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An observational analysis on the influence of parental allergic rhinitis, asthma and smoking on exhaled nitric oxide in offspring

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ABSTRACT

Background: Parental allergic diseases and smoking influence respiratory disease in the offspring but it is not known whether they influence fractional exhaled nitric oxide (FeNO) in the offspring. We investigated whether parental allergic diseases, parental smoking and FeNO levels in parents were associated with FeNO levels in their offspring.

Methods: We studied 609 offspring aged 16–47 years from the Respiratory Health in Northern Europe, Spain and Australia generation (RHINESSA) study with parental information from the Respiratory Health in Northern Europe (RHINE) III study and the European Community Respiratory Health Survey (ECRHS) III. Linear regression models were used to assess the association between offspring FeNO and parental FeNO, allergic rhinitis, asthma and smoking, while adjusting for potential confounding factors.

Results: Parental allergic rhinitis was significantly associated with higher FeNO in the offspring, both on the paternal and maternal side (percent change: 20.3 % [95%CI 5.0–37.7], p = 0.008, and 13.8 % [0.4–28.9], p = 0.043, respectively). Parental allergic rhinitis with asthma in any parent was also significantly associated with higher offspring FeNO (16.2 % [0.9–33.9], p = 0.037). However, parental asthma alone and smoking were not associated with offspring FeNO. Parental FeNO was not associated with offspring FeNO after full adjustments for offspring and parental factors.

Conclusions: Parental allergic rhinitis but not parental asthma was associated with higher levels of FeNO in offspring. These findings suggest that parental allergic rhinitis status should be considered when interpreting FeNO levels in offspring beyond childhood.

1. Introduction

Fractional exhaled nitric oxide (FeNO) is a marker of type-2 airway inflammation [1] which is often elevated in patients with allergic asthma [2]. FeNO is produced in response to inflammatory cytokines and signals local type-2 driven inflammation [3]. Exhaled nitric oxide

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mainly reflects the activity of inducible nitric oxide synthase (iNOS) in respiratory epithelium. It is useful in assessing the presence and degree of type 2- airways inflammation and it reflects upregulation of iNOS due to IL-4 and IL-13 cytokine release by T-helper type 2 cells and innate lymphoid cells type 2.

FeNO measurement has the advantage of being non-invasive and can guide asthma treatment therefore is used increasingly in clinical practice in the assessment of patients with suspected and confirmed asthma [4,5]. There are however many individual-related, cross-sectional factors that can influence FeNO levels, including active smoking, which is associated with lower levels of FeNO [6–8], whereas older age [7,9], male sex [9–12], increased height and atopy [7,9,11,12] are associated with higher FeNO levels. Additionally, parental allergic disease activity may influence allergic disease risks in children, in addition to genetic inheritance and shared environment [13]. Therefore, aside from personal factors, some parental factors are also suspected to influence FeNO levels in offspring. Parental history of asthma or allergy may be independent determinants of increased FeNO in offspring at 12–14 years of age [14]. Maternal history of asthma has been independently associated with elevated FeNO levels in infants <3 years of age [15]. Furthermore, higher FeNO values have been found in older healthy children (not asthmatic and not sensitized to common allergens) of atopic mothers [16]. Maternal atopic disease (notably maternal asthma) can also modify the effect of prenatal and early postnatal environmental factors on offspring FeNO [17]. However, these relationships have not been found for paternal atopic disease [15,17].

Prediction of offspring FeNo based on parental factors have been studied in children below 14 years of age, however studies assessing the impact of parental factors on offspring beyond younger childhood years–indicating long term impact of parental factors, have been limited. Furthermore, we are not aware of studies assessing the prediction of parental FeNO on offspring FeNO beyond childhood, independently of parental risk factors such as asthma and atopy. This is important to determine as factors such as raised parental FeNO levels that are not explained by asthma and atopy may potentially be used as a risk factor or part of a risk scoring system for higher FeNO levels in the offspring. The Swedish based Global Asthma and Allergy Excellence Network (GA^2LEN) study, which consisted of a postal survey based on asthma, rhinitis and chronic rhinosinusitis and follow-up with clinical examinations, found parental smoking during childhood, particularly both parents smoking, was associated with lower FeNO levels later in adulthood in subjects with mild asthma [12]. In a Swedish population-based cohort study of approximately 500 subjects (where subjects were followed from adolescence to early adulthood) it was found that higher baseline FeNO levels and reported family history of asthma were risk factors for incident asthma in males. However, the role of family history of asthma on FeNO levels in early adulthood was not assessed [18].

