

Eosinophil levels predict lung function deterioration in apparently healthy individuals

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Background: While chronic respiratory diseases are among the leading causes of mortality and morbidity worldwide, little is known about the effect of blood eosinophil levels on lung function trajectories among healthy individuals.

Methods: We analyzed data of apparently healthy individuals (n=18,089) recruited for the Tel Aviv Medical Center Inflammation Survey. Blood eosinophil levels were compared between participants with normal and those with abnormal lung function. Multivariate regression was used to assess the OR of forced expiratory volume in 1 second (FEV₁) deterioration according to baseline eosinophils in subjects with normal lung function (n=4,141) during a follow-up period of 4 years.

Results: Participants with an abnormal, as opposed to a normal, pulmonary function test (PFT) (n=1,832, 10.1%) had significantly higher eosinophil levels, expressed as a percentage or count (2.99%±2.00% compared to 2.67%±1.88% and 0.2210e3/μL±0.163/μL compared to 0.1810e3/μL±0.183/μL, respectively; *P*<0.001 for both). Among participants with a normal PFT at baseline, those with an eosinophil percentage higher than 4% showed a higher risk for FEV₁ decline above 60 mL/year (OR=1.199, 95% CI=1.005–1.431, *P*=0.044).

Conclusion: Our study suggests that higher blood eosinophil levels can predict PFT deterioration even in apparently healthy subjects, implying that these individuals could benefit from frequent lung function evaluation.

Keywords: normal population, eosinophils, lung function, trajectory, inflammation

Introduction

Chronic respiratory diseases are among the leading causes of mortality and morbidity worldwide. Of all chronic respiratory diseases, airway diseases such as COPD and asthma are the most prevalent and have the highest social impact. In 2015, 3.2 million people died from COPD, while >300 million people currently suffer from asthma worldwide. Globally, these diseases are ranked among the top 20 conditions that cause disability.¹

Diagnosis of airway diseases relies on clinical, functional, and biological features, which usually direct therapeutic decision-making. Functional evaluation of airway diseases is done using spirometry, which measures airflow during forced expiration. This test is essential for the diagnosis of COPD and has a major impact on asthma management. Another airway disease biomarker is blood eosinophil levels, which is a surrogate marker for eosinophilic airway inflammation. Recently, with the development of specific anti-eosinophilic therapies (ie, anti-IL-5 and anti IL5Rα), eosinophilic airway inflammation has attracted considerable attention. These eosinophilic-directed therapies were shown to be effective for COPD and asthma patients, who demonstrated frequent exacerbations as well as high blood eosinophils.^{2,3}

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Since both asthma and COPD are heterogeneous demonstrating similar and overlapping characteristics, there has recently been a trend toward a precision medicine strategy for the management of patients with airway diseases, which is based on the identification of “treatable traits” in each patient.⁴ The highest lung function rate is reached in early adulthood, with early life events (such as maternal smoking, low birth weight, environmental exposure, and childhood respiratory infection) playing a critical role in the development of airway disease.^{5,6} A profound understanding of these early-stage airway disease parameters in apparently healthy individuals is vital when using the “treatable traits” strategy. Moreover, since the association between blood eosinophils and lung-function decline in patients with asthma or COPD has not been well confirmed, the use of blood eosinophils as a “treatable trait” raises the need for a more accurate understanding of the correlation between this biomarker and functional measurements.

Most studies on the association between these parameters were conducted on patients with airway disease (COPD or asthma) in order to predict exacerbations or lung function deterioration, while research on apparently healthy individuals has been limited. Therefore, in this study we sought to investigate the difference in lung function between people with high vs low eosinophil blood count in a cross-sectional study in a large cohort of 18,089 subjects, as well as the effect of blood eosinophil count at baseline on lung function trajectories among healthy people during 4 years of follow-up.

Methods

Population

We analyzed data collected between January 2004 and September 2016, from the Tel Aviv Medical Center Inflammation Survey, a registered databank of the Israeli Ministry of Justice, which encompasses a large cohort of subjects who attend the Tel Aviv Medical Center for routine annual checkups. These checkups included an interview with a physician, a physical examination, blood and urine tests, an exercise stress test, and a spirometry test.^{7–10}

Participants with any known lung disease, respiratory complaints, or any other inhaled therapy were excluded. Written informed consent was obtained from all participants and approved by the Tel Aviv Sourasky Medical Center Institutional Review Board (number TLV-02–049).

