

LETTER

Influence of sex, cigarette smoking and airway inflammation on treatable traits in CBIOPRED severe asthma

To the Editor

Asthma presents a major public health challenge in China, where it affects 45.7 million adults with an estimated prevalence of 4.2%; 26.2% of adults with asthma have airflow limitation.¹ Severe asthma is recognised in China with the recent publication of an expert consensus guidelines for the diagnosis and management of severe asthma.² Severe asthma has been defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming “uncontrolled” or that remains “uncontrolled” despite this therapy.³ More recently, the identification of a higher number of treatable traits in severe asthma compared to mild-moderate asthma has facilitated a strategy for the management of airways disease.⁴ However, the influence of various factors on the major treatable traits such as airflow obstruction and exacerbations is unclear. Therefore, we examined the role of sex and cigarette smoking on these traits and also their link to airway inflammation measured by inflammatory cell counts in induced sputum samples.

In the Chinese Biomarkers for the Prediction of Respiratory Disease Outcomes (C-BIOPRED) cohort of severe asthma, we compared the parameters of male to female non-smoking severe asthma (NSA) and male current smoking severe asthma (CSA) and ex-smoking (ESA) severe asthma at entry and at 1 year (Figure 1). Participants attended severe asthma university clinics where the diagnosis was ascertained and asthma treatment with adherence optimised. Non-smoking severe asthma were non-smokers for the past 12 months, with <5 pack-year smoking. CSA and ESA, exclusively male, had a smoking history of >5 pack-years. Severe asthma was defined according to European Respiratory Society and American Thoracic Society guidelines.³

There were no differences in clinical parameters and asthma control between NSA male and female but the pre-bronchodilator FEV₁ (% predicted) were lower in male compared to female participants while the bronchodilator response was similar in both groups. Fractional exhaled nitric oxide (FeNO) levels were higher in male (39.0 ppb) compared to 28.0 ppb in female ($p = 0.001$), but without any differences in sputum or blood eosinophil counts (Figure 1A,B; Supplementary Table S1).

Male NSA group was younger than CSA and ESA groups with the diagnosis of asthma made at a younger age (Supplementary Table S1). There was no difference in the number of exacerbations but greater healthcare resource utilization in ESA and NSA (18.5% and 21.8%, respectively) compared to 4.9% in CSA. Atopy incidence was highest in CSA (70%) compared to ESA and NSA (46.4% and 45.9%, respectively). There was no difference in the Asthma Control Questionnaire (ACQ) and total questionnaire of asthma quality of life in adults (AQLQ) scores apart from activity limitation score being lowest in ESA (Supplementary Table S2). There were no differences in baseline spirometric measurements and post-bronchodilator FEV₁ was similar in all groups. There was a lower FeNO in CSA (18.50 ppb) compared to ESA and NSA (37.00 and 39.00 ppb, respectively) (Supplementary Table S1), with no difference in blood eosinophil counts, but neutrophil counts were highest in ESA. CSA showed a trend towards higher sputum neutrophil (%) and lower eosinophil (%) counts compared to ESA and CSA ($p = 0.08$ and 0.07 , respectively).

We examined the potential influence of inflammatory markers on airflow obstruction and exacerbations by performing Spearman's correlation coefficients analysis (Figure 2). FEV₁ (% predicted) and FEV₁/Forced Vital Capacity ratio were negatively correlated with sputum neutrophil (%) in male and female NSA, but not in CSA and ESA (Figure 2). Exacerbations were negatively correlated with sputum neutrophils (%) in female NSA and positively correlated with sputum eosinophils in male and female NSA. Fractional exhaled nitric oxide was positively correlated with sputum eosinophils in male and female NSA, and with the improvement in post-bronchodilator FEV₁ (%) in CSA ($r = 0.926$; $p < 0.001$).