Although, the risk of parental factors on childhood FeNO levels have been studied previously, the role of parental factors into early adulthood and beyond are not well-explored and could indicate the long-term impacts of parental risk factors. This can add to existing knowledge on how FeNO values are interpreted in clinical practice and highlight the importance of parental risk factors on FeNO values in their offspring. We hypothesize that parental factors such as smoking, allergic status and FeNO levels are associated with FeNO levels in their offspring. Therefore, we aimed to study the effects of parental factors on offspring FeNO in a multi-generational study, where it would be possible to disentangle the role of the parental risk factors on their offspring.

2. Methods

2.1. Study population

This was a multi-generational observational study where the study population consisted of parents from the Respiratory Health in Northern Europe (RHINE III) study [19] and the European Community Respiratory Health Survey [20] (ECRHS III) and their offspring from the Respiratory Health in Northern Europe, Spain and Australia generation (RHINESSA) study [21]. In 10 ECRHS study centres, data on the offspring were collected within the RHINESSA study. The analytical database comprised of a parent (mother or father) and one of their offspring (randomly chosen from all offspring for the corresponding parent). Written informed consent was obtained from each participant of the ECRHS III and RHINESSA clinical study and the studies were approved by the medical research ethics committee for each study centre according to national legislation.

2.1.1. Parent population

ECRHS: Between 1991 and 1993, a postal screening questionnaire was administered to a random sample of 20–44 year-olds from the national population registers of 56 study centres (ECRHS I). ECRHS III was conducted between 2011 and 2013 and was the 3rd wave of data collection. This study includes the cohort from 10 study centres in Northern Europe, Spain and Australia (Aarhus [Denmark]; Bergen [Norway]; Gothenburg, Uppsala and Umeå [Sweden]; Reykjavik [Iceland]; Tartu [Estonia]; Huelva and Albacete [Spain]; and Melbourne [Australia]). The other ECRHS centres did not examine the participants' offspring and were therefore not part of the RHINESSA study.

The study population of the questionnaire-based RHINE study consisted of men and women from the ECRHS population in the seven centres in Northern Europe: Reykjavik, Iceland; Bergen, Norway; Umeå, Uppsala and Gothenburg, Sweden; Aarhus, Denmark; and Tartu, Estonia. Subjects were sent a postal questionnaire (RHINE II) in 1999–2001 and at follow-up (2010–2012) these subjects were again invited to respond to a follow-up questionnaire (RHINE III).

2.1.2. Offspring population

Offspring of parents from the ten ECRHS centres were invited to participate in both questionnaire and clinical examinations in 2012–2019. The questionnaires were web-based in all centres except for the Swedish centres, where postal questionnaires were used. For the current study, one offspring was chosen at random for each parent who had participated in RHINE III/ECRHS I/ECRHS III.

2.2. Baseline assessments and examinations

2.2.1. Questionnaire responses

Parental and offspring AR was defined as a "yes" to the question "Do you have any nasal allergies including hay fever?" Parental and offspring asthma was assessed by a response to the question "Have you ever had asthma?" Current asthma in parents was defined as reporting ever having had asthma and yes to any of the following: 1) wheeze in the last 12 months; 2) woken with tightness in the chest in the last 12 months; 3) woken with an attack of breathlessness in the last 12 months; 4) currently taking medication for asthma. In offspring, similar criteria for current asthma were used: yes to self-reported asthma and yes to any of the following: 1) chest wheezing or whistling at any time in the last 12 months; 2) chest wheezing or whistling at any time in the last 12 months without a cold; 3) Attacks of shortness of breath during the day when at rest in the last 12 months; 4) Attack of shortness of breath following activity in the last 12 months; 5) Woken by attack of shortness of breath in the last 12 months; 6) inhaled steroids in the last 12 months. Current smoking for parents and offspring was assessed using the question "Are you a smoker?" For subjects with parents who did not participate in RHINE III (due to certain centres not participating in RHINE III) the questionnaire responses for allergic rhinitis, asthma and smoking were used from ECRHS III instead. Participant height was measured by trained health technicians for parents and offspring.

