towards perennial allergens and the proportion with UAID were higher in the group with current asthma than in the non-asthmatic group. There was also a higher proportion of participants who used nasal steroids among those with current asthma (Table 1). Subject characteristics and FeNO levels in groups stratified by current rhinitis are included in online supplement. Subjects with current rhinitis were younger, encompassed more females and had a higher prevalence of current asthma, sensitization to perennial allergens, and treatment for asthma and rhinitis (Online Table 3).

3.1 | FeNO levels in relation to sensitization and upper airway inflammatory symptoms or diagnosis

When looking the whole study population, FeNO differed significantly between perennial (20.9 (19.9–21.9) ppb, $n = 763$), seasonal (18.2 (17.1–19.5) ppb, $n = 337$) and no sensitization (16.2 (15.8–16.3) ppb, $n = 3,446$) ($p < .01$ for all). As the number of subjects sensitized to only seasonal allergen was low and the relative difference in FeNO was smaller between seasonal and non-sensitized, we chose to group sensitization into perennial sensitization (± grass sensitization) or no perennial sensitization (either no sensitization or only grass sensitization) for stratified and multivariate analyses. Subjects with perennial sensitization had higher FeNO levels than those without, among both subjects with current asthma and non-asthmatic subjects (Table 2).

Current rhinitis was associated with higher FeNO in both subjects with current asthma and non-asthmatic subjects, whereas rhinoconjunctivitis only was associated with higher FeNO in non-asthmatic subjects (Table 2). No interaction with asthma status on the relation between FeNO and current rhinitis or rhinoconjunctivitis was found. When grouping rhinitis based on persistency and severity, no differences in FeNO levels were seen between those with persistent rhinitis and those with intermittent rhinitis or between those with moderate to severe rhinitis and those with mild rhinitis, neither among subjects with current asthma nor among non-asthmatic subjects (data not shown). Nasal polyposis was associated with increased FeNO in asthmatics only. No association with CRS was observed (Table 2).

3.2 | FeNO levels in relation to upper airway inflammatory symptoms or diagnosis—stratified analyses for asthma and IgE sensitization for perennial allergens

In non-asthmatic subjects with perennial sensitization, both current rhinitis and rhinoconjunctivitis related to higher FeNO. No such effects were seen in the other three groups of subjects (Table 3). In subjects with current asthma without perennial sensitization, those with nasal polyps had higher levels of FeNO than those without, while no such differences were seen for the other three groups (Table 3).

In non-asthmatic subjects, a significant interaction with perennial sensitization was found on the relationship between current rhinitis and FeNO (p interaction = 0.04), as well as on the relationship between rhinoconjunctivitis and FeNO (p interaction = 0.005).

3.3 | FeNO levels in relation to anthropometric variables, gender and smoking

There was a positive association between FeNO and height in patients with current asthma, as well as non-asthmatic subjects, whereas a positive association between FeNO and age and weight only was seen in non-asthmatic subjects (Online supplement). FeNO was higher in males than females among both subjects with current asthma and non-asthmatic subjects (Online Table 4). Current smokers had lower levels of FeNO than previous smokers and never smokers among both subjects with current asthma and non-asthmatic subjects (Online Table 4).

TABLE 3 FeNO levels (ppb) in relation to rhinitis and nasal polyposis, in subjects with current asthma and non-asthmatic subjects, stratified by perennial sensitization