At 1 year, in the NSA female, there was an improvement in ACQ5 and in total AQLQ reflected in the symptom, activity limitation and emotional domains, accompanied by an improvement in pre-bronchodilator FEV₁ (% predicted) from 67.8% to 72.23% ($p = 0.066$) (Figure 1C). In both male and female groups in NSA, there was a significant reduction in the bronchodilator response from 18.7% to 12.0% ($p = 0.002$) and from 21.50% to 12.15% ($p < 0.001$), respectively. There was no change in pre- and post-bronchodilator FEV₁ (% predicted), ACQ and AQLQ and FeNO and blood eosinophil counts in the CSA and ESA male participants (Figure 1D).

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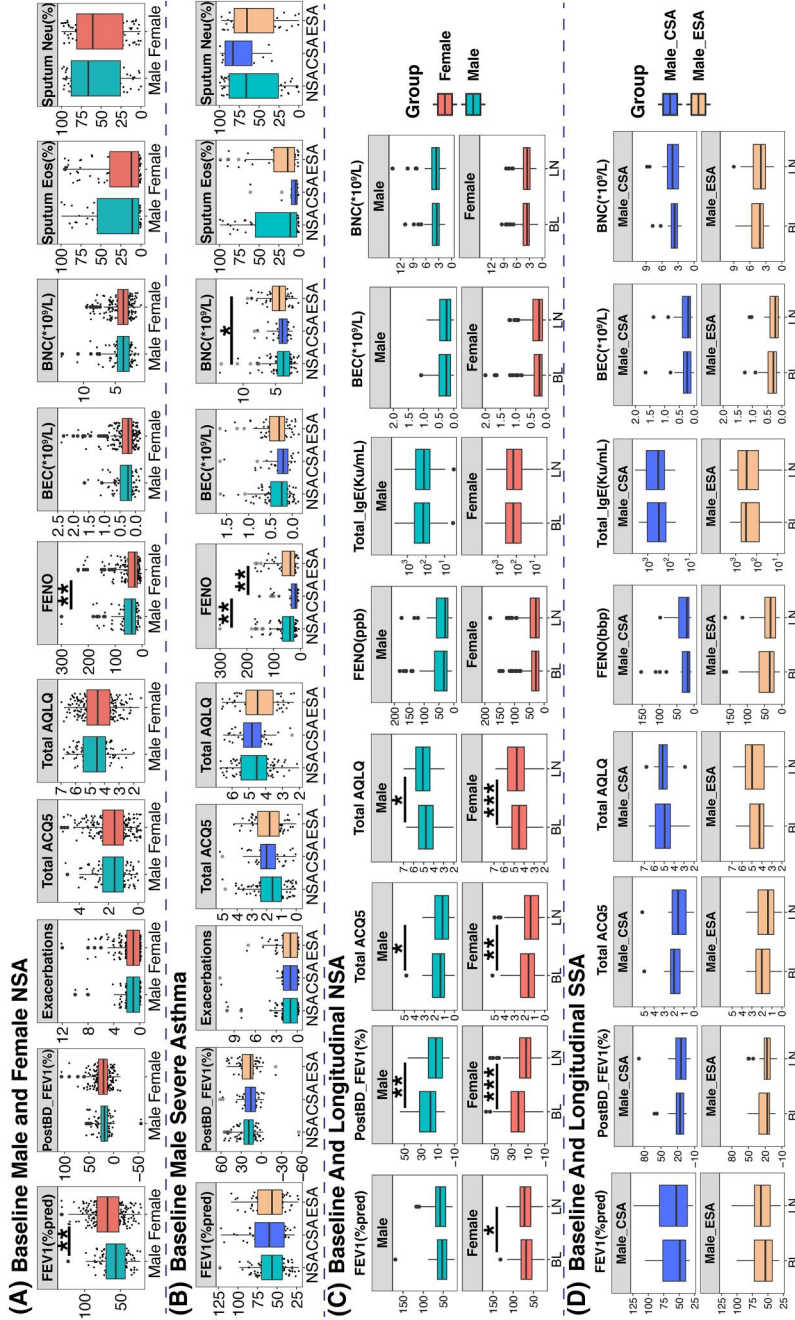


