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# Роль взвешенных микрочастиц атмосферного воздуха в формировании эозинофильного воспаления при T2-эндотипе бронхиальной астмы

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## АННОТАЦИЯ

**Обоснование.** Общеизвестно, аллергены являются индукторами эозинофильного воспаления при T2-эндотипе бронхиальной астмы, однако роль неспецифических факторов (микрочастицы атмосферного воздуха, РМ) изучена недостаточно.

**Цель** — на основе исследования отдельных биомаркеров охарактеризовать эозинофильное воспаление при T2-эндотипе бронхиальной астмы в условиях влияния микрочастиц атмосферного воздуха.

**Материалы и методы.** Обследовано 150 пациентов с бронхиальной астмой, из них включён в исследование 61 пациент в возрасте 18–65 лет с T2-эндотипом бронхиальной астмы: 34 — с аллергической (1-я группа), 27 — с неаллергической (2-я группа). Группа сравнения — 30 человек без бронхиальной астмы и других аллергических заболеваний — подобрана методом копия-пара. Наряду с общеклиническим и специфическим аллергологическим обследованием проведено определение концентрации IL-33, IL-25, IL-4, IL-5, IL-13, ДПП4 (мультиплексный анализ) и периостина (ИФА) в сыворотке крови. Проанализирована база данных ФБУЗ «Центр гигиены и эпидемиологии в Республике Татарстан (Татарстан)» по мониторингу содержания мелкодисперсных веществ атмосферного воздуха в г. Казани (2014–2020 гг.) с оценкой усреднённых за многолетний период (Avg) и максимальных среднегодовых (MaxAvg) концентраций PM<sub>2,5</sub> и PM<sub>10</sub> в зонах проживания. Статистическая обработка данных проведена с использованием пакета R (версия 4.0.5). Работа выполнена при поддержке гранта РФФИ в рамках проекта 19-05-50094.

**Результаты.** Выявлен высокий уровень абсолютного количества эозинофилов периферической крови и IL-5 у пациентов с бронхиальной астмой. Только у пациентов с аллергической астмой обнаружено повышенное содержание общего IgE ( $p=0,0001$ ), коррелирующее с высоким уровнем IL-4 ( $rS=0,38$ ;  $p=0,045$ ); кроме того, в этой же группе отмечалось высокое содержание IL-25 ( $p=0,009$ ). При этом различий в содержании IL-33 у пациентов с бронхиальной астмой выявить не удалось. Регрессионный анализ показал, что увеличение содержания PM<sub>2,5</sub>Avg на 1 мкг/м<sup>3</sup> ведёт к увеличению концентрации IL-33 и IL-25, повышение уровня PM<sub>10</sub>Avg — к увеличению концентрации IL-25 только у пациентов с неаллергической бронхиальной астмой. У пациентов с аллергической астмой при повышении уровня PM<sub>2,5</sub>Avg и PM<sub>10</sub>Avg статистически значимого увеличения IL-33 и IL-25 не выявлено.

**Заключение.** Результаты регрессионного анализа указывают на ведущую роль микрочастиц атмосферного воздуха в развитии и поддержании эозинофильного воспаления у пациентов с неаллергическим фенотипом бронхиальной астмы.

**Ключевые слова:** бронхиальная астма; эозинофильное воспаление; цитокины; биомаркеры; PM<sub>2,5</sub>; PM<sub>10</sub>.

## Как цитировать

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# The role of fine suspended particles of atmospheric air in the formation of eosinophilic inflammation in T2-endotype of asthma

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## ABSTRACT

**BACKGROUND:** Allergens induce eosinophilic inflammation in the T2 endotype of asthma. However, much less is known about the role of non-specific factors (suspended particles in the atmospheric air-PM).

**AIMS:** To define eosinophilic inflammation on the basis of several biomarkers in the T2 endotype of asthma exposed to PM.

**MATERIALS AND METHODS:** We studied 150 patients with asthma, and 61 patients with T2 endotype of asthma (ages 18–65 years) were enrolled. Group 1 included 34 patients with allergic asthma, and group 2 included 27 patients with non-allergic asthma. Moreover, 30 healthy matched controls without asthma and other allergic diseases were enrolled in the study. Clinical examination and allergy testing were performed. Additionally, serum levels of IL-33, IL-25, IL-4, IL-5, IL-13, DPP4 (multiplex assay), and periostin (ELISA) were evaluated. The analyses of the average annual concentrations (Avr) and the maximal annual concentrations (MaxAvr) of PM<sub>2.5</sub> and PM<sub>10</sub> in Kazan were conducted using the database of the Center for Hygiene and Epidemiology in the Republic of Tatarstan, being averaged over the period from 2014 to 2020 years in monitoring points at residential areas. Statistical analyses were performed using R version 4.0.5. The study was funded by RFBR (Project no. 19-05-50094).