	Current rhinitis		
	No	**Yes**	***p* value**
Current asthma and perennial sensitization	21.6 (17.5–26.8) *n* = 42	25.6 (22.5–29.2) *n* = 127	.2
Current asthma, no perennial sensitization	17.3 (15.3–19.5) *n* = 97	18.6 (16.7–20.9) *n* = 150	.4
Non-asthmatic subjects and perennial sensitization	18.1 (16.7–19.7) *n* = 241	20.6 (19.1–22.3) *n* = 243	.03
Non-asthmatic subjects, no perennial sensitization	15.9 (15.5–16.2) *n* = 2117	16.2 (15.8–16.8) *n* = 1067	.2
	Rhinoconjunctivitis		
	No	**Yes**	
Current asthma and perennial sensitization	25.2 (21.2–29.9) *n* = 68	24.1 (20.8–28.0) *n* = 101	.7
Current asthma, no perennial sensitization	18.0 (16.1–20.1) *n* = 135	18.2 (16.0–20.7) *n* = 112	.9
Non-asthmatic subjects and perennial sensitization	18.1 (17.0–19.4) *n* = 324	22.0 (19.9–24.3) *n* = 160	.002
Non-asthmatic subjects, no perennial sensitization	15.9 (15.6–16.2) *n* = 2696	16.4 (15.7–17.2) *n* = 488	.2
	Nasal polyposis		
	No	**Yes**	
Current asthma and perennial sensitization	23.8 (21.1–26.8) *n* = 150	28.5 (21.2–38.3) *n* = 19	.3
Current asthma, no perennial sensitization	17.4 (15.9–19.0) *n* = 214	23.2 (18.5–29.1) *n* = 32	.02
Non-asthmatic subjects and perennial sensitization	19.3 (18.2–20.4) *n* = 454	19.6 (15.6–24.5) *n* = 32	.9
Non-asthmatic subjects, no perennial sensitization	16.0 (15.7–16.3) *n* = 2592	16.0 (14.9–17.2) *n* = 198	1.0

Results presented as geometric means (95% confidence intervals). Missing data on current rhinitis and rhinoconjunctivitis in 4 subjects with current asthma and 25 non-asthmatic controls, as well as on self-reported nasal polyposis in 5 subjects with current asthma and 58 non-asthmatic subjects.

3.4 | Multivariate models of independent associations of upper airway inflammatory disorders and FeNO

In a multivariate regression model stratified by perennial sensitization and asthma, and adjusted for variables known to be associated with FeNO (smoking, gender, height and asthma medication), as well as for weight, study centre and use of nasal steroids, we found an independent association between FeNO and current rhinitis, as well as rhinoconjunctivitis, only in non-asthmatic subjects with perennial sensitization. No association between FeNO and nasal polyps was found in either subjects with current asthma or controls (Table 4). In subjects with current asthma and perennial sensitization, use of nasal steroids was associated with lower FeNO and continuous as well as intermittent use of ICS was associated with higher FeNO. No relation between FeNO and medication was seen in subjects with current asthma without perennial sensitization (Table 4).

In the same multivariate model including all study participants (adjusted for smoking, gender, height, weight, study centre, asthma medication, use on nasal steroids, as well as current asthma and perennial sensitization), current rhinitis and rhinoconjunctivitis were associated with higher FeNO. There was a significant interaction with perennial sensitization on the relationships between current rhinitis and rhinoconjunctivitis and FeNO, and a significant interaction with current asthma on the relationship between nasal polyposis and FeNO (Table 5). There was also an independent association between FeNO and asthma, as well as FeNO and perennial sensitization (Table 5).

4 | DISCUSSION

Current rhinitis and rhinoconjunctivitis were associated with higher FeNO with a significant interaction with perennial sensitization on

TABLE 4 Independent associations of upper airway inflammatory disorders and treatment on FeNO in subjects with current asthma and non-asthmatic subjects, stratified by perennial sensitization, adjusted for age, weight, height, gender, smoking status and centre

	Current asthma			Non-asthmatic subjects		
	Perennial atopy ($n = 168$)	No perennial atopy ($n = 243$)		Perennial atopy ($n = 482$)	No perennial atopy ($n = 3164$)	
	% difference (95% CI)	% difference (95% CI)	*p* value inter	% difference (95% CI)	% difference (95% CI)	*p* value inter
Current rhinitis	20.7 (−9.5–60.9)	7.8 (−10.0–29.2)	.7	**12.1(0.2–25.5)**	1.9 (−1.6–5.6)	**.02**
Nasal steroids preceding year	**−31.3 (−48.0–−9.2))**	9.3 (−9.8–32.4)	.06	−6.5 (−20.6–10.0)	3.9 (−2.3–10.6)	.9
Regular LTRA use	−31.3 (−67.2–44.1)	10.5 (−31.9–79.2)	.3	Not applicable		
Use of ICS						
Intermittent use	**40.0(3.9–88.5)**	−2.2 (−20.2–19.8)	.5			
Regular use	**67.1(14.7–143.4)**	5.4 (−14.6–30.1)	.12	Not applicable		
Nasal polyposis	15.5 (−21.1–68.9)	18.9 (−8.4–54.3)	.6	1.3 (−18.2–25.5)	1.6 (−5.0–8.7)	.9
Rhinoconjunctivitis	6.5 (−16.1–35.0)	5.0 (−12.2–23.5)	.7	**15.9(3.4–29.9)**	2.1 (−22.5–6.9)	**.003**