FIGURE 1 Panel A: Median (25%-75% Interquartile range [IQR]) values comparing male and female non-smoking severe asthma (NSA), Panel B: Median (25%-75% IQR) values of male non-smoking severe asthma (NSA), male current smoking severe asthma (CSA) and ex-smoking (ESA) severe asthma at baseline. Panel C: Median (25%-75% IQR) values of male and female non-smoking severe asthma (NSA) at baseline (BL) and at longitudinal (LN) follow-up at 1 year. Panel D: Median (25%-75% IQR) values of male smoking severe asthma (SSA) including male CSA, ESA severe asthma at baseline (BL) and at LN follow-up at 1 year. ACQ5, Asthma Control questionnaire five questions score; AQLQ, Asthma quality of life questionnaire score; BEC, Blood eosinophil count; BNC, Blood neutrophil count; Eos, eosinophil; FENO, Fractional exhaled nitric oxide; FEV₁, Forced expiratory volume in one second; IgE, Immunoglobulin E; Neu, neutrophil; ppb, parts per billion; PostBD-FEV₁ (%), percent improvement in FEV₁ after salbutamol bronchodilator

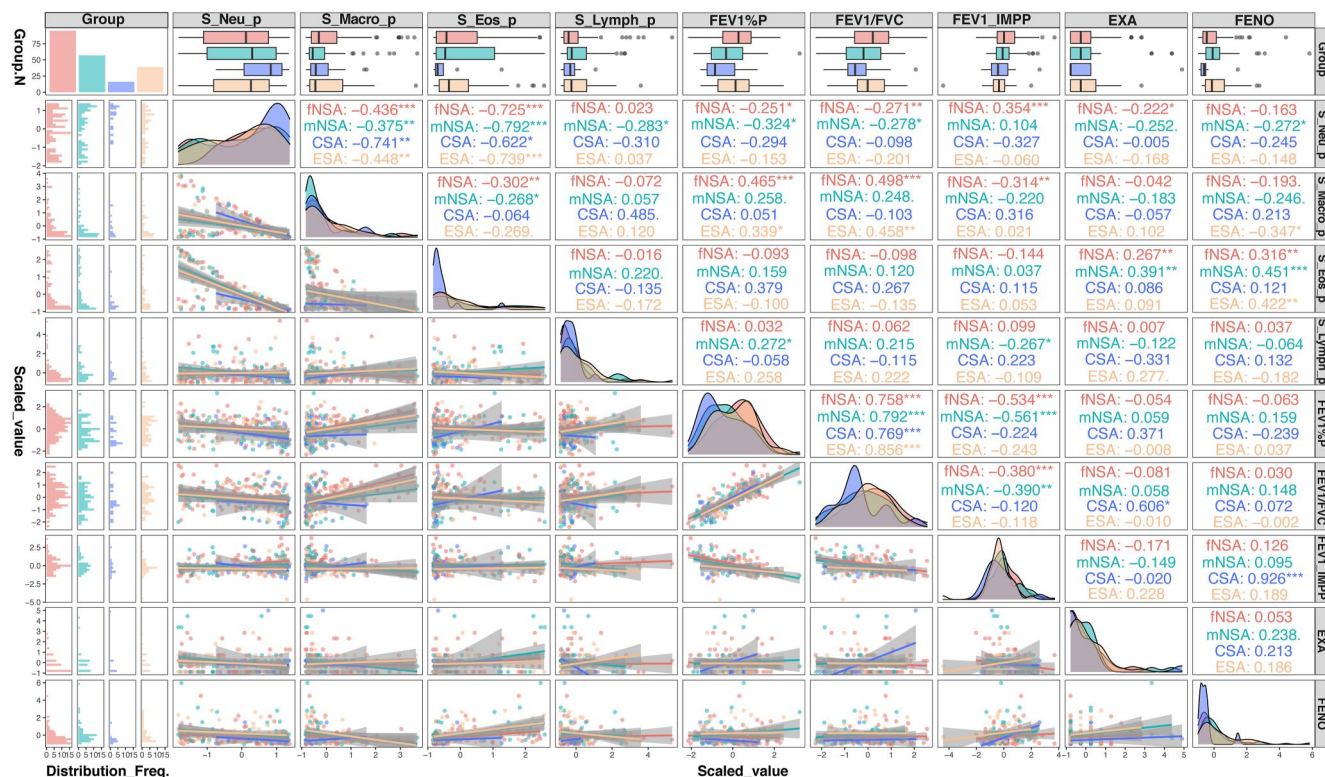


FIGURE 2 Correlation analyses for the three cohorts of severe asthma: non-smoking severe asthma (NSA, $N = 152$), current-smoking severe asthma (CSA, $N = 16$) and Ex-smoking severe asthma (ESA, $N = 39$). The correlation analysis was performed for the whole group ("Corr"), followed by CSA (pink), ESA (green) and NSA (blue), using Spearman correlation analysis. The graphic relationship of these parameters are shown together with the actual correlations and their significance ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$). The top row shows the median (25%–75% Interquartile range). EXA, Exacerbations in previous year; FENO, Fractional exhaled nitric oxide; FEV1%Pred, Pre-bronchodilator FEV1% Predicted; FEV1/Forced Vital Capacity (FVC), Pre-bronchodilator FEV1/FVC; FEV1IMPP, Post-bronchodilator improvement in FEV1% Predicted; fNSA, female non-smoking severe asthma; mNSA, male non-smoking severe asthma; S_Eos_p, sputum eosinophil percentage; S_Lymph_p, sputum lymphocyte percentage; S_Macro_p, sputum macrophage percentage; S_Neu_p, sputum neutrophil percentage

Non-smoking severe asthma women had a lesser degree of airflow obstruction with lower levels of FeNO, despite similar blood eosinophil counts compared to male NSA. This is in contrast to the report of a higher disease burden of asthma in women compared to men.⁵ It may be because of the post-menopause (as female NSA were aged 54 years) who were not obese and who have a lower age-adjusted risk of asthma than premenopausal women.^{6,7} There is also the consideration that asthma sometimes improves after the menopause.⁸ At 1 year, FEV₁ in women improved, together with asthma control and quality of life measures, an indication of the continued benefits of the post-menopausal period on asthma. Unfortunately, we did not collect any information on the menopause or the use of hormone replacement therapy in the women.

