Smoking Status Modifies the Relationship between Th2 Biomarkers and Small Airway Obstruction in Asthma

Shuyuan Chu,1,2,3 Libing Ma,1 Jianghong Wei,1 Jiying Wang,1 Qing Xu,1 Meixi Chen,1 Ming Jiang,1 Miao Luo,1 Jingjie Wu,1 Lin Mai,1 Guofang Tang,1 and Biwen Mo1,2

1Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Guilin Medical University, Guilin, Guangxi, China
2Laboratory of Respiratory Disease, Affiliated Hospital of Guilin Medical University, Guilin, Guangxi, China
3Duke Global Health Institute, Duke University, Durham, NC, USA

Correspondence should be addressed to Shuyuan Chu; emilyyuanchu@163.com and Biwen Mo; 1042587352@qq.com

Received 28 July 2021; Revised 20 October 2021; Accepted 29 October 2021; Published 28 November 2021

Academic Editor: Anita Pye

Copyright © 2021 Shuyuan Chu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Cigarette smoking and Th2-inflammation are both crucial in the pathogenesis of asthma. However, it is unknown whether smoking can affect the association between Th2-inflammation and small airway obstruction in adults with asthma.

Methods. Adults diagnosed with asthma by a pulmonologist according to Global Initiative for Asthma guidelines were recruited from September 2016 to April 2018 to participate in this study. Participants were divided into two groups, the small airway obstruction group (those with FEF25–75% predicted value \( \leq 65\% \)) and the normal small airway function group (those with FEF25–75% predicted value \( > 65\% \)). Final data analysis included 385 and 93 people in the Obstructive Group and the Normal Group, respectively. Total serum IgE level and blood eosinophil count were used as biomarkers of the Th2 phenotype.

Results. The Obstructive Group had a larger fraction of smokers, higher blood eosinophil count, and lower lung function than the Normal Group. Current-smoking status was associated with an increased risk of small airway obstruction (adjusted odds ratio = 4.677, 95% confidence interval [1.593–13.730]); and log-IgE level was associated with a decreased risk of small airway obstruction (0.403 [0.216–0.754]). Smoking status stratified analysis showed an association between log-IgE level and a decreased risk of small airway obstruction only in never-smoker asthmatics (0.487 [0.249–0.954]).

Conclusions. Current-smoking status and total serum IgE are, respectively, associated with small airway obstruction. Smoking status modifies the relationship between Th2 biomarkers and small airway function. These findings contribute to the understanding of risk factors associated with asthma endotyping.

1. Introduction

Asthma is a highly complex disease with unclear endotypes. It is known that Th2 response promotes development of asthma [1]. Eosinophil counts and IgE level in blood are widely accepted as reliable Th2 biomarkers in asthma diagnosis and management [2, 3]. Forced expiratory flow (FEF) at 25–75% predicted value (25–75%pred) has been used as an ancillary biomarker of small airway function in asthma management [2, 4]. FEF25–75%pred is related to asthmatic symptoms, bronchial hyper-reactivity, and blood eosinophilia [5]. Prebronchodilator FEF25–75%pred is also a sensitive indicator for the early detection, severity, and progression of asthma [6]. Interestingly, Th2-type cytokine gene polymorphisms are related with FEF25–75 value in asthma patients [7], suggesting that Th2 response may promote small airway obstruction. In this study, hence, we aim to investigate the relationship between Th2 biomarkers, namely, blood eosinophil counts and serum IgE level, and small airway obstruction based on FEF25–75%pred measurements.

Smoking is a well-established risk factor of asthma. The effect of smoking status on the burden of asthma has been increasingly recognized [8]. Although current smoking has been associated with increased mortality rate in asthma patients [9], we could not find studies that have investigated the role of smoking status (current smoking, ex-smoking, and never smoking) in the association between Th2-type
biomarkers and small airway function in asthma patients. In this study, we also aim to examine whether smoking status modifies the relationship between Th2 inflammatory response and small airway function (FEF25–75%pred). We expect the findings of this study will help understand asthma endotypes involved in the pathways linking smoking, Th2-type inflammation, and small airway obstruction.