Perennial = perennial +/- grass sensitization, non-perennial = no sensitization or sensitization only towards grass, LTRA = leukotriene receptor antagonist, ICS = inhaled corticosteroids. CI = confidence interval, results presented as % difference ($(10^{\beta\text{-coefficient}} - 1) \times 100$), with 95% CI, expressed as % difference in relation to reference group (ie no rhinitis, no treatment, no nasal polyposis, no rhinoconjunctivitis). 95% CIs that do not include 0 are statistically significant ($p < .05$) and are highlighted in bold. *p* value inter = *p* value for interaction with perennial sensitization in relation to each variable and log FeNO.

TABLE 5 Independent associations of upper airway inflammatory disorders and treatment on FeNO in all subjects, with information on interaction with current asthma and perennial sensitization. Also adjusted for age, weight, height, gender, smoking status and centre

	% difference (95% CI) All subjects $n = 4057$	*p* interaction asthma	*p* interaction perennial sensitization
Current asthma	**14.5 (7.1–22.4)**	n.a.	.1
Perennial sensitization	**18.4 (13.4–23.7)**	.1	n.a.
Nasal steroids	0.2 (−5.0–5.6)	.2	.12
LTRA	−2.6 (−27.8–31.4)	n.a.	.17
ICS			
Intermittent use	4.7 (−6.8–17.6)		.4
Regular use	**20.2 (5.2–37.3)**	n.a.	**.02**
Current rhinitis	**4.4 (0.9–7.9)**	.2	**.03**
Rhinoconjunctivitis	**4.8 (0.7–9.2)**	.6	**.03**
Nasal polyposis	5.3 (−1.0–12.0)	**.03**	.7

Perennial = perennial +/- grass sensitization, non-perennial = no sensitization or sensitization only towards grass, LTRA = leukotriene receptor antagonist, ICS = inhaled corticosteroids. CI = confidence interval, results presented as % difference ($(10^{\beta\text{-coefficient}} - 1) \times 100$), with 95% CI, expressed as % difference in relation to reference group (ie no rhinitis, no treatment, no nasal polyposis, no rhinoconjunctivitis). 95% CIs that do not include 0 are statistically significant ($p < .05$) and are highlighted in bold. Upper airway inflammatory disorders (current rhinitis, rhinoconjunctivitis and nasal polyposis), as well as interactions, were added to the model individually. *p* interaction = *p* value for interaction with perennial sensitization or current asthma in relation to each variable and log FeNO.

the relationships between current rhinitis and rhinoconjunctivitis and FeNO. When subjects were stratified by asthma and perennial sensitization and adjustment was made for further confounders, the associations with higher FeNO in current rhinitis and in rhinoconjunctivitis were consistent in non-asthmatic controls sensitized to perennial allergens. Moreover, treatment with nasal steroids related