Study procedures

Blood samples for routine blood counts were drawn from each participant upon arrival at the center after a 12-hour overnight fast.

Pulmonary function measurements were performed using a computerized spirometer (KoKo Spirometer; Ferraris Respiratory, Louisville, CO, USA). All tests were performed during the morning hours. Three to six trials were performed on each subject, until two reproducible and acceptable, error-free trials were obtained. Calibration was performed at least once a day. According to American Thoracic Society guidelines, the common parameters measured in spirometry, forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) values are considered normal when measured $>80\%$ of the predicted value,¹¹ thus we used these values to differentiate normal and abnormal results. FEV_1/FVC ratio is suggestive for obstructive pattern when it is measured <0.7 in adults, hence was considered abnormal. A prospective 4-year follow-up was performed on a subpopulation of the cohort who had normal lung function at baseline and returned annually for checkups.

Statistical analyses

All continuous variables are displayed as means (SD) for normally distributed variables or median (IQR) for variables with abnormal distribution, while categorical variables are displayed as numbers (%) of patients within each group.

The levels of eosinophil blood count in patients with normal lung function ($FEV_1 >80\%$ and $FVC >80\%$ and $FEV_1/FVC >0.7$) and patients with abnormal lung function ($FEV_1 <80\%$ or $FVC <80\%$ or $FEV_1/FVC <0.7$) were compared by a Student's *t*-test for normally distributed variables and by Mann–Whitney *U*-test for nonnormally distributed variables. To assess associations among categorical variables, we used a chi-squared test.

To quantify the contribution of eosinophil levels to the change of the FEV_1 test, we used logistic regression models (Enter method), where pulmonary function tests (PFTs) were regarded as the dependent variables, and potential confounding parameters together with eosinophil levels were regarded as the independent variables. These confounders included parameters with known or suspected influences on PFTs. Continuous variables included age and first FEV_1 , while dichotomized variables were gender, smoking, and diabetes.

The IBM SPSS Statistics 22.0 statistical package was used to perform all statistical analyses (IBM Corporation, Armonk, NY, USA).

Results

Our study screened 19,914 individuals who completed a spirometry test as part of a complete health screening evaluation. From them, 1,825 were excluded due to pulmonary disease diagnosis (6.5%) or regular treatment with inhaled medication

Table 1 Population characteristics

| | Normal PFT ($FEV_1 > 80$ and $FVC > 80$ and $FEV_1/FVC > 0.7$) | | |
|-------------------------------|--|----------------|---------|
| | Normal | Abnormal | P-value |
| Participants, n (%) | 16,257 (89.9) | 1,832 (10.1) | |
| Age, years, mean (SD) | 44.19 (10.83) | 47.43 (11.56) | <0.001 |
| Gender % (male) | 63 | 71 | <0.001 |
| Smoking % | 15.6 | 21.5 | <0.001 |
| Ever smoked % | 39.4 | 48.1 | <0.001 |
| BMI, kg/m^2 , mean (SD) | 26.23 (4.23) | 27.06 (4.85) | <0.001 |
| Metabolic syndrome % | 11.2 | 19.6 | <0.001 |
| DM % | 3.3 | 5.7 | <0.001 |
| HTN % | 10.8 | 17.8 | <0.001 |
| SBP, mmHg, mean (SD) | 121.39 (15.23) | 125.43 (16.88) | <0.001 |
| DBP, mmHg, mean (SD) | 76.57 (8.8) | 78.43 (9.04) | <0.001 |
| Pulse at rest, bpm, mean (SD) | 70.85 (11.96) | 71.36 (12.23) | 0.088 |
| METS, kcal/kg/hour, mean (SD) | 11.91 (3.52) | 11.23 (3.22) | <0.001 |

Note: P-values ≤ 0.05 are shown in bold.

Abbreviations: BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; HTN, hypertension; METS, metabolic equivalents; PFT, pulmonary function test.

(any respiratory medication [2.5%], bronchodilators [1.2%], or inhaled steroids [1%]). Following these exclusion criteria, our study included 18,089 apparently healthy individuals. PFTs identified 1,832 subjects (10.1%) with abnormal PFT (either $FEV_1 < 80\%$ predicted, $FVC < 80\%$ predicted or $FEV_1/FVC < 0.7$). Participants with abnormal PFTs were older, more likely to be male and smokers, as well as having other cardiovascular comorbidities, such as hypertension, diabetes, metabolic syndrome, and a higher body mass index (BMI). Characteristics according to PFT results for the entire study cohort are presented in Table 1.