2.2.2. FeNO measurement

Parental FeNO was measured in accordance with the recommendations of the American Thoracic Society [22], with the exception that

only single measurements were performed, and measurements were performed throughout the year (both in or out of the pollen season). Subjects were told to avoid smoking, eating, drinking and strenuous exercise in the hour before the measurement. An electrochemical analyser (NIOX MINO; Aerocrine AB, Sweden) was used to measure FeNO levels at an expiratory flow rate of 50 mL/s (detected levels from 5 to 300 ppb; all values under 5 ppb were given arbitrary values of 3.5 ppb). FeNO was measured for offspring in RHINESSA using either an electrochemical analyser (NIOX MINO; Aerocrine AB) or NIOX Vero® which have been shown to exhibit good agreement [23].

2.2.3. Immunoglobulin E (IgE) sensitisation and total IgE

In ERCHS III, IgE analysis was performed in a single central laboratory (AMC Amsterdam) by using the ImmunoCAP system (Thermo Fisher Scientific). In all centres, total IgE and specific IgE were measured against *Dermatophagoides pteronyssinus* (house dust mite), timothy grass, and cat. IgE sensitisation was defined as the presence of IgE titres for a specific allergen $\geq$0.35 kU_A/L.

In RHINESSA allergic sensitisation was also defined as positive specific IgE (IgE $\geq$0.35 kU_A/L) towards inhalant allergens *Dermatophagoides pteronyssinus*, cat, timothy grass and birch (ImmunoCAP; Thermo Fisher Scientific, Immunodiagnostics).

2.3. Statistical analysis

All analyses were performed in SPSS v26 (IBM, Armonk, NY). Linear regression models were used to assess the percent change in offspring FeNO by various offspring factors, where log-transformed values of offspring FeNO was the dependent variable. The equation *(exp [log value] -1)*100* was used to determine percent change in offspring FeNO by different offspring factors. Each offspring factor was assessed individually for its relationship to offspring FeNO.

We assessed mean offspring FeNO in groups with and without parental diseases/risk factors and t-tests used to obtain p-values for differences between groups.

We used linear regression models to also assess the percent change in offspring FeNO by presence of parental risk factors (parental AR, asthma and smoking). Here, offspring FeNO was compared between fathers with AR vs no parents with AR, and mothers with AR vs no parents with AR. Similar groups were analysed for paternal/maternal asthma, and paternal/maternal smoking. Log transformed values of FeNO were again used as the dependent variable where the same equation as previous was used to obtain the percent change in offspring FeNO by parental allergic disease status or parental smoking. We also assessed percent increase in offspring FeNO per 1 % increase in parental FeNO using linear regression models of log transformed values of both parental and offspring FeNO, where the coefficient was used to show the percent change in offspring FeNO. For all analyses, known confounders from existing literature were used in model adjustments. A two sided p value < 0.05 was considered statistically significant.

3. Results

For the purposes of this study, we selected only offspring who had valid information on FeNO (n = 975) within the RHINESSA study. After exclusion of any missing key variables (including age, age outliers, sex, height, smoking, asthma and allergic rhinitis) in RHINESSA and excluding parents with missing information on participation in RHINE III, there were 635 RHINESSA subjects available for analysis with corresponding information on parental risk factors. For centres that did not participate in RHINE III, the questionnaire responses from ECRHS III were used.

Three analyses of offspring FeNO were carried out. In our cohort of 635 offspring, we excluded 68 offspring that had missing information on parental smoking status when assessing the effect of parental smoking on offspring FeNO (n = 567). When assessing the effect of parental allergic diseases such as asthma and AR on offspring FeNO we excluded 26 offspring from our cohort of 635 (n = 609) that had missing information on parental allergic diseases. When assessing the effect of parental FeNO on offspring FeNO we excluded offspring with missing information on parental FeNO (n = 183), and also missing information on covariates such as parental smoking (n = 66) from our cohort of 635 offspring (n = 360). Fig. 1 illustrates the flow of participants through the study.