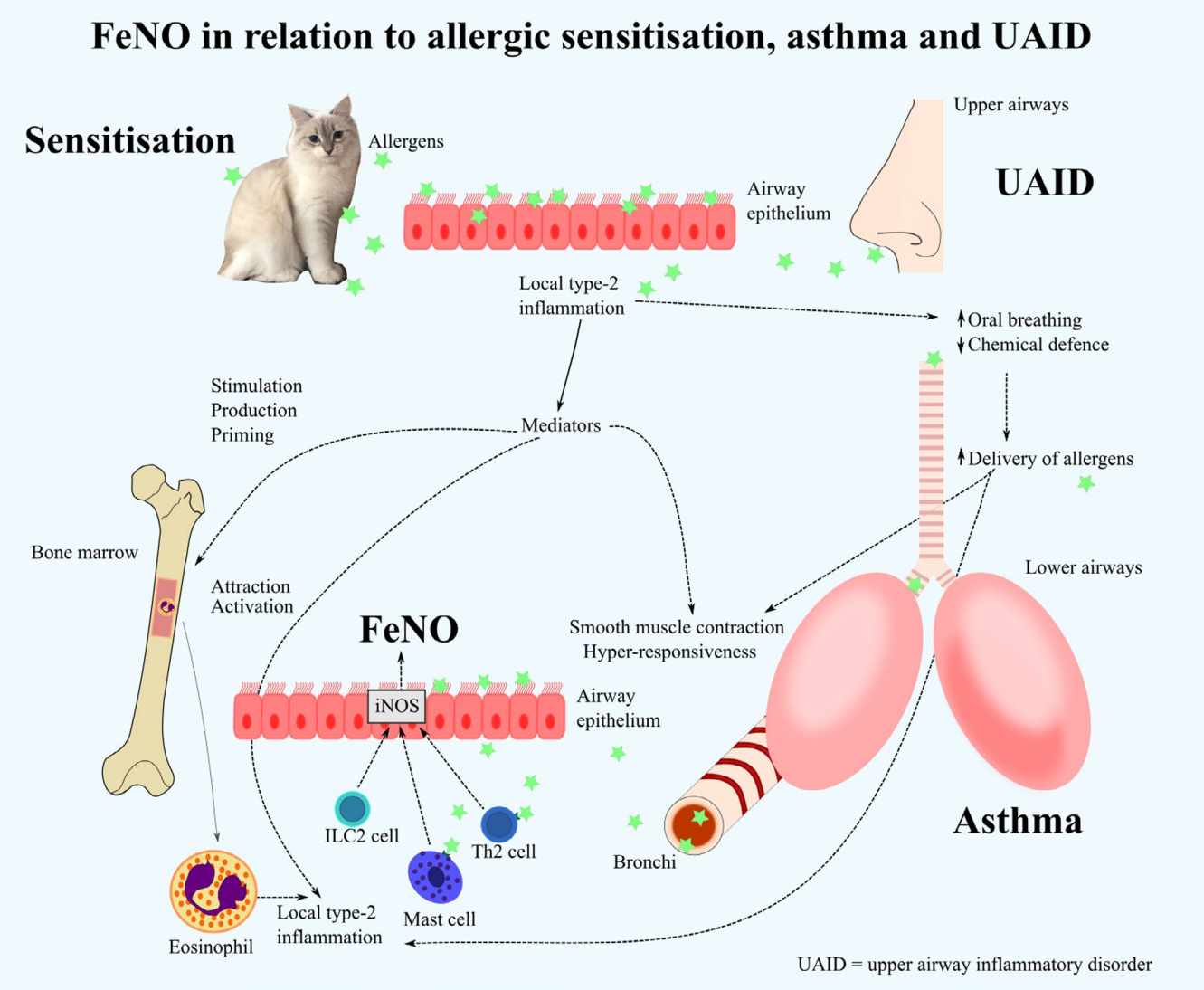


FIGURE 2 Schematic illustration of the relation between FeNO and allergic sensitization, asthma and upper airway inflammatory disorders

to lower FeNO levels in asthmatic subjects sensitized to perennial allergens.

The association of allergic rhinitis with higher FeNO levels has previously been found in both subjects with asthma[26,38] and non-asthmatic subjects,[24] as has a positive association between quality of life and FeNO during allergen exposure in children with rhinoconjunctivitis.[39] IgE sensitization is a major determinant of FeNO, leading to increased FeNO values in both healthy subjects[16,40–42] and subjects with rhinitis and asthma.[21,23,43] Hedman et al. recently reported, in a study of mono- and dizygotic twins, that the relation between FeNO and asthma is mostly governed by genetic factors influencing IgE levels.[44] However, Olin et al. suggested that increased FeNO was found in subjects with sensitization towards airborne allergens only if they had symptoms of airway inflammation (ie asthma or rhinitis).[45] Our study confirmed the association between FeNO and perennial sensitization in both subjects with current asthma and non-asthmatic controls. Most studies on the relationship between AR and FeNO have not been adjusted for sensitization or type of sensitization, although a study by Jouaville et al. on 1,156 children showed higher FeNO in non-asthmatic subjects with sensitization and rhinitis than in non-asthmatic subjects with sensitization, but without rhinitis.[23] Our study results are in line with this evidence and suggest that there is a relationship between FeNO and rhinitis, but that this relation is influenced by perennial sensitization. When the study population was stratified by asthma and perennial sensitization, no relation between FeNO and rhinitis was seen in non-asthmatic or asthmatic subjects without sensitization towards perennial allergens. The effect size of rhinitis and rhinoconjunctivitis on FeNO was around 5% when looking at the whole population, and this effect was about one third of the effect of asthma and perennial sensitization on FeNO. The size effect of 5% might be questioned regarding its clinical relevance. However, we think that the main finding is that upper airway inflammatory symptoms interacts with perennial sensitization in the association with FeNO as a marker of