**RESULTS:** We detected increased blood eosinophil count and IL-5 levels in patients with asthma. High levels of total IgE ( $p=0.0001$ ) that correlated with IL-4 levels were observed only in patients with allergic asthma ( $rS=0.38$ ;  $p=0.045$ ). Moreover, elevated IL-25 levels were found in patients with allergic asthma ( $p=0.009$ ). No significant differences in IL-13 levels in patient with asthma were found. The regression analysis revealed that the PM<sub>2.5</sub>Avr increase by 1 mcg/m<sup>3</sup> increases IL-33 and IL-25 levels, but the PM<sub>10</sub>Avr increase raises the IL-25 levels only in patients with non-allergic asthma. No significant increase in IL-25 and IL-33 levels under exposure to PM<sub>2.5</sub>Avr and PM<sub>10</sub>Avr was detected in patients with allergic asthma.

**CONCLUSIONS:** The results of this study indicate the pivotal role of fine suspended particles in the development and maintenance of eosinophilic inflammation in patients with non-allergic asthma.

**Keywords:** asthma, eosinophilic inflammation, cytokines, biomarkers, particulate matter.

## To cite this article

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## BACKGROUND

Currently, despite certain advances in the diagnosis and treatment of asthma, several patients fail to achieve disease control. This fact necessitates the search for new therapeutic approaches that consider various etiopathogenetic alternatives of the development of chronic inflammation [1].

Studies in the last 25 years directed toward researching the clinical and pathogenetic features of asthma have made it possible to define the concept of disease phenotypes and endotypes. In 1999, Wenzel et al. [2] examined tissue samples obtained by endobronchial biopsy and suggested two subtypes of inflammation, depending on the involvement of eosinophils. This became the basis for distinguishing asthma endotypes, namely, Th2-high (eosinophilic) and Th2-low (non-eosinophilic) [3]. Continuing research in this direction, Simpson et al. [4] studied the cellular composition of induced sputum of patients with asthma and found other cells along eosinophils, particularly neutrophils. This significantly expanded the concept of the possible mechanisms of chronic inflammation development in asthma and allowed, in addition to eosinophilic version, to additionally distinguish neutrophilic, mixed granulocytic, and paucigranulocytic types of inflammation [5]. Further investigation of pathogenetic mechanisms has led to the emergence of new data indicating an involvement of type 2 innate lymphoid cells in the formation and maintenance of eosinophilic inflammation in asthma [3]. Thus, the modern concept of the problem allows distinguishing two asthma endotypes, i.e., T2 endotype, where eosinophilic inflammation develops, and non-T2 endotype, which is characterized by a neutrophilic or paucigranulocytic inflammation [6]. More than 50% of patients with asthma have a T2 endotype. Studies on the pathogenetic features of eosinophilic inflammation made it possible to distinguish its biomarkers: absolute count of peripheral blood eosinophils, eosinophil count in induced sputum, nitric oxide levels in exhaled air, and levels of total IgE, periostin, dipeptidylpeptidase-4 (DPP4), and some cytokines (thymic stromal lymphopoietin [TSLP], IL-25, IL-33, IL-4, IL-5, and IL-13) in the blood serum [7]. However, the value of individual biomarkers in the characterization of eosinophilic inflammation continues, which is unclear.

The development of eosinophilic inflammation in the bronchial mucosa in these patients can be induced by secondary agents — specific (allergens) and nonspecific (viruses, microorganisms, and pollutants), which get into contact with the epithelium of the respiratory tract, leading to its damage and release of alarmins (TSLP, IL-25, and IL-33). Moreover, allergens cause the development of antibody immune response with the participation of Th2 lymphocytes producing IL-4, IL-13, and IL-5, B-lymphocytes, differentiating in plasma cells, and synthesizing allergen-specific IgE, and the activation of type 2 innate lymphoid cells (ILC2). In turn, nonspecific stimuli such as ambient

particulate matter (PM), when the epithelium of the respiratory tract is exposed to them, lead to the preferential activation of innate immunity mechanisms involving ILC2, which synthesizes IL-13 and IL-5 [8, 9].

Ambient PM is a mixture of solid and liquid particles with different chemical compositions, shapes, and sizes. Particle size is essential because, depending on this parameter, fine particles can reach different parts of the respiratory tract [10]. Thus, the following fractions are distinguished according to the aerodynamic particle size: PM10 (aerodynamic particle diameter of  $<10\ \mu\text{m}$ ), PM2.5 (aerodynamic particle diameter of  $<2.5\ \mu\text{m}$ ), and PM0.1 (aerodynamic particle diameter of  $<0.1\ \mu\text{m}$ ). PM10 can reach the bronchi, and PM2.5 can reach the bronchioles [11, 12]. In addition, ambient PM such as transition metals and quinones from gasoline and diesel combustion products, cigarette smoke, and secondary organic aerosols formed in the atmosphere, when inhaled and deposited in the respiratory tract, can induce chemical reactions and formation of active forms of oxygen ( $\text{OH}$ ,  $\text{O}_2^-$ ,  $\text{HO}_2$ ,  $\text{O}_3$ , and  $\text{H}_2\text{O}_2$ ) that lead to oxidative stress and epithelium damage [13].