Subject characteristics are presented in Table 1 for the parent and offspring populations. Data are presented as means (±SD) unless otherwise stated. For variables that did not have normal distributions, median values with 25–75th percentiles are presented (FeNO).

Mean (±SD) age of parents was 54 (±7) years and mean age for offspring was 29 (±7) years (Table 1). Similar proportions of parents and offspring were male, had prevalent AR or asthma at baseline. Baseline height and FeNO values were similar for parents and offspring (Table 1). Prevalence of current smoking was higher in parents than in their offspring. Prevalence of allergic sensitisation was higher in offspring than in parents.

Table 2 shows cross-sectional analyses to describe percent difference in offspring FeNO by offspring risk factors. Higher values of offspring FeNO (% increase) were associated with male sex, increasing height, current/ever asthma, AR and allergic sensitisation.

There were statistically significantly higher mean FeNO levels in offspring with parents with AR and asthma ($p < 0.001$ and 0.004 respectively) (Table 3). No differences in offspring FeNO were found with regards to parental smoking (p-value 0.45).

Mean FeNO levels in offspring by maternal and paternal AR and asthma are shown in Supplement Figure 2 and Supplement Figure 3, respectively.

Parental AR was significantly associated with higher FeNO in the offspring after adjusting for offspring age, sex, height, current smoking, AR, allergic sensitisation and parental asthma (Table 4, model 2). Both paternal and maternal AR were associated with higher FeNO in the offspring ($p = 0.008$ and $p = 0.043$, respectively). We additionally adjusted the analysis for in and out of pollen season, where March–September was considered in season for all centres except Australia, where September–January was considered in pollen season. We found our results to remain unchanged after this adjustment (not shown).

In a sensitivity analysis, we further adjusted Table 4, model 2 for current asthma in offspring and found that the associations between parental AR and offspring FeNO remained significant (change in offspring FeNO by any parent with AR: 14.5 % [2.9–27.4], $p = 0.013$). When stratified by sex of the parent, these findings were significant for paternal but not maternal AR (paternal AR: 17.9 % [2.9–35.1], $p = 0.017$, maternal AR: 13.1 % [−0.3 – 28.3], $p = 0.056$). Maternal but not paternal asthma was significantly associated with offspring FeNO, however, this association did not remain significant after adjusting maternal asthma for parental AR within model 2 adjustments. Having either parent with both AR and asthma was associated with higher offspring FeNO after adjustments (16.2 % [0.9–33.9], $p = 0.037$. Parental smoking was not significantly associated with offspring FeNO.

Parental FeNO was not significantly associated with offspring FeNO in models adjusted for offspring factors and parental risk factors. (Table 5, Model 5). Analysis to test if the association between parental and offspring FeNO was dependent on parental allergic sensitisation showed no significant interaction (results not shown).

4. Discussion

Of the parental factors investigated in this multi-generational study, we found only parental AR to be significantly associated with offspring FeNO.

This finding remained significant even after taking into account plausible confounders including AR in the offspring and parental asthma. After taking into account offspring asthma this finding

