Original research

Type-2 inflammation and lung function decline in chronic airway disease in the general population

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ABSTRACT
Background It is unclear if type-2 inflammation is associated with accelerated lung function decline in individuals with asthma and chronic obstructive pulmonary disease (COPD). We tested the hypothesis that type-2 inflammation indicated by elevated blood eosinophils (BE) and fraction of exhaled nitric oxide (FeNO) is associated with accelerated lung function decline in the general population.

Methods We included adults from the Copenhagen General Population Study with measurements of BE (N=15 605) and FeNO (N=2583) from a follow-up examination and assessed forced expiratory volume in 1 s (FEV1) decline in the preceding 10 years. Based on predefined post-bronchodilator lung function, smoking history and asthma at follow-up examination, participants were assigned as not having airway disease, asthma with full reversibility (AR), asthma with persistent obstruction (APO), COPD, and not classifiable airflow limitation (NAL).

Results FEV1 decline in mL/year increased with 1.0 (95% CI 0.6 to 1.4, p<0.0001) per 100 cells/µL higher BE and with 3.2 (95% CI 2.0 to 4.5, p<0.0001) per 10 ppb higher FeNO. Adjusted FEV1 decline in mL/year was 18 (95% CI 17 to 20) in those with BE<300 cells/µL and FeNO<20 ppb, 22 (19–25) in BE≥300 cells/µL or FeNO≥20 ppb, and 27 (21–33) in those with BE≥300 cells/µL and FeNO≥20 ppb (p for trend<0.0001). Corresponding FEV1 declines were 24 (19–29), 33 (25–40) and 44 (31–56) in AR (0.002), 26 (14–37), 36 (12–60) and 56 (24–89) in APO (0.07), 32 (25–36), 27 (25–49) and 44 (31–56) in COPD (0.002), 26 (14–37), 36 (12–60) and 56 (24–89) in NAL (0.10), respectively.

Conclusions Type-2 inflammation indicated by elevated BE and FeNO is associated with accelerated FEV1 decline in individuals with chronic airway disease in the general population, and this association was most pronounced in an asthma-like phenotype.

INTRODUCTION
Type-2 inflammation is increasingly recognised as an important pathophysiological feature in patients with asthma and chronic obstructive pulmonary disease (COPD). Patients with this endotype are responsive to treatment with inhaled corticosteroids and may benefit from treatment with monoclonal antibodies specifically targeting type-2 signalling through interleukin (IL)-5, IL-4 and IL-13 pathways.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Type-2 inflammation is increasingly recognised as an important clinical feature in patients with asthma and chronic obstructive pulmonary disease (COPD). Patients with type-2 inflammation respond well to treatment with inhaled corticosteroids and are likely to benefit from treatment with monoclonal antibodies specifically targeting type-2 signalling through interleukin (IL)-5, IL-4 and IL-13 pathways. An important clinical question to address is whether type-2 inflammation in the long term is associated with accelerated decline of lung function.

WHAT THIS STUDY ADDS
⇒ By using a large-scale Danish population-based cohort with randomly selected individuals, we found that the presence of type-2 inflammation indicated by elevated blood eosinophils and fraction of exhaled nitric oxide is associated with accelerated decline of forced expiratory volume in 1 s in individuals with chronic airway disease, and that this association was most pronounced in individuals with an asthma-like phenotype.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Future studies should investigate whether long-term treatment targeting type-2 signalling in asthma and COPD can normalise lung function decline and hence halt disease progression.

and quantify the degree of type-2 inflammation. Elevated blood eosinophils and FeNO have been associated with uncontrolled disease activity in chronic airway disease, including increased symptoms, lower lung function and frequent exacerbations. Inhibiting IL-4 and IL-13 signalling in asthma patients with elevated blood eosinophils and/or FeNO improves lung function and symptoms and reduces daily oral corticosteroid dosage and frequency and severity of exacerbations. In patients with COPD with elevated blood eosinophils, inhibition of IL-5 signalling lowers exacerbation rates.
Improvement or preservation of lung function remains an important treatment goal in asthma and COPD given its high prognostic value. Patients with asthma and COPD experience accelerated lung function decline that may be caused by ongoing airway inflammation and lead to disease progression. 19–22 Although different mechanisms may explain accelerated lung function decline in asthma and COPD, the role of type-2 inflammation is important to clarify, as treatment specifically targeting this inflammatory process could potentially halt disease progression. In this study, we tested the hypothesis that type-2 inflammation indicated by elevated blood eosinophils and FeNO is associated with accelerated lung function decline in chronic airway disease in the general population. For this purpose, we included randomly selected individuals from the Danish general population with information on blood eosinophils and FeNO and a 10-year observation period of spirometric function.