Studies on cell cultures have shown that epithelial cytokines are released because of epithelial cell damage by PM, which leads to the stimulation of dendritic cell maturation and subsequent activation of Th2 lymphocytes [14]. Owing to their electrostatic properties and porous surface, suspended solids easily interact with aeroallergens (plant pollen allergens, house dust mites, mold spores, and animal hair), changing their allergenic properties [11]. Suspended particles, binding to pollen grains, accelerate the release of allergens and enhance their absorption in the respiratory tract [15].

Nevertheless, the presented data are based on the results of studies conducted mainly on cell cultures [14]. The number of studies on the effect of PM on eosinophilic inflammation development in patients with asthma is limited. Therefore, further research in this direction continues to be relevant.

**This study** aimed to characterize eosinophilic inflammation in the T2 endotype of asthma under the effect of ambient PM based on the analysis of individual biomarkers.

## MATERIALS AND METHODS

### Study design

An observational single-center cross-sectional sampling “case–control” study was conducted.

### Eligibility criteria

A total of 150 patients with asthma were examined, of which 61 patients with T2 asthma were included in the study. *Inclusion criteria:* aged 18–65 years and established clinical diagnosis of allergic or non-allergic T2 asthma.

*Exclusion criteria:* allergen-specific immunotherapy or biological therapy at the time of examination or medical records on the use of these therapy options earlier.

The control group consisted of 30 people who were selected by the copy-pair method from individuals comparable by sex, age, body mass index, and profession (occupation) but do not have symptoms of asthma and other allergic diseases. Both groups and the control group provided written informed consent to participate in the study, which involved the collection of biological material (blood serum).

## Terms and Conditions

The study was conducted at the Republican Center for Clinical Immunology of State Autonomous Healthcare Institution Republican Clinical Hospital of the Ministry of Healthcare of the Russian Federation (Kazan) and LLC "Clinical and Diagnostic Center Yasin" (Kazan), where patients with asthma referred for consultation by local therapists and the control group were examined.

## Study duration

The study was conducted from November 2019 to August 2022, and biological material (blood serum) was collected from February 2020 to May 2021.

## Description of medical intervention

The diagnosis of asthma was established in accordance with current clinical recommendations [16]. The examination program consisted of general clinical and specific allergological methods. General clinical methods included analysis of medical history, physical examination results, laboratory (including general blood test with differential white blood cell count and absolute eosinophil count), and instrumental methods of diagnostics (spirometry with bronchodilatation test — inhalation of 400 µg of salbutamol broncholytic). In turn, specific allergological examinations included the analysis of allergological history, skin prick testing with standard allergens, and total and specific IgE levels in blood serum. To determine the level of disease control, the asthma control test was performed [16]. Additionally, in the asthma group and control group, the levels of IL-33, IL-25, IL-4, IL-5, IL-13, and DPP4 in the blood serum was determined using MILLIPLEX MAP Human TH17 Magnetic Bead Panel – Immunology Multiplex Assay, MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel II – Immunology Multiplex Assay, and MILLIPLEX MAP Human Cardiovascular Disease Magnetic Bead Panel 6 – Cardiovascular Disease (CVD) Immunology Multiplex Assay (Merck, Germany), and periostin concentration was determined using enzyme-linked immunoassay (HUMAN PERIOSTIN/OSF-2 ELISA KIT).

In addition, a database of the Federal State Healthcare Institution "Center for Hygiene and Epidemiology in the Republic of Tatarstan (Tatarstan)" for monitoring the content of ambient PM in Kazan (<https://fbuz16.ru>) was analyzed from January 2014 (start of monitoring ambient PM) to December 2020 to characterize the concentrations of PM fractions in residential areas with the assessment of average annual

concentrations of PM<sub>2.5</sub> and PM<sub>10</sub> fractions (PM<sub>2.5</sub>Avr and PM<sub>10</sub>Avr), averaged over seven full calendar years, and maximum annual average concentrations of PM<sub>2.5</sub> and PM<sub>10</sub> fractions (PM<sub>2.5</sub>MaxAvr and PM<sub>10</sub>MaxAvr) of ambient PM over the same period. An approach based on the use of long-term averaged data as exposition parameters has been applied in epidemiological studies on the effect of ambient PM on public health [17, 18].