lower airway inflammation. Moreover, in non-asthmatic subjects with perennial sensitization current rhinitis is associated with 12% higher FeNO, which could be clinically relevant. Most likely, the increased FeNO in rhinitis in our analysis can be explained by an allergic inflammation in the lower airways triggered by an allergen response in the upper airways, or a simultaneous exposure to allergens in both the upper and lower airways, a schematic depiction of this relation is given in Figure 2. Previous studies have shown higher eosinophilic counts in induced sputum in subjects with AR than in healthy controls.[7,8] The lack of a significant relationship between FeNO and current rhinitis in subjects with current asthma might be explained by either the fact that the number of subjects with current asthma was relatively small, or that allergic sensitization was driving both higher FeNO and symptoms of rhinitis in asthmatic subjects, or that the additive effect of rhinitis on FeNO in subjects with asthma was diminished in the presence of asthma-related inflammation in the lower airways, and the fact that this relationship could be confounded by asthma treatment. Counterintuitively, asthma treatment related to higher FeNO levels in our population, which might be explained by subjects with more severe disease and higher degree of inflammation being prescribed ICS. These subjects may have higher FeNO levels even though they are clinically responding to ICS treatment.[46] The mean levels of FeNO in subjects with current asthma were within normal range in our study. As this is a population-based study, this may indicate that most of the subjects with current asthma had a mild or well-controlled asthma. However, the relation between ICS treatment and higher FeNO may reflect that the subpopulation with ICS treatment had a more severe asthma, reflected in increased lower airway inflammation and higher FeNO.

The elevated FeNO levels in subjects with rhinitis without asthma might be a biomarker for future onset of asthma. Several studies have shown that non-asthmatic subjects with AR and high FeNO at baseline have a higher prevalence of asthma at follow-up than those with lower FeNO, suggesting that FeNO may be a predictor of asthma development in subjects with AR.[47–49] However, it is unclear whether the presence of AR triggers both the march towards asthma and higher FeNO, or an underlying inflammation in the united airways clinically manifests as upper airway symptoms first. We have shown, in a cohort of adolescents, that subjects without rhinitis with high FeNO levels at baseline had a higher risk of developing new onset of rhinitis and persistent rhinitis than those with lower FeNO levels at baseline, in line with the united airway disease concept.[50]

Nasal corticosteroids related to lower FeNO levels in asthmatic subjects sensitized to perennial allergens. This finding is in line with the evidence of Oka et al. showing a reduction of FeNO and improvement in asthma quality of life scores after add-on therapy with nasal corticosteroids in adults.[51] However, the evidence on the effect on FeNO by treatment of upper airway disease with nasal corticosteroids in subjects with asthma is inconclusive, with longitudinal studies on nasal steroid treatment and FeNO in children not showing a significant decrease in FeNO upon treatment with nasal steroids.[52,53] It is not possible to deduce from our cross-sectional study if the relationship between nasal corticosteroids and FeNO is due to a lower level of inflammation in the upper airways resulting in lower inflammation in the lower airways.