METHODS

Study design and population

We used the Copenhagen General Population Study, an ongoing Danish population-based cohort initiated in 2003 with a subsequent follow-up examination approximately 10 years later.9 23 24 So far, approximately 110,000 individuals have been investigated over the years, of whom approximately 17,000 have attended the subsequent follow-up examination. All individuals in Denmark are assigned a unique identification number (Central Person Registration number) at birth or immigration and recorded in the national Danish Civil Registration System. We randomly invited and recruited individuals living in the Capital Region of Denmark from the national Danish Civil Registration System to reflect the adult Danish general population (response rate 43%). All participants completed a questionnaire, underwent a physical examination including spirometry and gave blood for biochemical analyses at the baseline examination and subsequent follow-up.

Type-2 inflammation

Blood eosinophils together with other white blood cells were measured on fresh samples by using the ADVIA 120 Hematology System (Siemens Healthcare, Munich, Germany). Analyses were subjected to daily precision testing by using internal quality control material and monthly accuracy testing by using an external quality control programme. Blood eosinophils were reported in 10^6 cells/L together with other leucocyte subpopulations and converted to cells/μL.

FeNO in expiratory volume was obtained using an online measurement technique with the portable hand-held device NIOX VERO (Aerocrine, Solna, Sweden) in accordance with the recommendations from the American Thoracic Society and the European Respiratory Society.25 The lowest detection limit was 5 ppb with a measurement range of 5–300 ppb. Measurements were performed with individuals in a sitting position without the use of a nose clip, as this may lead to accumulation of nitric oxide in the nasal region and promote leakage via the posterior nasopharynx.25 Individuals were required to inhale to their total lung capacity through the mouthpiece with a protective filter to avoid environmental containment and were guided via an animated interface to maintain a correct constant expiratory flow rate during exhalation. FeNO was not analysed if individuals failed to sustain a correct constant expiratory flow rate and automatically required the measurement to be repeated. FeNO was measured before spirometry and reversibility testing to avoid disturbance of FeNO levels in the airways. Maintenance of the apparatus was done regularly, as recommended by the manufacturer.

We chose to use the cut-points 150 cells/μL and 300 cells/μL for blood eosinophils and 20 ppb for FeNO that are used for treatment indication with monoclonal antibodies specifically targeting IL-5, IL-4 and IL-13 signalling, as this may suggest presence of type-2 inflammation and potential treatment response.14–18 Blood eosinophils were measured at baseline and follow-up examinations in 15,605 individuals. FeNO was only measured at follow-up examination consecutively in a random subgroup of 5000 individuals, of which 2853 individuals also had baseline information so lung function decline could be investigated.

Chronic airway disease and lung function decline

Individuals were assigned to clinical groups based on information on self-reported diagnosis of asthma and smoking history and on pre- and post-bronchodilator measurements of forced expiratory volume in 1s (FEV1) and forced vital capacity (FVC) at the follow-up examination of the Copenhagen General Population Study. This was done because we only performed pre-bronchodilator measurements of lung function at the baseline examination. We assigned participants into one of following five mutually exclusive clinical groups (figure 1): 1. Controls: individuals with pre-bronchodilator FEV1/FVC≥0.70 and without self-reported asthma. 2. Asthma with full reversibility: (1) individuals with pre-bronchodilator FEV1/FVC≥0.70 and self-reported diagnosis of asthma, (2) individuals with pre-bronchodilator FEV1/FVC<0.70 but post-bronchodilator FEV1/FVC≥0.70 and (3) individuals with pre- and post-bronchodilator FEV1/FVC<0.70 but with FEV1 reversibility ≥12% and ≥200 mL. 3. Asthma with persistent obstruction: individuals with pre- and postbronchodilator FEV1/FVC<0.70 and FEV1 reversibility <12% and <200 mL and with self-reported diagnosis of asthma. 4. COPD: individuals with pre- and post-bronchodilator FEV1/FVC<0.70 and FEV1 reversibility <12% and <200 mL and without self-reported diagnosis of asthma. 5. Not classifiable airflow limitation: individuals with pre-bronchodilator FEV1/FVC<0.70 who wished not to participate in reversibility testing and lacked post-bronchodilator measurements.