## Main study outcome

The study determined the role of individual biomarkers in the characterization of eosinophilic inflammation and the role of ambient PM in the development and maintenance of eosinophilic inflammation in patients with T2 asthma.

## Subgroup analysis

As a result of the examination, two groups were formed, namely, allergic asthma group ( $n=34$ ) and the non-allergic asthma group ( $n=27$ ). The levels of eosinophilic inflammation biomarkers were compared and analyzed, and the relationship between the indicated parameters and ambient PM was assessed.

## Outcome registration methods

The results of general clinical and specific allergological examinations were recorded in patient's individual card. Data on the levels of eosinophilic inflammation biomarkers were recorded in the journal of laboratory examinations.

## Ethical review

The study was approved by the local ethics committee of FSFEI HE "Kazan State Medical University" of the Ministry of Healthcare of the Russian Federation (Protocol No. 4 dated April 28, 2020).

## Statistical analysis

Considering the approaches adopted in one-stage studies of biomarkers, the sample size (91 blood serum samples) provides a statistical power of at least 95% [19]. The statistical analysis of data was performed using the R software package (version 4.0.5, USA). Descriptive analysis of the parameters, considering the deviation from the normal distribution, included the calculation of median and quartiles (Me [Q1; Q3]). Comparative analysis was based on the statistical significance of the difference in indicators according to the nonparametric Mann–Whitney Z-test. The Spearman coefficient was used to assess the correlation dependence of the indicators. To assess the relationship between serum levels of cytokines and the average annual concentrations of PM<sub>2.5</sub> and PM<sub>10</sub>, multivariate regression analysis was used. In the regression models, sex, age, and body mass index were used as cofounders. The critical level of significance ( $p$ ) when testing the statistical hypotheses was equal to 0.05.

## RESULTS

### Study population

We examined 61 patients aged 18–65 (mean age, 41.18) years with T2 asthma, including 21 men and 40 women. The allergic asthma group included 34 patients (mean age, 31.9 years), whereas the non-allergic asthma group included 27 patients (mean age, 49.0 years). The characteristics of the patients are presented in Table 1.

At the time of examination, 15 (44.12%) patients with allergic and 8 (29.63%) patients with non-allergic asthma did not receive basic anti-inflammatory therapy, which was associated with low adherence of a certain number of patients to treatment (willfully did not use the prescribed anti-inflammatory therapy and used only short-acting  $\beta_2$  agonists). Unfortunately, at present, treating patients with asthma in many regions of the world, including Russia, is a significant problem [20]. In 6 (9.84%) patients, asthma was diagnosed for the first time; thus, biomaterial was collected before the start of therapy with inhaled corticosteroids (ICS).

The control group consisted of 30 people who were selected by the copy-pair method from individuals comparable by sex, age, body mass index, and profession (occupation), but had no symptoms of asthma and other allergic diseases.

### Main results

The results showed high values of the absolute number of peripheral blood eosinophils in patients with allergic and non-allergic asthma: allergic asthma group, Me [Q1; Q3], 291.75 cells/ $\mu$ L [140.60; 516.50]; non-allergic asthma group, 286.00 cells/ $\mu$ L [170.00; 451.00], whereas in the control group, this marker did not exceed 56.50 cells/ $\mu$ L [48.50; 111.00] ( $p=0.000001$ ), which confirms the presence

of eosinophilic inflammation (Table 2). Moreover, IL-5 levels in the blood serum did not differ significantly in the allergic and non-allergic asthma groups, i.e., 6.33 pg/mL [2.32; 8.77] and 4.17 pg/mL [1.82; 14.64], respectively, and as expected, in both cases, it was significantly higher than in the control group, 2.32 pg/mL [2.32; 2.32] ( $p=0.006$  and  $p=0.017$ , respectively). In addition, despite the significantly high values of the absolute number of eosinophils and IL-5 in both groups, the correlation between these markers could not be found. However, after the exclusion of patients receiving basic anti-inflammatory therapy with ICS at the time of examination from both groups, a direct correlation was found between IL-5 levels in the blood serum and the absolute number of peripheral blood eosinophils ( $rS=0.47$ ;  $p=0.033$ ). Generally, similar data were obtained for IL-13, and its levels in the allergic and non-allergic asthma groups were 92.26 pg/mL [35.33; 305.46] and 205.05 pg/mL [54.01; 322.67], respectively, and was significantly higher than that in the control group ( $p=0.007$  and  $p=0.0001$ , respectively; Table 2). In addition, a correlation was not found between IL-13 levels and absolute number of peripheral blood eosinophils. Regarding IL-4, its level was high only in the allergic asthma group and correlated with high levels of total IgE ( $rS=0.38$ ;  $p=0.045$ ). Moreover, in the non-allergic asthma group, these parameters had low values and did not differ from that of the control group.