Interestingly, participants with abnormal PFT had significantly higher eosinophil levels, expressed as either percentage or count. Mean eosinophil percentage was $2.99\% \pm 2.00\%$ compared to $2.67\% \pm 1.88\%$; mean eosinophil count was $0.22 \times 10^3/\mu L \pm 0.163/\mu L$ compared to $0.18 \times 10^3/\mu L \pm 0.183/\mu L$, respectively; $P < 0.001$ for both (Figure 1).

Next, we decided to conduct a prospective study of participants with normal PFT in order to check whether eosinophil levels can predict PFT deterioration over time. This cohort included 4,141 participants with normal PFT at baseline. The mean follow-up period was 4.0 (3–5) years. At the end of follow-up, despite normal PFT at baseline, a decline to abnormal PFT was identified in 95 individuals during this relatively short period of time. While these individuals were older and presented with elevated BMI and hypertension, they did not demonstrate a higher eosinophil count compared to those with stable lung function values (Table 2). Nevertheless, we found that FEV_1 deterioration above 60 mL/year (twice the mean found in one-third of the

participants) was more frequent in participants with basal eosinophil levels $> 4\%$, $P = 0.026$ (Figure 2). This observation was also found following logistic regression analysis, when looking for other risk factors for accelerated lung function deterioration. Participants with an eosinophil level

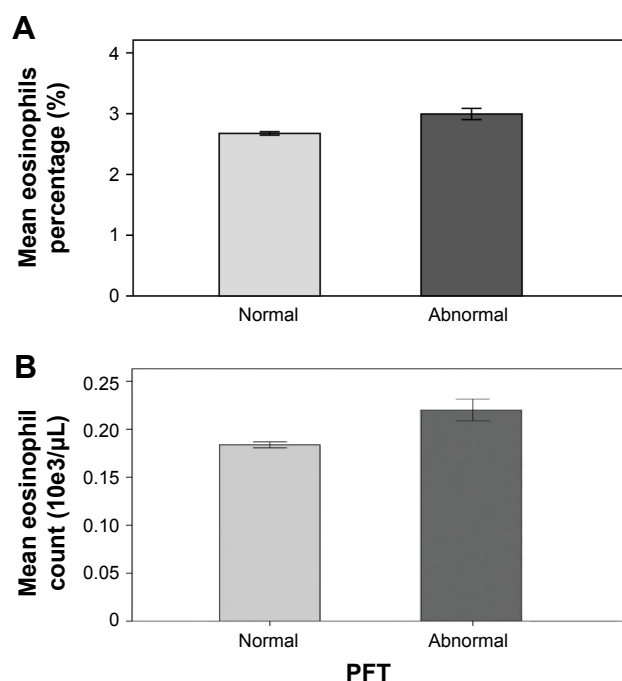


Figure 1 Elevated eosinophil percentage (A) and count (B) in participants with abnormal PFT.

Notes: Participants with abnormal PFTs present a higher eosinophil percentage (2.99 ± 2.0 vs 2.67 ± 1.88 , $P < 0.001$) and count (0.22 ± 0.16 vs 0.18 ± 0.18 , $P < 0.001$) than participants with normal tests.

Abbreviation: PFT, pulmonary function test.

Table 2 Characterization of participants with normal pulmonary function test (PFT) and 4 years of follow-up

| | Four-year follow-up | | |
|------------------------------------|---------------------|---------------------------|--------------|
| | Normal | Deterioration to abnormal | P-value |
| Participants, n (%) | 4,046 | 95 (2.3%) | |
| Age, years, mean (SD) | 43.77 (10.22) | 44.96 (11.85) | 0.021 |
| Gender % (male) | 70.0 | 67.4 | 0.568 |
| Smoking % | 13.6 | 11.6 | 0.563 |
| Ever smoked % | 37.1 | 38.9 | 0.706 |
| BMI, kg/m ² , mean (SD) | 26.08 (3.86) | 26.95 (4.85) | 0.029 |
| Metabolic syndrome % | 9.2 | 14.0 | 0.29 |
| DM % | 2.3 | 4.1 | 0.226 |
| HTN % | 9.3 | 16.8 | 0.013 |
| SBP, mean (SD) | 120.93 (14.19) | 122.417 (13.71) | 0.321 |
| DBP, mean (SD) | 76.55 (8.36) | 77.31 (8.52) | 0.382 |
| Pulse at rest, mean (SD) | 70.31 (11.77) | 70.97 (12.76) | 0.597 |
| METS, mean (SD) | 12.32 (3.13) | 11.88 (3.14) | 0.234 |
| Eosinophil percentage, mean (SD) | 2.66 (1.84) | 3.01 (2.22) | 0.065 |
| Eosinophil percentage >2% (%) | 58.4 | 62.8 | 0.393 |
| Eosinophil percentage >4% (%) | 18.0 | 22.3 | 0.283 |
| Eosinophil count, mean (SD) | 0.18 (0.13) | 0.18 (0.11) | 0.904 |