2. Methods

2.1. Participants Enrollment. We recruited participants in the Affiliated Hospital of Guilin Medical University, Guilin, China, from September 2016 to April 2018. All participants were adults (≥18 years old) who had been diagnosed with asthma according to the definition of Global Initiative for Asthma (GINA) guidelines [10]. Patients were excluded if they had chronic obstructive pulmonary disease (COPD), asthma according to the definition of Global Initiative for Asthma (GINA) guidelines [10]. Patients were excluded if they had a history of intubation within the prior 3 years, or had chronic obstructive pulmonary disease (COPD), or had had obstructive sleep apnea. The subjects were excluded as COPD patients when FEV1/FVC < 70% and had a reversibility of less than 15% after inhalation of 200 mg of salbutamol. Our study was approved by the Institutional Review Board (Ethics Committee) at the Affiliated Hospital of Guilin Medical University. Written informed consent was obtained from each participant.

Participants were divided into two groups based on their baseline FEF25–75%pred values. Those with a FEF25–75%pred < 65%pred small airway obstruction (obstructive group) and group with normal small airway function (normal group) [11, 12].

In stratified analyses, subjects were classified into current smokers, never smokers, and ex-smokers. If the subjects had been in smoking cessation at least three months before they were recruited into our study, they were classified as ex-smokers in our study [13].

2.2. Assessment of Clinical Characteristics and Risk Factors. All subjects underwent standardized spirometry test (CareFusion™ MasterScreen Pneumo, Germany) according to the European Respiratory Society/American Thoracic Society standards [14]. FEF50, FEF50%pred, FEF75, FEF75%pred, FEF25–75%, and FEF25–75%pred reflect small airway function. Forced expiratory volume in 1 second (FEV1), FEV1%pred, forced vital capacity (FVC), FVC%pred, and FEV1/FVC suggests airway obstruction. Peak expiratory flow (PEF) indicates upper airway resistance. The blood eosinophil count was assessed by Sysmex XN-2800™ automated hematology analyzers (Sysmex America, Inc., USA). The total serum IgE was tested using Cobas e 801 analyzer with Elecsys IgE II (Roche Diagnostics, Germany) according to manufacturer’s protocol. The cut-off value for high blood eosinophils was >400 μL and for high total IgE was >240 ng/mL. Health status was evaluated using the Asthma Quality of Life Questionnaire (AQLQ) [15] and the Short-Form 36 Questionnaire (SF-36) [16]. Asthma Control Test (ACT) [17] was used to assess symptom scores after the first-month initial treatment according to the GINA guideline.

2.3. Statistical Analysis. Group data were expressed as the mean ± standard deviation (SD) or median (range). Differences were evaluated using independent-samples t test or Mann–Whitney-U test for continuous variables, or chi square test for categorical variables. The association between blood eosinophil count, total serum IgE level, and small airway obstruction was assessed using unconditional logistic regression models with LOGISTIC procedure of SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The results were presented as odds ratios (OR) and 95% confidence intervals (CI). P values < 0.05 were considered statistically significant.

3. Results

A total of 478 subjects were selected for final analyses, when we excluded subjects if they had no records of FEF25–75% pred, blood eosinophil count, total serum IgE level, or smoking status (Supplementary Figure 1).