Since post-bronchodilator measurements were not available at the baseline examination, estimation of lung function decline was based on pre-bronchodilator measurements of FEV1. FEV1 decline was calculated by subtracting FEV1 at follow-up with FEV1 at baseline about 10 years earlier to obtain total decline during follow-up and by dividing with follow-up time in years to obtain the average annual FEV1 decline.

Statistical analyses

Wilcoxon’s non-parametric rank-sum test and Pearson’s χ^2 test were used to compare characteristics of individuals with chronic airway disease to controls. Box plots were used to display annual FEV1 decline according to clinical cut-points for blood eosinophils and FeNO and differences were assessed using Kruskal-Wallis test. Association of blood eosinophils and FeNO with annual FEV1 decline was investigated by using multiple linear regression analyses to account for potential confounding and visually depicted by using quadratic prediction plots with 95% CIs. Associations were investigated in all individuals and according to type of chronic airway disease, including as an
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The average annual FEV₁ decline was estimated according to clinical cut-points for blood eosinophils and FeNO by using multiple linear regression analyses. Analyses were also performed in controls to investigate whether this association also exists in individuals without chronic airway disease. All analyses were multivariable adjusted for a priori decided potential confounders obtained at follow-up examination, including age, age-squared, sex, height, smoking status, tobacco consumption (pack-years), and airway medication. Sensitivity analyses were performed by stratifying according to active smoking and treatment with airway medication. Analyses were performed using STATA/SE 15.1 for Windows (StataCorp), and a two-sided p<0.05 was considered as significant.

RESULTS
In total, 15 605 individuals in the Copenhagen General Population Study had information on blood eosinophils and 2853 on FeNO at follow-up examination (figure 1). Among all individuals with blood eosinophil counts, 3519 (23%) had airflow limitation with prebronchodilator FEV₁/FVC<0.70 at the follow-up examination (29% among those with FeNO measurement had airflow limitation). All those with airflow limitation were asked to undergo bronchial reversibility testing, but 38% wished not to perform the test and lack information on post-bronchodilator FEV₁ and FVC (31% among those with FeNO measurement). At the follow-up examination, 11 328 individuals (1902 individuals with FeNO) were classified as controls, 1519 (331) as asthma with full reversibility, 176 (44) as asthma with persistent obstruction, 1232 (320) as COPD, and 1350 individuals (256 individuals with FeNO) had not classifiable airflow limitation. Characteristics of the participants at the follow-up examination according to type of airway disease are provided in table 1. Individuals with asthma with persistent obstruction, COPD, and not classifiable AL were on average older, more often active smokers with a higher cumulative tobacco consumption and had lower lung function. Individuals with asthma with full reversibility and persistent obstruction reported more often to be on treatment with airway medication compared with individuals

Figure 1  Flow chart. Number of individuals depicted represent those with information on blood eosinophils, while those with information on FeNO in parentheses. AL, airflow limitation; COPD, chronic obstructive pulmonary disease; FeNO, fraction of nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.


with COPD and not classifiable airflow limitation. While the average FeNO was overall similar, besides COPD which was lower, blood eosinophils were highest in those with asthma with persistent obstruction followed by COPD and not classifiable airflow limitation.

FEV₁ decline was higher with higher blood eosinophil counts in all individuals after multivariable adjustment in a dose-dependent manner but seemed to reach a form of plateau beyond higher FeNO compared with the other clinical groups, statistical significance could not be obtained.

Corresponding FEV₁ declines were 24 (19–29), 33 (25–40) and 36 (29–41) mL/year (95% CI 1.0 to 6.0, p=0.006) in asthma with full reversibility and COPD, and then not classifiable airflow limitation (figure 3). Corresponding FEV₁ declines per 10 ppb higher FeNO were 4.2 mL/year (95% CI 0.8 to 7.6, p=0.02) in asthma with full reversibility, 5.9 mL/year (95% CI 0.4 to 11, p=0.04) in asthma with persistent obstruction, 1.5 mL/year (95% CI −2.8 to 5.7, p=0.51) in COPD, 2.5 mL/year (95% CI −0.6 to 5.6, p=0.12) in not classifiable airflow limitation, and 2.9 mL/year (95% CI 1.4 to 4.3, p<0.0001) in controls, respectively. Effect modification was only present in those with asthma with persistent obstruction (p for interaction=0.04) suggesting an even higher FEV₁ decline with higher FeNO compared with the other clinical groups.