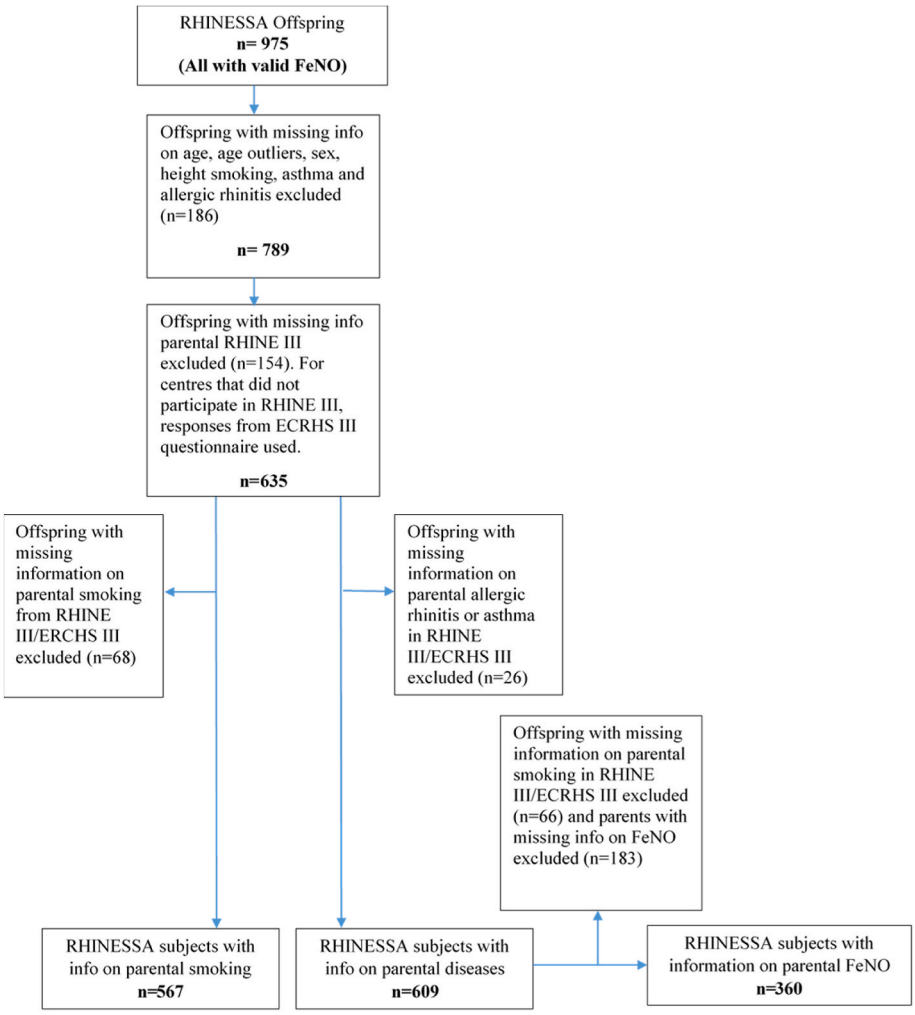

Fig. 1. Flowchart of offspring and parent participants through the study.

Table 1
Characteristics of the participants (n = 609).

Baseline	Parents (n = 609)	Offspring (n = 609)
Age (year)	53.7 (±6.6)†	29.1 (±7.2)
Sex (male)	274 (45.0)	273 (44.8)
Height (cm)	172.1 (±9.7)‡	173.8 (±9.5)
Current-smoker (n, %)	101 (18.6) §	65 (10.7)
Allergic rhinitis (n, %)	203 (33.3)	217 (35.6)
Ever asthma (n, %)	122 (20.0)	131 (21.5)
Current asthma (n, %)	88 (14.4)	89 (14.6)
FeNO (ppb) median (25-75th percentile)	17 (12–25) ¶	16 (12–24)
Allergic sensitisation [β] (any allergen ≥0.35 kU_A/L (n, %)	82 (24.5)	223 (42.7)

Data presented as mean (±standard deviation) unless otherwise stated. Median and 25th and 75th percentile presented for FeNO values †Age at RHINE III examination in 607 subjects ‡ height in 601 subjects § Smoking in 543 subjects ¶ Information on FeNO available in 420 parents. [β]Information on allergic sensitisation available in 335 parents and 522 offspring. Allergens included for parental population: *D. Pteronyssinus*, cat and timothy, and for offspring population this included *D. Pteronyssinus*, cat and timothy and birch.

Table 2
Linear regression analysis to assess percent difference in offspring FeNO by offspring factors (n = 609).

	Percent difference in offspring FeNO (%)	p-value
Age (per 10 years)	0.7 (−5.6 to 7.6)	0.822
Sex (male vs female)	28.2 (16.9–40.5)	<0.001
Height (per 10 cm)	9.4 (4.1–14.9)	<0.001
Current smoking (vs non smoking)	−9.4 (−22.1 to 5.4)	0.201
Ever asthma	30.5 (16.7–45.9)	<0.001
Current asthma	30.0 (14.0–48.0)	<0.001
Allergic rhinitis	28.3 (16.5–41.1)	<0.001
Allergic sensitisation (any allergen ≥0.35 kU_A/L (n, %)[a]	46.8 (33.6–61.1)	<0.001

[a] IgE ≥0.35 kU_A/L. Allergic sensitisation assessed in 522 subjects (*D. Pteronyssinus*, cat and timothy and birch).

remained for paternal AR but not maternal AR.