Table 1 illustrates baseline characteristics of subjects in the Obstructive Group and in the Normal Group. When compared with the Normal Group, the Obstructive Group subjects were older, had lower family income, were a higher fraction of ex and current smokers, and had higher blood eosinophil count, worse health status, and worse symptom score after the first-month initial treatment of asthma. In contrast, the Normal Group was showed a higher prevalence of inhaled corticosteroid (ICS) or long-acting beta-agonist (LABA) (ICS = 86, 92.5%; LABA = 86, 92.5%) than the Obstructive Group (ICS = 316, 82.1%; LABA = 315, 81.8%). In each group, there were three patients who took oral glucocorticoid methylprednisolone plus ICS. Moreover, the Obstructive Group had lower baseline lung function including small airway function than the Normal Group. As illustrated in Table 2, in the Obstructive Group, FEV1, FEV1%pred, FVC, FVC%pred, PEF, PEF%pred, FEF50, FEF50%pred, FEF75, FE75%pred, FEF25–75%, and FEF25–75%pred were all lower than the Normal Group.

We investigated the association between Th2-type biomarkers, smoking status, and small airway obstruction. Table 3 shows that the status of current smoking was associated with an increased risk of small airway obstruction (adjusted OR = 4.677, 95% CI 1.593–13.730). Interestingly, log10 transformed IgE level in serum was associated with a decreased risk of small airway obstruction (adjusted OR = 0.403, 95% CI 0.216–0.754).

We further explored the association between Th2-type biomarkers and small airway function in stratified analysis by smoking status. In never smokers, we found an association between log10 transformed IgE level in serum and a decreased risk of small airway obstruction (OR = 0.487, 95% CI 0.249–0.954) (Table 4). This association was not found in smokers (ex or current smokers).

4. Discussion

In our study, the small airway obstructive group had a greater fraction of smokers, higher eosinophil count in blood, and lower lung function than the normal group. We
found that current-smoking status was associated with an increased risk of small airway obstruction. Smoking history is related with abnormal peripheral airway function of adult patients with asthma [18]. Current smoking is associated with lower lung function of asthmatic patients [19, 20]. Furthermore, among adults with newly onset asthma, FEF25–75% is significantly reduced in current regular smokers and in recent (<1 year) ex-smokers when compared with never smokers [21]. This is due to pathological injury in the small airways by cigarette smoking. Cigarette smoking could promote small airway obstruction by enhancing mucin overproduction, lung inflammation, small airway epithelial-mesenchymal transition, and remodeling [22–24]. Our study is consistent with those previous findings and further demonstrates the association between current smoking and FEF25–75%pred, indicating an association between current smoking and an increased risk of small airway obstruction.

Table 1: Baseline characteristics of subjects.