In general, individuals with both elevated blood eosinophils (≥300 cells/µL) and FeNO (≥20 ppb) had a higher FEV₁ decline compared with those with normal or only a single elevated type-2 biomarker (figure 4). Adjusted FEV₁ decline was 18 mL/year (95% CI 17 to 20) in those with blood eosinophils <300 cells/µL and FeNO<20 ppb, 22 mL/year (19–25) in those with blood eosinophils ≥300 cells/µL or FeNO≥20 ppb, and 27 mL/year (21–33) in those with blood eosinophils ≥300 cells/µL and FeNO≥20 ppb (P for trend<0.0001). Same trend could be detected when individuals were stratified according to chronic airway disease (figure 3); however, due to lower sample sizes in some groups, statistical significance could not be obtained. Corresponding FEV₁ declines were 24 (19–29), 33 (25–40) and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of 15 605 individuals in the general population with 10 years follow-up according to chronic airway disease</th>
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<tbody>
<tr>
<td></td>
<td>All (N=15 605)</td>
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<tr>
<td>Age—year</td>
<td></td>
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<tr>
<td></td>
<td>65.0 (56.8–72.4)</td>
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<tr>
<td>Height—cm</td>
<td>170 (163–177)</td>
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<td>FEV₁, —L</td>
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<tr>
<td>FVC, —L</td>
<td>3.69 (3.06–4.45)</td>
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<tr>
<td>FEV₁ % of predicted value</td>
<td>99 (88–109)</td>
</tr>
<tr>
<td>FVC % of predicted value</td>
<td>104 (94–114)</td>
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</table>

Data presented as median and 25th and 75th percentiles or number (per cent). Number may not add up to 100% due to rounding. Based on the Copenhagen General Population Study, 
*P<0.05 for comparison with controls.
†Only for current and former smokers.
‡Number of individuals with available information on FeNO: All (N=2853), controls (N=1902), asthma with full reversibility (N=131), asthma with persistent obstruction (N=44), COPD (N=320) and not classifiable AL (N=256).
AL, airflow limitation; COPD, chronic obstructive pulmonary disease; FeNO, fraction of nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.
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44 (31–56) in asthma with full reversibility (p for trend=0.002), 26 (14–37), 36 (24–60) and 56 (24–89) in asthma with persistent obstruction (p for trend=0.07), 32 (27–36), 31 (24–38) and 44 (24–65) in COPD (p for trend=0.46), 32 (27–36), 31 (24–38) and 44 (24–65) in not classifiable airflow limitation (p for trend=0.10), and 14 (12–16), 17 (13–21) and 16 (8–24) in controls (p for trend=0.17), respectively. Raw FEV₁ declines according to blood eosinophils and FeNO are provided in online supplemental figures 1 and 2.

In sensitivity analyses, FEV₁ decline increased with higher blood eosinophils and FeNO in non-smokers but did not reach statistical significance in smokers despite higher coefficients without sign of effect modification (online supplemental figures 3 and 4). In contrast, FEV₁ decline increased significantly with higher blood eosinophils and FeNO in those with and without airway medication, and there was an interaction suggesting an even higher decline in those with airway medication (online supplemental figures 3 and 4).

**DISCUSSION**

By using a large-scale Danish cohort with randomly selected individuals from the general population, we found that type-2 inflammation indicated by elevated blood eosinophils and FeNO is associated with accelerated FEV₁ decline in individuals with chronic airway disease. This association was most pronounced in individuals with an asthma-like phenotype.