Parental AR is a strong hereditary risk factor for AR in children [24], with both maternal and paternal AR increasing this risk in the offspring. This could be a plausible explanation for the increased FeNO in offspring of parents with AR.

However, the association we observed between parental AR and offspring FeNO, was independent of offspring AR and offspring allergic sensitisation. Nevertheless, we cannot exclude that subclinical airways inflammation, signalled by FeNO, later can develop into disease [25]. Our findings indicated that type 2 inflammation related to AR was associated with type 2 inflammation in offspring as measured by FeNO. This is consistent with the previous findings that low grade systemic inflammation in pregnant women and their offspring is correlated [26] and IL-5 exposure in utero can result in airway reactivity in adult offspring [27]. Additionally, reducing type 2 inflammation in mothers

Table 3
Geometric mean offspring FeNO (ppb) (with 95 % CI) in exposed and non-exposed groups of parental diseases.

	Prevalence (%)	No	Yes	p-value
Parental allergic rhinitis (n = 609)	33.3	16.0 (15.2–16.8)	20.6 (18.7–22.7)	<0.001
Parental asthma (n = 609)	20.0	16.8 (16.0–17.7)	20.0 (17.6–22.6)	0.004
Parental current smoking (n = 567)	18.6	17.0 (16.1–18.0)	16.2 (14.7–18.0)	0.448

Table 4
Percent change in offspring FeNO by presence of parental factors.

Parental risk factor		Model 1	p-value	Model 2	p-value
Allergic rhinitis	Paternal (n = 90)	32.8 (17.4–50.5)	**<0.001**	20.3 (5.0–37.7)	**0.008**
	Maternal (n = 113)	26.2 (12.4–41.6)	**<0.001**	13.8 (0.4–28.9)	**0.043**
	Any parent (n = 203)	29.1 (17.1–42.3)	**<0.001**	15.6 (4.0–28.5)	**0.007**
Asthma	Paternal (n = 58)	15.8 (−0.9–35.4)	0.065	−1.3 (−15.9–16.0)	0.878
	Maternal (n = 64)	21.7 (4.8–41.1)	**0.010**	10.7 (−4.7–28.8)	0.182
	Any parent (n = 122)	18.8 (5.8–33.4)	**0.004**	4.7 (−7.3–18.4)	0.457
Allergic rhinitis and asthma	Paternal (n = 43)	37.9 (16.8–62.7)	**<0.001**	16.0 (−2.9–38.5)	0.101
	Maternal (n = 42)	33.9 (13.7–57.8)	**<0.001**	17.0 (−2.6–40.4)	0.093
	Any parent (n = 85)	35.9 (19.6–54.3)	**<0.001**	16.2 (0.9–33.9)	**0.037**
Smoking	Paternal (n = 48)	−12.6 (−26.5–3.9)	0.126	−11.5 (−25.4–4.9)	0.159
	Maternal (n = 58)	2.6 (−12.5–20.2)	0.750	5.0 (−10.1–22.6)	0.538
	Any parent (n = 106)	−4.6 (−15.6–7.8)	0.448	−3.0 (−13.9–9.4)	0.624

Model Adjustments: Allergic rhinitis: Model 1: Unadjusted, Model 2: Allergic rhinitis in offspring, age, sex, height, current smoking in offspring, parental asthma and offspring sensitisation to any allergen*.
Asthma: Model 1: Unadjusted, Model 2: Current asthma in offspring, offspring age, offspring sex, offspring height, current smoking in offspring and parental allergic rhinitis.
Allergic rhinitis AND asthma: Model 1: Unadjusted. Model 2: Current asthma in offspring, allergic rhinitis in offspring, offspring age, offspring sex, offspring height, current smoking in offspring and offspring sensitisation to any allergen*.
Smoking; Model 1: Unadjusted, Model 2: Offspring age, offspring sex, offspring height and current smoking in offspring.
Reference group for AR analyses = no parents with AR (n = 406), reference group for asthma analyses = no parents with asthma (n = 487), reference group for smoking analyses = no parents current smokers (n = 461), reference group for AR AND asthma analyses = both parents with neither allergic rhinitis nor asthma (n = 369).
*Information on allergic sensitisation in offspring available for fewer subjects, therefore for model 2 AR analyses: reference group = 358 (paternal AR = 77, maternal AR = 87 and any parent with AR = 164). For model 2 AR with asthma analyses: reference group = 323 (paternal AR with asthma = 35, maternal AR with asthma = 32, any parent with AR and asthma = 67).