Note: P-values ≤ 0.05 are shown in bold.

Abbreviations: BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HTN, hypertension; METS, metabolic equivalents.

higher than 4% were more likely to have FEV₁ deterioration above 60 mL/year (OR=1.199, 95% CI=1.005–1.431, $P=0.044$), in addition to male gender (OR=1.835, $P<0.001$), higher FEV₁ levels at the baseline (OR=1.061, $P<0.001$),

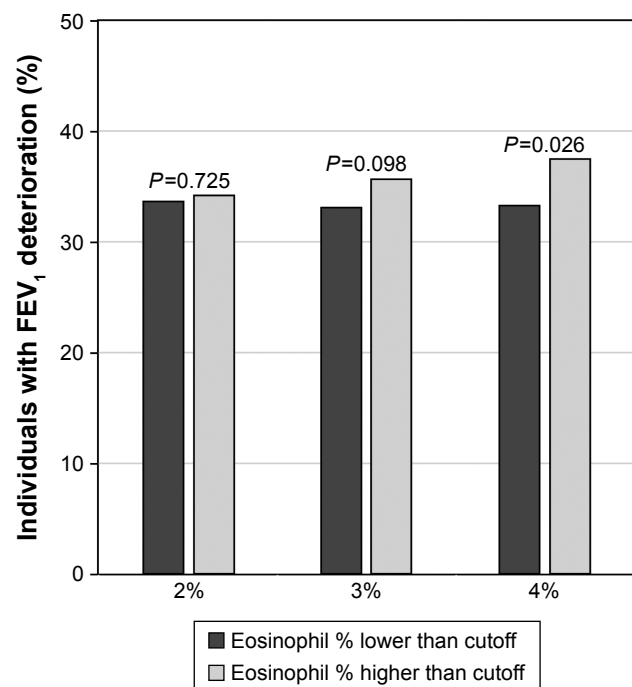


Figure 2 Percentage of people with FEV₁ decline above 60 mL/year compared by eosinophils percentage.

Note: Participants with higher eosinophil levels are more likely to have FEV₁ deterioration.

Abbreviation: FEV₁, forced expiratory volume in 1 second.

and diabetes mellitus (OR=1.649, $P=0.026$) as presented in Table 3. The eosinophil cutoff level of 3% presented only a trend toward significance on FEV₁ deterioration above 60 mL/year (Table 3).

Moreover, the average decline in FEV₁ of the normal PFT cohort was 33.95 ± 76.5 mL/year. The FEV₁ decline in men was significantly higher than in women. The mean FEV₁ decline in men was 37.34 ± 81.96 compared to 26.07 ± 61.24 mL/year in women; $P<0.001$. The distribution of mean FEV₁ change per year is shown in Figure 3. When analyzing FEV₁/FVC and FVC parameters, no association was found between eosinophil numbers and FEV₁/FVC or FVC decline ($P=0.663$ and $P=0.322$, respectively).

Discussion

In this study, we found an association between lung function and eosinophil blood count in a large cohort of apparently healthy individuals. Furthermore, we found that higher blood eosinophil counts were associated with lower FVC, FEV₁, or FEV₁/FVC ratio at baseline, with an increased deterioration rate of FEV₁ after 4 years of follow-up.