| Variable                          | Total subjects (n = 478) | Obstructive group (n = 385) | Normal group (n = 93) | P value |
|-----------------------------------|-------------------------|-----------------------------|-----------------------|---------|
| Gender (male)                     | 200 (41.8%)             | 165 (42.9%)                 | 35 (37.6%)            | 0.360   |
| Age (median[rangel])              | 45[18, 78]              | 46[18, 78]                  | 41[18, 66]            | 0.003   |
| BMI (kg/m2)                       | 23.1 ± 3.3              | 23.1 ± 3.3                  | 23.1 ± 3.2            | 0.840   |
| Education (yrs)                   |                         |                             |                       |         |
| ≤9                                | 297 (62.1%)             | 239 (62.1%)                 | 58 (62.4%)            |         |
| 10–12                             | 70 (14.6%)              | 61 (15.8%)                  | 9 (9.7%)              | 0.299   |
| 13–16                             | 102 (21.3%)             | 79 (20.5%)                  | 23 (24.7%)            |         |
| ≥17                               | 9 (1.9%)                | 6 (1.6%)                    | 3 (3.2%)              |         |
| Family income (10 thousand RMB/yr)|                         |                             |                       |         |
| <5.0                              | 283 (59.2%)             | 236 (61.3%)                 | 47 (50.5%)            |         |
| 5.0–9.9                           | 101 (21.1%)             | 81 (21.0%)                  | 20 (21.5%)            | 0.019   |
| 10.0–19.9                         | 75 (15.7%)              | 51 (13.2%)                  | 24 (25.8%)            |         |
| ≥20.0                             | 12 (2.5%)               | 11 (2.9%)                   | 1 (1.1%)              |         |
| Smoking history (yes)             | 129 (27.0%)             | 114 (29.9%)                 | 15 (16.1%)            | 0.011   |
| Smoking history (pack-year)       | 6.3 ± 14.0              | 7.1 ± 14.8                  | 2.9 ± 9.3             | 0.001   |
| Smoking status                    |                         |                             |                       |         |
| Current smoking                   | 79 (16.5%)              | 70 (18.2%)                  | 9 (9.7%)              | 0.031   |
| Ex-smoking                        | 50 (10.5%)              | 44 (11.4%)                  | 6 (6.5%)              |         |
| Never smoking                     | 349 (73.0%)             | 271 (70.4%)                 | 78 (83.9%)            |         |
| Blood eosinophil count (uL)       | 325 ± 405               | 345 ± 435                   | 242 ± 230             | 0.028   |
| Blood eosinophils >400 uL         | 132 (27.6%)             | 115 (29.9%)                 | 17 (18.3%)            | 0.025   |
| Total IgE in blood (ng/ml)        | 775.805 ± 898.192       | 742.625 ± 870.746           | 913.163 ± 997.238    | 0.100   |
| Total IgE >240 ng/ml              | 354 (74.1%)             | 279 (72.5%)                 | 75 (80.6%)            | 0.106   |
| Blood eosinophils >400 uL plus total IgE >240 ng/ml | 106 (22.2%) | 91 (23.6%) | 15 (16.1%) | 0.118 |
| ICS (yes)                         | 402 (84.1%)             | 316 (82.1%)                 | 86 (92.5%)            | 0.014   |
| LABA (yes)                        | 401 (83.9%)             | 315 (81.8%)                 | 86 (92.5%)            | 0.012   |
| LTRA (yes)                        | 25 (5.2%)               | 18 (4.7%)                   | 7 (7.5%)              | 0.396   |
| AQLQ                              |                         |                             |                       |         |
| Symptoms score                    | 5.1 ± 1.1               | 5.0 ± 1.1                   | 5.6 ± 1.0             | <0.001  |
| Activity limitation score         | 5.2 ± 1.1               | 5.2 ± 1.1                   | 5.6 ± 1.0             | <0.001  |
| Emotional function score          | 5.3 ± 1.2               | 5.2 ± 1.2                   | 5.6 ± 1.1             | 0.002   |
| Environmental stimuli score       | 4.8 ± 1.3               | 4.7 ± 1.3                   | 5.0 ± 1.3             | 0.084   |
| Total                             | 5.2 ± 1.0               | 5.1 ± 1.0                   | 5.5 ± 0.9             | <0.001  |
| SF-36                             |                         |                             |                       |         |
| Bodily pain                       | 1.9 ± 1.1               | 2.0 ± 1.1                   | 1.8 ± 1.0             | 0.102   |
| Physical functioning              | 26.3 ± 3.6              | 26.0 ± 3.7                  | 27.4 ± 3.0            | <0.001  |
| Physical role                     | 6.8 ± 1.8               | 6.6 ± 1.8                   | 7.3 ± 1.4             | <0.001  |
| General health                    | 15.7 ± 1.4              | 15.7 ± 1.4                  | 15.4 ± 1.2            | 0.117   |
| Vitality                          | 15.4 ± 2.3              | 15.4 ± 2.2                  | 15.3 ± 2.4            | 0.716   |
| Social functioning                | 7.0 ± 1.2               | 7.0 ± 1.2                   | 7.0 ± 1.4             | 0.901   |
| Emotional role                    | 5.2 ± 1.3               | 5.1 ± 1.3                   | 5.6 ± 1.0             | 0.001   |
| Mental health                     | 20.0 ± 2.5              | 19.9 ± 2.5                  | 20.3 ± 2.5            | 0.260   |
| Reported health transition        | 3.3 ± 0.9               | 3.4 ± 0.9                   | 3.1 ± 1.0             | 0.008   |
| Total                             | 101.5 ± 7.3             | 101.1 ± 7.4                 | 103.1 ± 6.6           | 0.015   |
| ACT score*                        | 18.7 ± 3.9              | 18.4 ± 3.9                  | 20.2 ± 3.5            | <0.001  |