during pregnancy by anti-inflammatory treatment upon FeNO levels, results in a reduction of asthma in the offspring [28]. A likely explanation as to why we found associations for parental AR and not asthma could be that the main treatment option for asthma, inhaled corticosteroids, acts to reduce type 2 inflammation in the lower airways whereas AR treatment would not affect the inflammation in the lower airways to the same extent. Therefore, we see effects of type 2 inflammation in the offspring more so in parents with AR where type 2 inflammation is likely to have gone untreated for longer periods of time. We further adjusted the models for current asthma in the offspring. As the results remained significant for paternal AR, asthma in the offspring was also not an explanation for this association. Previous studies have shown that increased FeNO can predict later onset of rhinitis [25] and wheeze [29] so this could be another potential explanation.

Table 5
Percent increase in offspring FeNO per 1 % increase in parental FeNO (n = 360).

	Percent increase in offspring FeNO	p-value
Model 1	0.13 (0.02–0.23)	**0.020**
Model 2	0.13 (0.03–0.24)	**0.015**
Model 3†	0.09 (−0.01–0.20)	0.089
Model 4†	0.10 (−0.03–0.22)	0.122
Model 5‡	0.02 (−0.12–0.15)	0.813

Model 1: Unadjusted.
Model 2: Offspring age, offspring sex, offspring height, offspring smoking.
†Model 3: Offspring age, offspring sex, offspring height, offspring smoking, current asthma in offspring, allergic rhinitis in offspring, offspring allergic sensitisation (any allergen ≥0.35).
†Model 4: Offspring age, offspring sex, offspring height, offspring smoking, current asthma in offspring, allergic rhinitis in offspring, offspring allergic sensitisation (any allergen ≥0.35), parental smoking, parental asthma, and parental allergic rhinitis.
‡Model 5: Offspring age, offspring sex, offspring height, offspring smoking, current asthma in offspring, allergic rhinitis in offspring, offspring allergic sensitisation (any allergen ≥0.35), parental smoking, parental asthma, and parental allergic rhinitis, parental allergic sensitisation (any allergen ≥0.35).
† = 323.
‡n = 296.

Parental asthma alone was not associated with offspring FeNO levels in adulthood after adjusting for potential confounders. Although an association was found between both maternal asthma and offspring FeNO levels, this finding was mainly explained by parental AR. Previous studies of parental factors on predicting offspring FeNO have been limited to children [15,17]. Studies assessing the effect of parental factors on offspring beyond childhood have been limited. In contrast to studies assessing the effect of parental factors on childhood FeNO, we found that parental asthma did not predict FeNO levels in offspring, once they were adults or reaching adulthood. It might also be that the immediate effects of parental factors on childhood FeNO levels differ from those that drive FeNO levels later in life, indicating different mechanisms. Studies have mainly found maternal asthma to be a risk factor for increased levels of childhood FeNO [15,17]. We also found that maternal asthma was a stronger risk factor compared to paternal asthma for increased offspring FeNO levels. However, the association between maternal asthma and offspring FeNO did not remain significant once adjusting for parental AR within model 2 adjustments. A recent GWAS study supports the findings of our study where FeNO was found to have a significant genetic correlation with seasonal AR but not with asthma [30]. It was concluded in the study that the lack of a genetic correlation to asthma could have been due to sample size, but the presence of a genetic correlation between AR and FeNO supports the hypothesis that there is a common genetic background for allergic diseases and allergy biomarkers such as FeNO.

We did not find any significant association between parental FeNO and offspring FeNO levels after adjusting for current asthma in offspring, AR in offspring and offspring allergic sensitisation (any allergen ≥0.35) indicating that any association between parental and offspring FeNO can be explained by offspring atopic disease/status.