Substantial proportion of patients with asthma and COPD experience an accelerated lung function decline compared with healthy individuals. Accelerated loss of lung function is believed to arise from local inflammatory processes in the airways and lung parenchyma, which seems to be further accelerated during acute exacerbations. Lung function decline
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seems highest for those with asthma-COPD overlap followed by COPD and asthma. In this study, we tested the hypothesis that the presence of type-2 inflammation is associated with accelerated lung function decline. There is a good biological rationale for defining type-2 inflammation with blood eosinophils and FeNO, as they seem to have complementary additive prognostic and predictive effects. Indeed, type-2 inflammation indicated by elevated blood eosinophils and FeNO has previously been associated with increased symptoms, lower lung function and frequent exacerbations in patients with obstructive lung disease, especially those with an asthma-like phenotype. Therefore, we expected that patients with type-2 inflammation also would experience accelerated FEV₁ decline; however, that this association also seems to exist in individuals without chronic airway disease is intriguing. We observed an association between higher blood eosinophils and FeNO with higher FEV₁ decline on a continuous scale in both those with and without chronic airway disease, suggesting that there is an association even in individuals with blood eosinophils and FeNO within a normal range. Therefore, it is possible that type-2 inflammation not only plays a role for the prognosis of individuals with established chronic airway disease but is also related to the natural course of FEV₁ in individuals without a diagnosis of chronic airway disease. Interestingly, when stratified according to type of chronic airway disease, the association seems to be strongest in those with asthma-like phenotype, both in those with full reversibility and in those with persistent obstruction.

Figure 3  FeNO and lung function decline according to chronic airway disease. All analyses were multivariable adjusted for covariates obtained at follow-up examination, including age, age-squared, sex, height, smoking status, tobacco consumption (pack-years) and airway medication. Individuals beyond 100 ppb were included in analyses but not in graphs for visual purposes. Shaded areas indicate 95% CIs. Dashed line indicates cut-point for FeNO that is used for treatment indication with monoclonal antibodies specifically targeting IL-5, IL-4 and IL-13 signalling, as this may suggest presence of type-2 inflammation and potential treatment response. AL, airflow limitation; COPD, chronic obstructive pulmonary disease; FeNO, fraction of nitric oxide; FEV₁, forced expiratory volume in 1 s.
Few previous studies have explored blood eosinophils and FeNO as markers of lung function decline, and the results from these studies support our findings. In a subsample of the Canadian Cohort of Obstructive Lung Disease study with 1120 older individuals, blood eosinophils $\geq 300$ cells/$\mu$L were an independent risk factor for accelerated FEV$_1$ decline in those with (N=547) and without COPD (N=573) during a mean follow-up of 5.5 years.

In the Dunedin Multidisciplinary Health and Development Study, where spirometry and blood eosinophils were assessed at ages 21, 26, 32 and 38 years in 971 individuals (N=269 with asthma), higher blood eosinophils were associated with accelerated decline of both FEV$_1$/FVC and FEV$_1$, especially in those with $\geq 400$ cells/$\mu$L. In the Adult-Onset Asthma and Inflammatory Subphenotypes study including 141 individuals with newly diagnosed asthma, higher FeNO levels were associated with accelerated FEV$_1$ decline during 5 years of follow-up.

Thus, there seems to be a consistent and robust relationship between the two most commonly used markers of type-2 inflammation and accelerated lung function in individuals with and without chronic airway disease. In this study, we now demonstrate in a large random sample from the general population that not only separately but also combined, elevated blood eosinophils and FeNO associated with an accelerated FEV$_1$ decline over a period of 10 years, and this association seems primarily to include individuals with asthma-like phenotype irrespective of presence of airflow limitation. This finding is interesting in the light of the recent results from the BOREAS trial of dupilumab in patients with COPD with frequent exacerbation and blood eosinophils $\geq 300$ cells/$\mu$L. In this 1-year trial, the subgroup of patients who also had an FeNO $\geq 20$ ppb were those who benefitted the most regarding reduction of exacerbation frequency and improvement of lung function and symptoms. Our finding that type-2 inflammation in patients with asthma and COPD not only is associated with symptoms and risk of future exacerbations, but also relates to the long-term FEV$_1$-trajectory raises an important question of whether treatments specifically targeting this type of inflammation could normalise lung function decline. Systematic reviews on the effect of inhaled corticosteroid on long-term changes of lung function in asthma and COPD suggest a modest reduction of the decline of FEV$_1$ in both conditions, and it would be of considerable interest to study whether long-term treatment with more specific drugs targeting IL-5, IL-4 and IL-13 signalling can ameliorate lung function decline. Recent results from the Liberty Asthma QUEST trial have shown that treatment with dupilumab attenuated lung function decline over 52 weeks in patients with uncontrolled moderate-to-severe asthma with FeNO $\geq 35$ ppb compared with placebo, suggesting that targeted treatment of type-2 inflammation may halt disease progression.