The level of another biomarker of eosinophilic inflammation — periostin — in the allergic and non-allergic asthma groups did not differ from that of the control group (10.00 mg/L [3.50; 27.00]). However, when comparing this marker in the allergic and non-allergic asthma groups, statistically significant differences were found: in the allergic asthma group, the level of periostin was 11.94 mg/L [4.30; 25.03],

**Table 1.** Characteristics of patients with allergic and non-allergic phenotype of asthma

Indicators		Allergic asthma; $n=34$	Non-allergic asthma; $n=27$
Mean age, years		31.9	49.0
Sex	Male	15	6
	Female	19	21
Severity of asthma, $n$ (%)	Mild	5 (14.7)	2 (7.4)
	Moderate	21 (61.8)	12 (44.4)
Concomitant conditions, $n$ (%)	Severe	8 (23.5)	13 (48.2)
	Allergic rhinitis	32 (94.1)	0
Number of patients receiving basic therapy with corticosteroids, $n$ (%)	CRSwNP	0	11 (40.7)
	ICS as monotherapy or in combination with LABA	18 (52.94)	14 (51.85)
Number of patients who did not receive basic therapy, $n$ (%)	ICS and SCS in combination with LABA and/or LAMA	1 (2.94)	5 (18.52)
		15 (44.12)	8 (29.63)

**Note:** CRSwNP, chronic rhinosinusitis with nasal polyps; ICS/SCS, inhaled/systemic corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LAMA, long-acting muscarinic receptor antagonists.

**Table 2.** Differences in biomarkers of eosinophilic inflammation in patients with T2 asthma and control group

Biomarkers	Allergic asthma Me [Q1; Q3]	Non-allergic asthma Me [Q1; Q3]	Control group Me [Q1; Q3]	<i>p</i>
IgE, IU/mL	251.50 [165.20; 496.10]	61.02 [24.01; 84.05]	-	0.0001 <sup>a</sup>
Eosinophil count, cells per $\mu$ L, abs.	291.75 [140.60; 516.50]	286.00 [170.00; 451.00]	56.50 [48.50; 111.00]	0.000001 <sup>b</sup> 0.000001 <sup>c</sup>
IL-25, pg/mL	0.03 [0.03; 0.11]	0.03 [0.025; 0.03]	0.025 [0.025; 0.025]	<0.009 <sup>a</sup> <0.021 <sup>b</sup>
IL-33, pg/mL	9.15 [1.80; 23.82]	3.73 [1.80; 10.55]	1.80 [1.80; 22.23]	-
IL-4, pg/mL	0.42 [0.05; 1.49]	0.05 [0.01; 0.30]	0.10 [0.01; 0.38]	0.005 <sup>a</sup> 0.001 <sup>b</sup>
IL-5, pg/mL	6.33 [2.32; 8.77]	4.17 [1.82; 14.64]	2.32 [2.32; 2.32]	0.006 <sup>b</sup> 0.017 <sup>c</sup>
IL-13, pg/mL	92.26 [35.33; 305.46]	205.05 [54.01; 322.67]	40.28 [27.62; 9.87]	0.007 <sup>b</sup> 0.0001 <sup>c</sup>
Periostin, mg/L	11.94 [4.30; 25.03]	6.85 [2.10; 35.80]	10.00 [3.50; 27.00]	0.012 <sup>a</sup>
DPP4, pg/mL	1121.50 [893.40; 1212.00]	926.27 [665.11; 1118.00]	1167.00 [957.32; 1311.00]	0.045 <sup>c</sup>

**Note:** Statistical significance of differences between the following groups: <sup>a</sup> allergic asthma and non-allergic asthma; <sup>b</sup> allergic asthma and control group, and <sup>c</sup> non-allergic asthma and control group. Statistical significance was calculated using the Mann–Whitney test.

whereas in the non-allergic asthma group, it was significantly lower at 6.85 mg/L [2.10; 35.80] ( $p=0.012$ ).

Generally, similar data were recorded in relation to DPP4 levels, and its values in the allergic asthma group did not differ from that in the control group, i.e., 1121.50 pg/mL [893.40; 1212.00] and 1167.00 pg/mL [957.32; 1311.00], respectively, and that in the non-allergic phenotype asthma group was even lower than that in the control group, 926.27 pg/mL [665.11; 1118.00] ( $p=0.045$ ).