* ACT score after the first-month initial treatment. BMI, body mass index. ICS, inhaled glucocorticoid. LABA, long-acting beta-agonist. LTRA, leukotriene receptor antagonists. AQLQ, Asthma Quality of Life Questionnaire. SF-36, Short-Form 36 Questionnaire. ACT, asthma control test.
In this study, we also found that higher total serum IgE level was associated with a decreased risk of small airway obstruction. However, this IgE-airway obstruction association was only found in never smokers when stratified analyses were conducted by smoking status. Although the P value was 0.036 for that association, the 95% CI (0.216–0.754) further confirmed it and showed the strength of the effect. However, these results are not consistent with...
previous reports. Thus, it should be carefully deliberated. Previously total serum IgE level was found to be higher in smokers without asthma, whereas their FEF25–75%pred was lower than nonsmoking siblings [25]. Our study differs from this previous study, which included nonasthmatic subjects and did not separate ex-smokers or current smokers from all smokers. Furthermore, the authors assessed the effect among nonasthma subjects instead of asthma patients and did not investigate the effect of ex-smoking and current smoking. In contrast, a similar relationship was found in a previous study of 90 asthmatic subjects. It found that FEF25–75 value was higher in subjects with lower total serum IgE [26]. However, that study only analyzed subjects without smoking and current smoking, whereas our study included asthmatic subjects of never smoking, ex-smoking, or current smoking in a larger sample size. That may be related to the modification of smoking status in the association between IgE level and small airway obstruction. Thus, we further explored the effect of smoking status on the association between Th2 biomarkers and small airway obstruction by smoking status stratification.

When subjects were stratified on smoking status, our results showed an association between an increase of serum IgE level and a decreased risk of small airway obstruction in never-smoker asthmatic patients but not in current-smokers or ex-smokers. This finding suggests that IgE levels in current smokers or ex-smokers should be higher than that in never smokers in our study, perhaps partly due to the effect of smoking. It has been reported that smoking could attenuate the decrease of IgE level in steroid-naive patients with asthma [27]. In smoking-discordant monozygotic twins, total serum IgE is significantly higher in the smokers than in their nonsmoking siblings [25]. Studies using animal models of asthma found that cigarette smoke exposure could reduce allergen-induced total IgE in serum and Th2 response in the lung, in which nicotine played a key role [28, 29]. In contrast to total IgE in blood, blood eosinophil count is unchanged with cotinine exposure in asthma patients, even though blood eosinophil count is increased in controls [30]. Those may be the reasons that we observed the association between total serum IgE and small airway obstruction based on smoking status, but not blood eosinophil count. Therefore, our result suggests that smoking status may modify the association between IgE and small airway obstruction, which may be related with an endotype involved smoking, Th2-type inflammation, and small airway function. Thus, when total IgE level and small airway obstruction are assessed by pulmonologists, precise smoking status should be considered.

We acknowledge that we assessed eosinophil count and IgE level in blood, instead of eosinophils and Th2-type cytokines in the airway. Biomarkers in the airway could reflect local inflammation, whereas eosinophil count and IgE level in blood could indicate systematic inflammation. Since asthma is widely accepted as a systemic disease and systemic inflammation is a characteristic of asthma endotype, particularly in patients with serious symptoms [31], it may be more helpful to reflect asthma endotype that we assessed eosinophil count and IgE level in blood. Second, we did not assess Th2-type cytokines but only eosinophil count and IgE level in blood. Blood eosinophil count and total serum IgE level are classic biomarker of Th2 response, which could directly reflect phenotype of systematic inflammation.