Strengths of this study include a large-scale population-based cohort with randomly selected individuals who were followed for a sufficiently long time in order to estimate lung function decline.

Yet, our study also has some potential limitations. Although we could distinguish between different types of chronic airway disease, our definitions may be subject to discussion. We had data to differentiate between reversible and irreversible airflow limitation in many of the participants, yet asthma and COPD are complex diseases that may be difficult to define as many patients show similar clinical presentation and have common risk factors. We relied on self-reported asthma and in the absence of supporting physiology, we cannot be certain that a sizeable number of these individuals do not have asthma. A potential limitation is that more than one-third of individuals with prebronchodilator airflow limitation were not willing to perform reversibility test. We assigned them to a category of not classifiable airflow limitation. These individuals could have COPD or asthma. Clinicians often encounter patients with airflow limitations that are difficult to label and must proceed with empiric therapy, which sometimes can lead to a more specific diagnosis. We believe that our findings that individuals with not classifiable airflow limitation also displayed accelerated lung function decline in the presence of type-2 inflammation could be seen as supportive of the concept of treatable clinical or physiological traits rather than the concept of pursuing a diagnostic label.

Another potential limitation of this study is lack of information on the type of airway medication used by the participants. It would be interesting to perform separate analyses on those on active treatment with inhaled corticosteroids and/or monoclonal antibodies specifically targeting IL-5, IL-4 and IL-13 signalling. However, we believe that this information would not change the results since most of the included individuals in this cohort were not on maintenance treatment and many of them with mild symptoms were underdiagnosed, especially those with COPD and not classifiable airflow limitation.

In addition, our estimation of lung function declines was adjusted for treatment with airway medication (yes vs no).

Finally, we assigned the participants into the clinical groups of chronic airway disease and determined type-2 inflammation using information from the follow-up visit and not from the.
Figure 5  Lung function decline according to elevated blood eosinophils and FeNO in chronic airway disease. All analyses were multivariable adjusted for covariates obtained at follow-up examination, including age, age-squared, sex, height, smoking status, tobacco consumption (pack-years) and airway medication. AL, airflow limitation; COPD, chronic obstructive pulmonary disease; FeNO, fraction of nitric oxide; FEV₁, forced expiratory volume in 1 s.

baseline visit. This was done since information on both pre- and postbronchodilator FEV\textsubscript{1} and FVC as well as blood eosinophils and FeNO was only available at follow-up examination, which lies 10 years after the baseline spirometry evaluation. A potential limitation to consider here is that some individuals with chronic airway disease perhaps do not have their disease at the baseline examination but may have developed it during follow-up, and levels of blood eosinophils and FeNO may not be stable over time but fluctuate. It is, however, important to notice that chronic airflow limitation develops gradually over many years, and more than half of patients with COPD developed the disease from low lung function in their twenties to forties despite normal or only slightly accelerated age-related lung function decline.\textsuperscript{41}

In conclusion, our study shows that the presence of type-2 inflammation indicated by elevated blood eosinophils and FeNO is associated with accelerated FEV\textsubscript{1} decline in individuals with chronic airway disease in the general population, and that this association was most pronounced in individuals with an asthma-like phenotype. Future studies should investigate whether long-term treatment specifically targeting type-2 signalling could normalise lung function decline and halt disease progression in patients with asthma and COPD.

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### Contributors

YC and PL (the manuscript’s guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies in the study as planned (and, if relevant, registered) have been explained. YÇ and PL revised the manuscript for important intellectual content. BGN provided administrative, technical or material support. PL obtained funding and supervised the study.

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### Competing interests

YC reports grants from Sanofi and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Sanofi outside the submitted work. JV reports personal fees from ALK, AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline and Teva outside the submitted work. PL reports grants and personal fees from AstraZeneca and Sanofi and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Sanofi outside the submitted work. SA, JLM, IV and BGN have nothing to disclose.

### Data availability statement

Data are available on reasonable request. Additional data regarding technical details, statistical code and derivative data are available from the principal investigator at peter.lange@sund.ku.dk. Data access for further analyses is possible through direct collaborative agreement or through locally managed access arranged through the study’s principal investigator.

### Supplemental material

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