Many observational studies are prone to certain limitations that should be considered when interpreting the results. The study design is cross-sectional in nature, with no repeated offspring FeNO measurements. Therefore, it was not possible to draw any conclusions on longitudinal patterns in offspring FeNO. Measuring FeNO at one time point also did not allow us to consider seasonal variation in FeNO that may

occur due to pollen season. However, when we have adjusted for pollen season, the results for parental AR on offspring FeNO were unchanged, in line with previous epidemiological studies that have found that adjusting for in or out of the pollen season did not affect the associations found with FeNO [31].

We did not examine asthma by severity or with and without treatment, which is a limitation as FeNO may have been affected by this at the time of measurement. This is however unlikely to have affected the results to a great extent as continuous ICS treatment was found only in 37 % in an earlier study where the effect of ICS treatment on FeNO was also relatively modest in a population-based study [12].

Information on household smoking was available only for a minority of the participants of the RHINESSA cohort therefore the role of environmental tobacco smoke at the time of FeNO measurement could not be ascertained. However, the prevalence of environmental tobacco smoke in non-smokers in RHINE III has been found to be low [32], therefore it is likely that being exposed passively to tobacco smoke was also uncommon at the time RHINESSA was carried out. As we only included offspring that had the relevant information on parental factors (smoking, allergic diseases or FeNO), we cannot exclude a potential selection bias that is more likely to go in the direction where healthier parents are more likely to have answered the questions. This would also likely affect the power of the study as fewer parents with exposures or medical conditions would be included. We do have data missing from both cohorts and this can be considered a limitation as it can also reduce the power due to smaller sample sizes available after excluding missing data. The number of parents and offspring with information on FeNO and important confounders was limited to 360, of which fewer subjects had information on allergic sensitisation -which could be considered a relatively small sample size. However, it is extremely rare to have detailed information on both parents and offspring where both physical examination and questionnaire responses are available including measurements such as FeNO. Therefore, we consider the sample size to have high quality data used to examine the relationships between parental FeNO and offspring FeNO. We did not have information from both parents for many offspring in the RHINESSA cohort with most offspring having information from either parent. This is a limitation as information from both parents would allow us to assess the maternal and paternal line effects for each offspring, rather than assessing this in the population as a whole.

This is the first multi-generational study assessing a range of parental factors on the influence on offspring FeNO with findings suggesting independent relationships between parental AR and offspring FeNO levels. Our findings indicate the potential long-term impacts of certain parental risk factors and adds knowledge into how we interpret FeNO values in clinical practice.

5. Conclusions

Parental AR was associated with higher levels of FeNO in offspring which could be considered by clinicians when interpreting FeNO levels in an individual by asking questions relevant to parental allergic history. Further studies are however needed to understand the clinical significance of these associations and to study whether elevated FeNO levels should be evaluated differently in individuals with or without parental AR in a clinical context.

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Ethics approval

Written informed consent was obtained from each participant of the ECRHS III and RHINESSA clinical study and the studies were approved by the medical research ethics committee for each study centre according to national legislation.

CRediT authorship contribution statement

S. Zaigham: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Formal analysis, Conceptualization. **R.J. Bertelsen:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **S.C. Dharmage:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **V. Schlünssen:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **N.O. Jõgi:** Writing – review & editing, Methodology, Investigation. **L. Palacios Gomez:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Conceptualization. **M. Holm:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **A. Oudin:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **M.J. Abramson:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **T. Sigsgaard:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **R. Jõgi:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **C. Svanes:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **A.C. Olin:** Writing – review & editing, Visualization, Methodology, Investigation. **B. Forsberg:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **C. Janson:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Funding acquisition, Data curation. **E. Nerpin:** Writing – review & editing, Methodology, Investigation. **A. Johannessen:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **A. Malinovschi:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

SZ has received a grant from Bror Hjerpstedts stiftelse and a travel grant from Swedish Heart Lung foundation for the current project

SCD has received investigator initiated grants from AZ and GSK for unrelated research.

LPG has received a speaker's fee from Boehringer-Ingelheim

MJA holds investigator initiated grants from Pfizer, Boehringer-Ingelheim, Sanofi and GSK. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK.

RJ has been involved in Boehringer-Inghelheim advisory board. ACO Is a chair-holder and a board member of PExA AB.

All other authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.niox.2024.06.001.

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