5. Conclusions

Current-smoking status and total serum IgE are, respectively, associated with small airway obstruction. Smoking status modifies the relationship between Th2 biomarkers and small airway function. These findings contribute to further understanding of risk factors associated with asthma endotyping.

Data Availability

The dataset generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Supplementary Materials

Supplementary Figure 1. Selection of study subjects. FEF, forced expiratory flow. %pred, % predicted. STROBE Statement, checklist of items that should be included in reports of cohort studies. (Supplementary Materials)

Acknowledgments

The authors thank Professor Jim Zhang in Duke Global Health Institute of Duke University for his support of data analysis, writing assistance, and language editing. This work was supported by grants from the National Natural Science Foundation of China (Nos. 81960007, 81760012, 81760009, and 81560007) and the Guangxi Natural Science Foundation (No. 2017GXNSFBA198069) in China.

References

[1] P. J. Barnes, “Th2 cytokines and asthma: an introduction,” *Respiratory Research*, vol. 2, no. 2, pp. 64–65, 2001.
[2] G. Ciprandi, M. A. Tosca, M. Silvestri, and F. L. M. Ricciardolo, “Inflammatory biomarkers for asthma endotyping and consequent personalized therapy,” *Expert Review of Clinical Immunology*, vol. 13, no. 7, pp. 715–721, 2017.
[3] M. Naqvi, S. Choudhry, H.-J. Tsai et al., “Association between IgE levels and asthma severity among African American, Mexican, and Puerto Rican patients with asthma,” *The Journal of Allergy and Clinical Immunology*, vol. 120, no. 1, pp. 137–143, 2007.
[4] L. Liu, W. Liu, C. Liu et al., “Study on small airway function in asthmatics with fractional exhaled nitric oxide and impulse oscillometry,” *The Clinical Respiratory Journal*, vol. 12, no. 2, pp. 483–490, 2018.
K. Maneechotesuwan, P. Sujaritwongsanon, and M. R. Miller, J. Hankinson, V. Brusasco et al., “Stand-

E. A. Gilpin, J. P. Pierce, A. J. Farkas, and A. J. Farkas, G. Ciprandi, F. Gallo, and I. Cirillo, “FEF25-75% and asthma in

I. Cirillo, C. Klersy, G. L. Marseglia et al., “Role of FEF25%–75% as a predictor of bronchial hyperreactivity in allergic patients,” Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology, vol. 96, no. 5, pp. 692–700, 2006.

G. Ciprandi, F. Gallo, and I. Cirillo, “FEF25-75 and asthma in clinical practice,” Iranian Journal of Allergy, Asthma, and Immunology, vol. 17, no. 3, pp. 295–297, 2018.

E. A. Gilpin, J. P. Pierce, A. J. Farkas, and A. J. Farkas, “Duration of smoking abstinence and success in quitting,” JNCI Journal of the National Cancer Institute, vol. 89, no. 8, p. 572, 1997.

M. R. Miller, J. Hankinson, V. Brusasco et al., “Standardisation of spirometry,” European Respiratory Journal, vol. 26, no. 2, pp. 319–338, 2005.

K. F. Xu, X. C. Luo, Y. Chen et al., “The use of Juniper’s asthma quality of life questionnaire in Chinese asthmatics,” Zhonghua Fa Chong Za Zhi, vol. 42, no. 11, pp. 760–763, 2003.

L. Li, H. M. Wang, and Y. Shen, “Chinese SF-36 Health Survey: translation, cultural adaptation, validation, and normalisation,” Journal of Epidemiology & Community Health, vol. 57, no. 4, pp. 259–263, 2003.