Currently-smoking severe asthma patients subjects had lower eosinophilic inflammation, likely to be a suppressive effect of current smoking, with higher sputum neutrophilia.⁹ However, the degree of neutrophilia was related to airflow obstruction in NSA as previously reported.¹⁰ Interestingly, the level of eosinophilic inflammation was correlated with the number of exacerbations in the previous year, supporting its link with Type-2 inflammation.¹¹ In the C-BIOPRED cohort, we have shown that sex differences and the effect of smoking are important influences on the treatable

traits of severe asthma, with a likelihood of improvement in females at 1 year follow-up and lower type-2 inflammatory markers in currently-smoking asthmatics. Importantly, our data indicate that in severe asthma, while neutrophilic inflammation may be linked to airflow obstruction, eosinophilia is associated with exacerbation rates.

AUTHOR CONTRIBUTIONS

Cong Dong: Conceptualization (Equal), Formal analysis (Equal), Visualization (Equal), Writing – original draft (Equal). **Xiaoqing Yang:** Data curation (Equal), Validation (Equal). **Wei Luo:** Methodology (Equal), Resources (Equal). **Ethan Fan:** Formal analysis (Equal), Investigation (Equal), Resources (Equal), Software (Equal), Visualization (Equal). **Nkouibert Pryseley Assam:** Data curation (Equal), Funding acquisition (Equal), Investigation (Equal), Resources (Equal). **Jian Kang:** Data curation (Equal), Investigation (Equal), Resources (Equal). **Yunhui Zhang:** Data curation (Equal), Investigation (Equal), Resources (Equal). **Mao Huang:** Data curation (Equal), Investigation (Equal), Resources (Equal). **Jinfu Xu:** Data curation (Equal), Investigation (Equal), Resources (Equal). **Kewu Huang:** Data curation (Equal), Investigation (Equal), Resources (Equal). **Qiang Li:** Data curation (Equal), Investigation (Equal), Resources (Equal). **Xiangyan Zhang:** Data curation (Equal),

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KEYWORDS

baseline and longitudinal, gender, severe asthma, smoking

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONSENT

All participants gave written and signed informed consent.

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