In our study, we found no relation between persistency or severity of rhinitis and FeNO. This is somewhat surprising, as previous studies on subjects with AR have reported higher FeNO in persistent than intermediate rhinitis,[24,51,54] as well as in moderate to severe than mild rhinitis.[51]

A relationship between nasal polyposis and higher FeNO was seen only in univariate analysis in subjects with current asthma and not in non-asthmatic controls. CRS with nasal polyps has an impact on asthma severity, health-related quality of life and asthma exacerbations[27,28] and is related to higher FeNO.[30–32] Treatment of type-2 inflammation with dupilumab reduces the size of nasal polyps as well as the severity of symptoms.[55] In our multivariate analysis of all subjects, we found a significant interaction with asthma on the relation between FeNO and nasal polyposis although no significant relation between FeNO and nasal polyps was found. Nor was any significant association between FeNO and nasal polyps found in the multivariate model stratified by asthma and perennial sensitization. This might be explained by the lower number of individuals in each stratum after stratification or due to the fact that the definition of nasal polyposis in our study only was based on self-reported doctor's diagnose of polyposis and no objective examinations.

The main strength of our analysis is that the ECRHS is a large multi-centre survey including many subjects with current asthma and non-asthmatic controls. The questionnaires were administered through interviews, with clear instructions to the participating centres, the methods for measurements of FeNO were standardized, and sensitization was measured at a single central laboratory. The main limitation of our study is that we carried out a cross-sectional analysis of the relationship between FeNO and UAID with no information on the development of respiratory symptoms and diagnosis over time. Other major limitations are the high amount of missing data on IgE sensitization in subjects with asthma and, to a lesser degree, in non-asthmatic subjects, and that IgE sensitization only have been assessed against three allergens, due to limited resources. This may result in misclassification of sensitization, with an underestimation of both perennial and seasonal sensitizations. However, cat and house dust mite are the most prevalent perennial sensitization and timothy grass the most prevalent seasonal sensitization in Europe even though there is a wide difference in pattern of sensitizations between countries in Europe.[37,56] A further limitation is the large heterogeneity in asthma treatment and levels of FeNO between the participating centres. Information on doctor's diagnosis of CRS or nasal polyposis, as well as asthma, was self-reported by the study participants and no objective confirmation of the diagnoses was included in the study.

5 | CONCLUSIONS

Current rhinitis and rhinoconjunctivitis were related to increase FeNO and the relationship was modified by presence of IgE

sensitization towards perennial allergens. Specifically, current rhinitis was associated with higher FeNO, with a significant interaction with perennial sensitization, which suggests a need to take IgE sensitization towards perennial allergens into account when evaluating the importance of FeNO in subjects with current rhinitis. The finding on increased FeNO in non-asthmatic subjects with current rhinitis, sensitized to perennial allergens, suggested that these subjects had high levels of type-2 inflammation and might therefor be at higher risk of developing asthma, but this, as well as the use of FeNO in monitoring patients with rhinitis need to be studied in future, longitudinal studies.