J. Lin, N. Su, G. Liu et al., “The impact of concomitant allergic rhinitis on asthma control: a cross-sectional nationwide survey in China,” Journal of Asthma, vol. 51, no. 1, pp. 34–43, 2014.

S. Kjellberg, B. K. Houltz, O. Zetterström, P. D. Robinson, and P. M. Gustafsson, “Clinical characteristics of adult asthma associated with small airway dysfunction,” Respiratory Medicine, vol. 117, pp. 92–102, 2016.

E. W. de Roos, L. Lahousse, K. M. C. Verhamme et al., “Asthma and its comorbidities in middle-aged and older adults; the Rotterdam Study,” Respiratory Medicine, vol. 139, pp. 6–12, 2018.

K. Manechotesuwan, P. Sujaritwongsanon, and T. Suthamsmai, “IgE production in allergic asthmatic patients with different asthma control status,” Medical Journal of the Medical Association of Thailand, vol. 93, no. Suppl 1, pp. S71–S78, 2010.

J. J. K. Jaakkola, S. Hernberg, T. K. Lajunen, P. Sripajiboonkij, L. P. Malmberg, and M. S. Jaakkola, “Smoking and lung function among adults with newly onset asthma,” BMJ open respiratory research, vol. 6, no. 1, Article ID e000377, 2019.

G. Wang, R. Wang, B. Ferris et al., “Smoking-mediated up-regulation of GAD67 expression in the human airway epithelium,” Respiratory Research, vol. 11, no. 1, p. 150, 2010.

L. Ma, M. Jiang, X. Zhao, J. Sun, Q. Pan, and S. Chu, “Cigarette and IL-17A synergistically induce bronchial epithelial-mesenchymal transition via activating IL-17R/NF-κB signaling,” BMC Pulmonary Medicine, vol. 20, no. 1, p. 26, 2020.

H. Xia, J. Xue, H. Xu et al., “Androgapholide antagonizes the cigarette smoke-induced epithelial-mesenchymal transition and pulmonary dysfunction through anti-inflammatory inhibiting HOTAIR,” Toxicology, vol. 422, pp. 84–94, 2019.

C. H. Ericsson, M. Svartengren, B. Mosberg, and P. Camner, “Bronchial reactivity, lung function, and serum immunoglobulin E in smoking-discordant monogamous twins,” American Review of Respiratory Disease, vol. 147, no. 2, pp. 296–300, 1993.

K. M. Beeh, M. Koll, and R. Buhl, “Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals,” European Respiratory Journal, vol. 16, no. 4, pp. 609–614, 2000.

T. Nagasaki, H. Matsumoto, N. Nakaji et al., “Smoking attenuates the age-related decrease in IgE levels and maintains eosinophilic inflammation,” Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology, vol. 43, no. 6, pp. 608–615, 2013.

C. Tilm, H. Bucher, H. Haas, M. J. Duechs, E. Wex, and K. J. Erb, “Effects of conventional tobacco smoke and nicotine-free cigarette smoke on airway inflammation, airway remodelling and lung function in a triple allergen model of severe asthma,” Clinical & Experimental Allergy, vol. 46, no. 7, pp. 957–972, 2016.

N. C. Mishra, J. R. Sima-Ah, R. J. Langley et al., “Nicotine primarily suppresses lung Th2 but not goblet cell and muscle cell responses to allergens,” The Journal of Immunology, vol. 180, no. 11, pp. 7655–7663, 2008.

T. Jacinto, A. Malinovschi, C. Janson, J. Fonseca, and K. Alving, “Differential effect of cigarette smoke exposure on exhaled nitric oxide and blood eosinophils in healthy and asthmatic individuals,” Journal of Breath Research, vol. 11, no. 3, Article ID 036006, 2017.

Z. Liang, L. Liu, H. Zhao et al., “A systemic inflammatory endotype of asthma with more severe disease identified by unbiased clustering of the serum cytokine profile,” Medicine, vol. 95, no. 25, Article ID e3774, 2016.