Previous studies have already shown that blood eosinophils are associated with lower FEV₁ in asthmatic patients¹² and an accelerated FEV₁ decline in COPD patients.¹³ However, data on healthy individuals remain scarce. One epidemiologic study of adolescents and young adults, published two decades ago, found a weak but statistically significant inverse relationship between eosinophil count

Table 3 Predictors for FEV₁ deterioration above 60 mL/year: a multiple logistic regression analysis with FEV₁ deterioration above 60 mL/year as the dependent variable

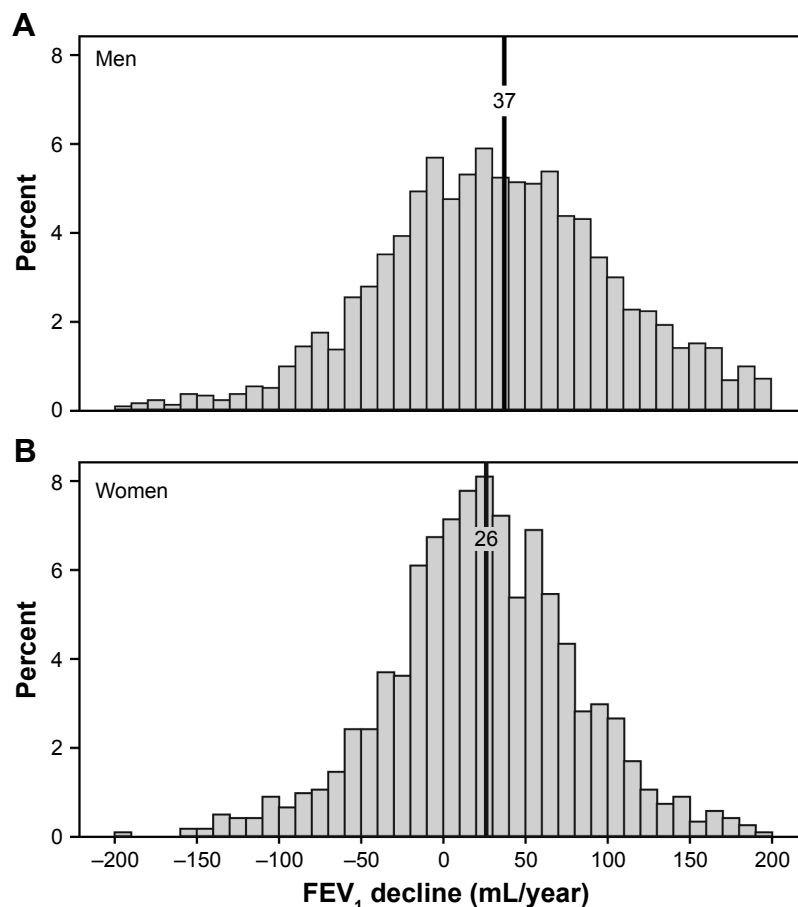
| Parameters | Eosinophils >4% | | | | Eosinophils >3% | | | |
|------------------------|-----------------|--------|-------|------------------|-----------------|--------|-------|------------------|
| | Exp (β) | 95% CI | | P-value | Exp (β) | 95% CI | | P-value |
| | | Lower | Upper | | | Lower | Upper | |
| Eosinophil cutoff | 1.199 | 1.005 | 1.431 | 0.044 | 1.116 | 0.964 | 1.291 | 0.14 |
| First FEV ₁ | 1.061 | 1.054 | 1.068 | <0.001 | 1.061 | 1.054 | 1.068 | <0.001 |
| Ever smoked | 1.09 | 0.943 | 1.259 | 0.243 | 1.088 | 0.942 | 1.257 | 0.250 |
| Gender (male) | 1.837 | 1.567 | 2.153 | <0.001 | 1.838 | 1.568 | 2.154 | <0.001 |
| Age | 0.991 | 0.984 | 0.998 | 0.010 | 0.991 | 0.984 | 0.998 | 0.010 |
| DM | 1.649 | 1.062 | 2.562 | 0.026 | 1.652 | 1.063 | 1.063 | 0.026 |

Notes: The effects of each variable are reported (presented as Exp [β], 95% CI, and P-value). P-values ≤0.05 are shown in bold.

Abbreviations: DM, diabetes mellitus; Exp (β), exponentiation of the B coefficient; FEV₁, forced expiratory volume in 1 second.

and FEV₁ in nonatopic and nonasthmatic individuals, who had no evidence of bronchial hyperresponsiveness.¹⁴ However, this was a small-scale observational study, and the correlation between eosinophil count and lung function was much more significant in asthmatic, atopic, and bronchial hyperresponsive patients. Our findings, in a larger cohort of apparently healthy individuals, present a direct and significant correlation between eosinophils and lung function.