We paid special attention to the assessment of alarmins. In the allergic asthma group, the IL-25 level was 0.03 pg/mL [0.03; 0.11], which was significantly higher than those in the non-allergic asthma ( $p=0.009$ ) and control ( $p=0.021$ ) groups. Moreover, the results of the correlation analysis demonstrated a direct relationship between IL-25 and IgE ( $rS=0.41$ ;  $p=0.042$ ), IL-25 and IL-4 ( $rS=0.45$ ;  $p=0.043$ ), IL-25 and IL-13 ( $rS=0.81$ ;  $p=0.000001$ ) in the allergic asthma group. In addition, no significant differences were found in the levels of IL-33 in the blood serum of the asthma and control groups.

Simultaneously, we studied the relationship between the levels of ambient PM (PM<sub>2.5</sub>; PM<sub>10</sub>) and individual biomarkers of eosinophilic inflammation (Fig. 1). The regression analysis showed that an increase in the PM<sub>2.5</sub>Avr level by 1  $\mu$ g/m<sup>3</sup> leads to an increase in IL-33 and IL-25 levels in the non-allergic asthma group by 19.810 $\pm$ 8.948 and 0.014 $\pm$ 0.005 pg/mL, respectively (Table 3). Additionally, IL-25 levels increased

in patients by 0.006 $\pm$ 0.002 pg/mL and increased PM<sub>10</sub>Avr levels. Moreover, significant increase was not found in IL-33 and IL-25 levels with high levels of PM<sub>2.5</sub>Avr and PM<sub>10</sub>Avr in the allergic asthma group. Regression analysis data also confirmed that an increase in PM<sub>10</sub>Avr levels in ambient air by 1  $\mu$ g/m<sup>3</sup> leads to an increase in IL-13 levels by 6.228 $\pm$ 2.878 pg/mL in the non-allergic asthma group, and an increase in PM<sub>2.5</sub>Avr by 1  $\mu$ g/m<sup>3</sup> leads to an increase in DPP4 levels by 74.210 $\pm$ 32.180 pg/mL.

### Additional study results

Although ambient PM is involved in the pathogenesis of both allergic and non-allergic asthma, significant regression models were obtained only for the non-allergic asthma group.