ACKNOWLEDGEMENTS

The coordination of ECRHS III was supported by the Medical Research Council (Grant Number 92091), and the following grants contributed to funding ECRHS III: Australia: National Health & Medical Research Council. Belgium: Antwerp South, Antwerp City—Research Foundation Flanders (FWO), grant code G.0.410.08.N.10 (both sites). Estonia: Tartu—SF0180060s09 from the Estonian Ministry of Education. Estonian Research Council Personal Research Grant no 562. France: (All) Ministère de la Santé, Programme Hospitalier de Recherche Clinique (PHRC) national 2010. Bordeaux—INSERM U897 Université Bordeaux Segalen. Grenoble—Comité Scientifique AGIRadom 2011. Paris—Agence Nationale de la Santé, Région Ile de France, domaine d'intérêt majeur (DIM). Germany: Erfurt—German Research Foundation HE 3294/10-1. Hamburg—German Research Foundation MA 711/6-1, NO 262/7-1. Iceland: Reykjavik—The Landspítali University Hospital Research Fund, University of Iceland Research Fund, ResMed Foundation, California, USA, Orkuveita Reykjavíkur (Geothermal plant), Vegagerðin (The Icelandic Road Administration (ICERA). Italy: All Italian centres were funded by the Italian Ministry of Health, Chiesi Farmaceutici SpA. Verona received additional funding from the Cariverona Foundation, Education Ministry (MIUR). Norway: Norwegian Research Council grant no 214123, Western Norway Regional Health Authorities grant no 911631, Bergen Medical Research Foundation. Spain: Fondo de Investigación Sanitaria (PS09/02457, PS09/00716, PS09/01511, PS09/02185, PS09/03190), Servicio Andaluz de Salud, Sociedad Española de Neumología y Cirurgía Torácica (SEPAR 1001/2010), Fondo de Investigación Sanitaria (PS09/02457). Barcelona—Fondo de Investigación Sanitaria (FIS PS09/00716). Galdakao—Fondo de Investigación Sanitaria (FIS 09/01511). Huelva—Fondo de Investigación Sanitaria (FIS PS09/02185) and Servicio Andaluz de Salud. Oviedo—Fondo de Investigación Sanitaria (FIS PS09/03190). 'ISGlobal acknowledges support from the Spanish Ministry of Science and Innovation through the "Centro de Excelencia Severo Ochoa 2019-2023" Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program.' Sweden: All centres were funded by the Swedish Heart and Lung Foundation, the Swedish Asthma and Allergy Association, the Swedish Association against Lung and Heart Disease, and the Swedish Research Council for Health, Working Life and Welfare (FORTE). Göteborg also received further funding from the Swedish Council for Working Life and Social Research. Umeå also received funding from a Västerbotten County Council ALF grant. Switzerland: The Swiss National Science Foundation (grants no 33CSCO-134276/1, 33CSCO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099), The Federal Office for Forest, Environment and Landscape, The Federal Office of Public Health, The Federal Office of Roads and Transport, the canton governments of Aargan, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais, and Zürich, the Swiss Lung League, the Lung Leagues of the cantons Basel Stadt/Basel, Landschaft, Geneva, Ticino, Valais, and Zurich, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission 018996 (GABRIEL), Wellcome Trust WT 084703MA. UK: Medical Research Council (Grant Number 92091). Support was also provided by the National Institute for Health Research through the Primary Care Research Network.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

C Krantz and A Malinovschi conceived, designed or analysed and interpreted the data; drafted the article or revised it; provided intellectual content of critical importance to the work described; and are accountable for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. S Accordini, K Alving, A G Corsico, P Demoly, D S Ferreira, B Forsberg, J Garcia-Aymerich, T Gislason, J Heinrich, C Janson, R Jõgi, A Johannessen, B Leynaert, A Marcon, J Martínez-Moratalla Rovira, E Nerpin, D Nowak, A-C Olin, M Olivieri, A Pereira-Vega, C Raherison-Semjen, F Gómez Real, T Sigsgaard and G Squillacioti conceived, designed or analysed and interpreted the data; drafted the article or revised it; provided intellectual content of critical importance to the work described.

DATA AVAILABILITY STATEMENT

The data used in this analysis contain sensitive and identifying personal information from participants in multiple centers across Europe. The participants of the ECRHS study did not provide consent that their data be made public and permission to do so has not been granted by all relevant center-based ethical committees. ECRHS has a data sharing policy and will make the data available upon request to qualified researchers working within institutions with evidence that they comply with current GDPR ethical and professional standards and requirements if all local participating centers are able to gain relevant permissions (contact via ECRHS data manager (James Potts, j.potts@imperial.ac.uk) and program manager (Sabrina Kapur, sabrina.kapur@imperial.ac.uk); Professor Debbie Jarvis, d.jarvis@imperial.ac.uk, or any member of the ECRHS Steeting Committee, www.ecrhs.org/steering.htm).

ORCID

Christina Krantz https://orcid.org/0000-0001-9591-8532
Pascal Demoly https://orcid.org/0000-0001-7827-7964
Elisabet Nerpin https://orcid.org/0000-0003-3880-2132
Christer Janson https://orcid.org/0000-0001-5093-6980
Andrei Malinovschi https://orcid.org/0000-0002-4098-7765

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How to cite this article: Krantz C, Accordini S, Alving K, et al; the European Community Respiratory Health Survey III. Cross-sectional study on exhaled nitric oxide in relation to upper airway inflammatory disorders with regard to asthma and perennial sensitization. *Clin Exp Allergy*. 2022;52:297–311. doi:10.1111/cea.14019