Moreover, our study is the first to show prospectively that an eosinophil percentage higher than 4% is a predictor for accelerated FEV₁ deterioration. Concordant to our results, a recently published study on young adults with or without asthma showed that blood eosinophils associated with airflow obstruction and enhanced decline in lung function;¹⁵ however, this study was based on a cohort of children who were followed-up until young adulthood (~17 years), and authors

**Figure 3** Distribution of FEV₁ decline by gender.

Notes: The mean FEV₁ decline in men (A) was 37.34±81.96 mL/year, while in women (B), the FEV₁ decline was only 26.07±61.24 mL/year ($P<0.001$).

Abbreviation: FEV₁, forced expiratory volume in 1 second.

did not exclude other comorbidities. Our study was focused on apparently healthy older individuals (mean age 45). Our study was focused on apparently healthy older individuals (mean age 45), with mean follow-up of 4 years. Although the follow-up period was much shorter, a significant correlation between blood eosinophils and lung functions was found, reinforcing that eosinophilia is a major risk factor for lung function decline even in older subjects. In the era of “treatable trait strategy” in obstructive lung diseases,¹⁶ understanding the role of blood eosinophils as a biomarker in the development of obstructive lung diseases is of significant importance.

Another interesting finding of this study was the association between cardiovascular risk factors and lung function. We found that older age, diabetes, hypertension, high BMI, metabolic syndrome, and, not surprisingly, a history of smoking, were more prevalent in the abnormal PFT group at baseline. In addition, older individuals and those with diabetes or hypertension had an increased FEV₁ deterioration rate in the prospective follow-up of 4 years. Our regression analysis suggests that male gender, higher baseline FEV₁ results, and diabetes are predictors of higher eosinophil counts, suggesting that these risk factors may influence lung function via eosinophilic inflammation.

Associations between cardiovascular risk factors and lung function have been well established. Similar to our findings, Gunnell et al showed that higher FEV₁ is associated with lower blood pressure, cholesterol, glucose, and BMI,¹⁷ while Yeh et al showed that reduced pulmonary function was observed in American Indians with metabolic syndrome or diabetes mellitus.¹⁸ Moreover, an Italian population-based cohort study of more than 12,000 subjects showed that increased pulmonary function was associated with a higher probability of a first coronary or cerebrovascular event.¹⁹ These studies were all cross-sectional and did not show the effect of cardiovascular risk factors on lung function deterioration over time.

Eosinophil levels play a central role in some features of airway disease, and their presence in sputum or blood can identify responders to corticosteroids and other anti-eosinophilic therapies.²⁰ Therefore, our results may have a beneficial effect on lung function surveillance and monitoring, as well as preventive therapeutic options in subjects who demonstrate high blood eosinophils or the combination of blood eosinophilia and cardiovascular risk factors.

Treating patients with inhaled corticosteroids was found to be effective in multiple asthma and COPD studies.^{21,22} Regarding subjects with eosinophilic inflammation, our study raises several questions: can eosinophil-targeted treatments

be used to prevent future obstructive lung disease in these individuals? Can blood eosinophil counts predict future airway obstruction in healthy individuals? Should PFT be monitored in healthy individuals with high eosinophil counts? Indeed, future prospective randomized control studies are needed in order to answer these questions.

Limitations

Our study has several limitations. The first two limitations include selection bias and regression to the mean for the estimates of decline in FEV₁. The longitudinal study included only participants who came for annual follow-up visits. The relative low number is mainly due to participants who did not attend our routine health examinations for the follow-up visits. This introduced a certain selection bias, although every effort was made to include all of the participants admitted to our medical center within the recruitment period. Although our aim was to investigate lung function trends in apparently healthy individuals, using the Tel Aviv Medical Center Inflammation Survey cohort exposed the study to the selection of healthier individuals. Furthermore, the use of baseline FEV₁ measurements introduced potential bias with respect to regression to the mean.²³ As in our analysis, subjects with a higher FEV₁ tended to have a more rapid decline in FEV₁. Third, the differences found in both the percentage and absolute counts are very small in absolute numbers. Fourth, our mean follow-up was 4 years, which is a relatively short time period for the investigation of lung function trajectories. Nevertheless, we were able to show a significant link between the biomarker studied and lung function trends in this cohort of apparently healthy individuals.

Conclusion

To the best of our knowledge, this is the first study to describe the close association between blood eosinophils and lung function trajectories in subjects with no respiratory disease, suggesting that blood eosinophils are a novel risk factor for the development of airflow obstruction even in healthy individuals.

Disclosure

The authors report no conflicts of interest in this work.

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