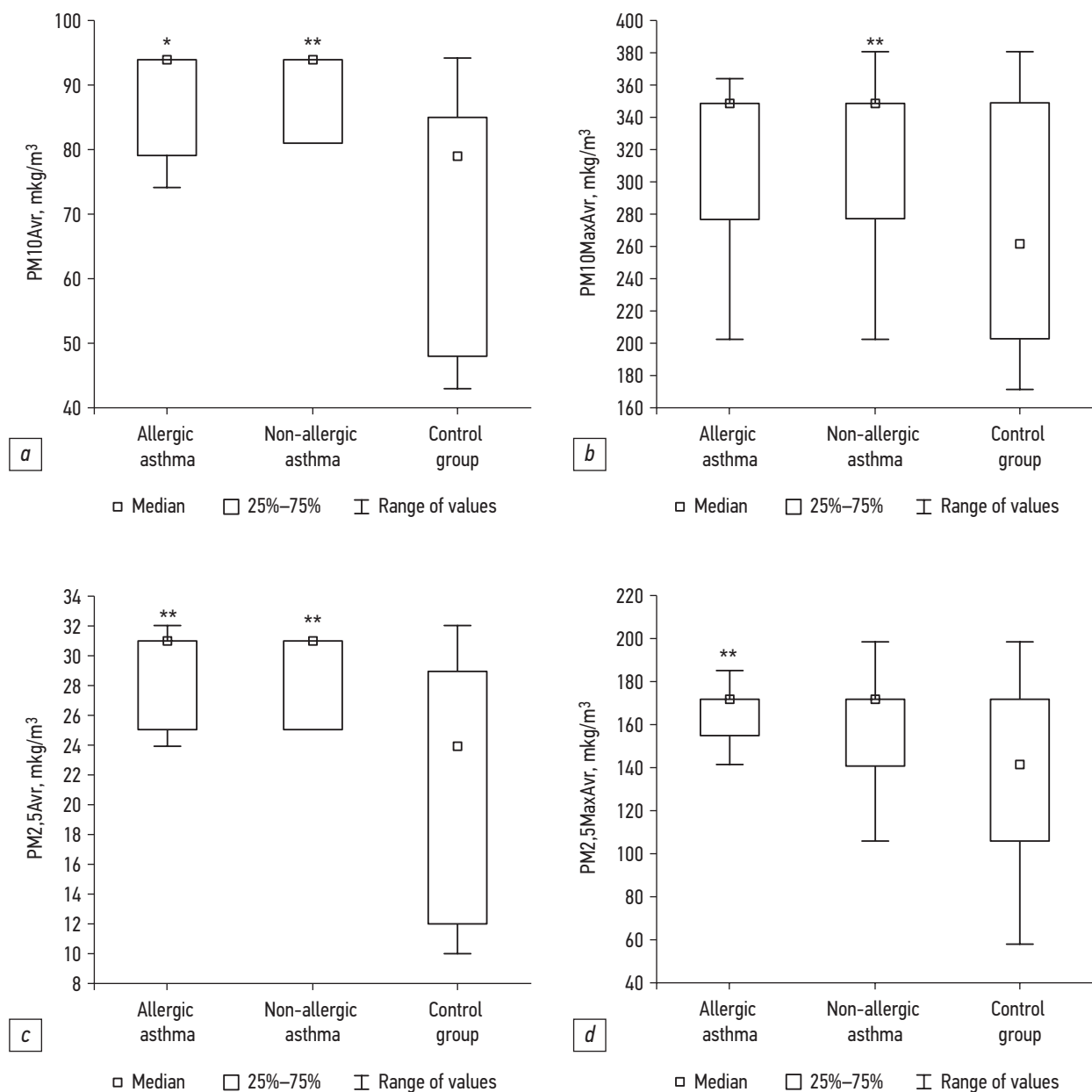
### Adverse events

No adverse events were observed during the study.

## DISCUSSION

### Summary of the main result of the study

This paper describes eosinophilic inflammation in T2 asthma under the influence of ambient PM. Moreover, the role of ambient PM in the development and sustaining of eosinophilic inflammation in patients with T2 asthma is determined.



**Fig. 1.** Ambient air pollution in the residence of patients with asthma and controls: *a*, PM10Avr; *b*, PM10MaxAvr; *c*, PM2,5Avr; *d*, PM2,5MaxAvr.

**Note:** Statistical significance was calculated using the Mann–Whitney test in the following groups: allergic asthma and control group, non-allergic asthma and control group; \*  $p < 0.05$ ; \*\*  $p < 0.001$ .

## Discussion of the main result of the study

Data indicate the presence of eosinophilic inflammation in patients of both groups. This is evidenced by the high absolute number of peripheral blood eosinophils and increased IL-5 levels in the blood serum of the allergic and non-allergic asthma groups. In addition, a direct correlation was found between IL-5 levels in the blood serum and absolute number of peripheral blood eosinophils in patients not receiving therapy with ICS and/or systemic corticosteroids, which is associated with the possible effect of this drug on the severity of eosinophilic inflammation. Other authors revealed similar findings [21, 22]. In addition, IL-13 influences the development

of peripheral blood eosinophilia by inducing the expression of chemokine molecules, particularly eotaxin-1 [9, 23]. Our study highlighted significantly high levels of IL-13 in both groups.

The results regarding IL-4 and IgE levels were also anticipated. High IL-4 levels were found only in patients with allergic asthma, and it correlated with high levels of total IgE. In addition, in the non-allergic asthma group, the levels of these markers were low and did not differ from that of the control group. Our results generally correspond to the development of eosinophilic inflammation in allergic asthma because IL-4 promotes the differentiation of Th2 lymphocytes and the switch from IgM heavy-chain synthesis to IgE [9].

**Table 3.** Coefficients of regression models

Biomarkers	Non-allergic asthma (J45.1) and control group	Allergic asthma (J45.0) and control group	Allergic asthma (J45.0) and non-allergic asthma (J45.1)
	$\beta_{J45.1} \pm SE, \beta_{PM} \pm SE$	$\beta_{J45.0} \pm SE$	$\beta_{J45.1*PM} \pm SE$
IL-33, pg/mL	-	-	$\beta_{BA\ j45.1*PM2.5Avr} = 19.810 \pm 8.948$ $p = 0.039^b$
DPP4, pg/mL	-	-	$\beta_{BA\ j45.1*PM2.5Avr} = 74.210 \pm 32.180$ $p = 0.034^c$
IL-25, pg/mL	-	-	$\beta_{BA\ j45.1*PM2.5Avr} = 0.014 \pm 0.00$ $p = 0.013^d$ $\beta_{BA\ j45.1*PM10Avr} = 0.006 \pm 0.002$ $p = 0.011^d$
IL-13, pg/mL	$\beta_{BA\ j45.1} = 0.052 \pm 0.022$ $p = 0.021^a$	-	$\beta_{BA\ j45.1*PM10Avr} = 6.228 \pm 2.878$ $p = 0.039^e$
IL-5, pg/mL	$\beta_{BA\ j45.1} = 0.010 \pm 0.004$ $p = 0.028^a$	-	-
Eosinophils	$\beta_{BA\ j45.1} = 0.351 \pm 0.049$ $p = 0.001^a$	$\beta_{BA\ j45.0} = 0.404 \pm 0.164$ $p = 0.018$	-

**Note:** The table represents only significant coefficients of regression ( $p < 0.05$ ). These linear multivariate regression models include the following variables: asthma phenotype (J45.0, allergic asthma; J45.1, non-allergic asthma), variable of exposure (PM2.5Avr and PM10Avr), and variable of interaction between asthma and PM. Cofounders in multivariate regression models: <sup>a</sup> age, body mass index, and sex; <sup>b</sup> age, sex, body mass index, and total IgE; <sup>c</sup> sex, total IgE, and asthma severity; <sup>d</sup> age, sex, body mass index, and asthma severity; <sup>e</sup> sex and asthma severity. PM, particulate matter; SE, standard error.

Analysis data of other biomarkers of eosinophilic inflammation, periostin and DPP4, were unclear. Indeed, levels of periostin in the allergic and non-allergic asthma groups did not differ from those in the control group, whereas high levels of periostin were found in the allergic asthma group, which may be due to concomitant pathologies such as allergic rhinitis in a significant number of patients in this group and their lower body mass index. Kimura et al. [24] reported similar results; when they studied the levels of serum periostin in patients with asthma and allergic rhinitis, a negative correlation was found between body mass index and periostin levels. In addition, they revealed a trend toward an increase in the level of periostin in patients with allergic rhinitis.

Generally, similar data were registered in relation to DPP4, and its levels in the allergic asthma group did not differ from that in the control group, and in the non-allergic asthma group, they were even lower than that in the control group ( $p = 0.045$ ). These differences can probably be explained by the use of ICS as basic therapy in the vast majority of patients with asthma. Solanki et al. [25] also showed a significant decrease in levels of serum periostin in patients with asthma after 4 weeks of initiation of corticosteroid therapy. In addition, evidence revealed lower significance of periostin and DPP4 for characterizing eosinophilic inflammation in patients with asthma [26, 27].

We also assessed alarmins. Damage to the epithelium of the respiratory tract when exposed to allergens, pollutants, and tobacco smoke leads to the secretion of alarmins [8]. We registered significantly high levels of IL-25 in the allergic asthma group. Paplińska-Goryca et al. [28] reported similar data when studying the levels of IL-25 in induced sputum,

which revealed high levels of IL-25 in the allergic asthma group. As shown in previous studies, IL-25 enhances the production of IL-4, IL-5, and IL-13 by Th2 lymphocytes and IL-5 and IL-13 by ILC2 [29], whereas the inhibition of IL-25 leads to a decrease in the levels of Th2 cytokines [30]. In the present study, a relationship between IL-25 and total IgE, IL-25 and IL-4, IL-25, and IL-13 was found only in patients with allergic asthma, which generally fits into the concept of eosinophilic inflammation pathogenesis in allergic asthma.

However, we failed to identify significant differences in IL-33 levels in the blood serum of patients with allergic and non-allergic asthma. However, when assessing the relationship between the number of ambient microparticles and levels of alarmins using multivariate regression analysis, the level of PM2.5Avr increased by  $1 \mu\text{g}/\text{m}^3$ , which leads to an increase in the levels of IL-33 and IL-25 in the non-allergic asthma group. Alarmins released from epithelial cells upon exposure to PM activate ILC2, which synthesizes IL-5 and IL-13 [9]. In turn, IL-13 activates the synthesis of matrix peptides, including DPP4 [27]. In our study, an increase in PM10Avr by  $1 \mu\text{g}/\text{m}^3$  increased DPP4 levels by  $74.210 \pm 32.180$  pg/mL. In addition, in patients of the same group, with an increase in the amount of PM10Avr, level of IL-25 also increased. Thus, our data generally correlate with modern views on the development of eosinophilic inflammation in patients with non-allergic phenotype of T2 asthma. Moreover, in the allergic asthma group, no significant increase in IL-33 and IL-25 levels associated with higher levels of average annual concentrations of PM2.5 and PM10 in areas where patients live, which suggests the secondary role of ambient



PM compared with the influence of specific stimuli (allergens) in the induction of eosinophilic inflammation in the allergic asthma group.

### Study limitations

In this study, data on the content of ambient PM (PM<sub>2.5</sub> and PM<sub>10</sub>) are based on geospatial approach (distance from places of residence of the patient group and control group to monitor points of the “Hygiene and Epidemiology Center in the Republic of Tatarstan (Tatarstan)”). To obtain more accurate data in the future, reducing the distance between indicators’ measurement points is possible. In addition, our results can only be extrapolated to residents of industrial cities because the study considered data on the content of ambient PM within a large city, and its residents comprised the study population. The prevalence of patients with moderate and severe asthma is also a certain limitation.

### CONCLUSION

Regression analysis data demonstrate that ambient PM plays the main role in the development and maintenance of eosinophilic inflammation, primarily in patients with non-allergic phenotype of T2 asthma. Conversely, in patients with an allergic asthma, results indicate the secondary role of PM.

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The key part in the induction of eosinophilic inflammation in this case, clearly, belongs to allergens.

### ADDITIONAL INFORMATION

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