Chapter

Fine Particles in the Ambient Air as a Risk Factor of Bronchial Asthma in Adults

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Abstract

Air pollution with suspended particles and gaseous substances is assumed to be a possible risk factor for bronchial asthma. Bronchial asthma (BA) is one of the most common chronic non-communicable diseases in children and adults, characterized by variable respiratory symptoms and airflow limitation. Asthma is a heterogeneous disease with different underlying disease processes. The most common asthma phenotypes are allergic and non-allergic asthma, differing in the presence of atopy, the type of airway inflammation, responses to inhaled corticosteroid treatment. Meta-analyses, including cohort studies, support the role of fine particles in asthma in children. The question of whether the incidence of asthma in adults is associated with exposure to ambient particulate matter remains open. The chapter describes the effect of fine particles in the ambient air on the formation, course, and underlying mechanisms of different phenotype of bronchial asthma in adults. The role of ambient fine particles in the development of the eosinophilic non-allergic phenotype of bronchial asthma in adults (18–65 years old) has been proven. The hypothesis about different underlying mechanisms in response to exposure to particulate matter for various phenotypes of bronchial asthma was confirmed.

Keywords: bronchial asthma, asthma phenotypes, T2-endotype, fine particles, ambient air, epidemiological studies, adults

1. Introduction

Epidemiological studies from around the world indicate that particulate matter poses a serious health threat to public health [1]. Air pollution with suspended particles and gaseous substances is assumed to be a possible risk factor for bronchial asthma [2–4]. Bronchial asthma (BA) is one of the most common chronic non-communicable diseases in children and adults, characterized by variable respiratory symptoms and airflow limitation [5]. The global prevalence of physician-diagnosed asthma in adults is 4.3% (95% CI: 4.2%, 4.4%), with large differences between

countries [6]. Asthma is a heterogeneous disease with different underlying disease processes. Recognizable clusters of demographic, clinical, and/or pathophysiological characteristics are often called as asthma phenotypes [4]. Some of the most common are allergic and non-allergic asthma, differing in the presence of atopy, the type of airway inflammation, responses to inhaled corticosteroid treatment. Later, the term "endotype" was introduced as a conceptual basis for new ideas about the molecular heterogeneity of bronchial asthma [7], and T2- and non-T2-endotypes have now been described. Meta-analyses, including cohort studies, support the role of fine particles in asthma in children [8–11]. The question of whether the incidence of asthma in adults is associated with exposure to ambient particulate matter (PM) remains open: there are not enough studies, and the available data are contradictory—the relative risks were about 1.0 and, in most studies, did not reach a critical level of statistical significance [12–17]. Besides, adult asthma, unlike asthma in children, is associated with other risk factors and is known for its female predominance, uncommon remission, and unusual mortality [18]. The chapter describes the current literature data, as well as our study on the effect of fine particles in the ambient air on the formation, course, and possible underlying mechanisms of atopic allergic and eosinophilic non-allergic phenotypes of the T2-endotype of bronchial asthma in adults (18–65 years old).

Bronchial asthma is a heterogeneous disease characterized by the chronic inflammation of the airways [6]. The known variants of the combination of demographic, clinical, and/or pathophysiological characteristics are often called "bronchial asthma phenotypes" [6]. Several studies have shown that air pollution with PM increases the risk of bronchial asthma exacerbations and frequency of hospitalizations [2, 3, 19, 20] and worsens the quality of life of patients with asthma [21]. Meanwhile, the role of PM in the onset of bronchial asthma in adults is still open [22].

The earliest study reporting an association between long-term exposure to air pollution and the incidence of bronchial asthma described a cohort of non-smoking Seventh-day Adventists in California, USA [12]. Considering gender, age, education, smoking, and gaseous pollutants (ozone and sulfur dioxide) as confounders, no association was found between new cases of bronchial asthma and PM10 in the ambient air.

A Swiss cohort study with an 11-year follow-up showed that the incidence of bronchial asthma among non-smokers was associated with an increase in PM10 concentrations: hazard ratio 1.30 (95% CI: 1.05, 1.61) per 1 μg/m^3 of PM10, not being changed when adjusted by education, occupational exposure, secondhand smoking, asthma or allergies in parents, exposure to other pollutants, proximity to roads with heavy traffic, and functional state of the lungs [13].

A meta-analysis of the incidence of bronchial asthma among the adult population in six prospective cohorts followed up within the ESCAPE study revealed a positive but insignificant relationship between new cases of bronchial asthma and average annual concentrations of PM10 and PM2.5: odds ratio 1.04 (95% CI: 0.88, 1.23) and 1.04 (95% CI: 0.88, 1.23) by 10 μg/m^3 PM10 and 5 μg/m^3 PM2.5, respectively. The models included PM concentrations, as well as such confounders as gender, age, education, body mass index, smoking, and clinical aspects of BA [14]. Similar results were obtained in a cohort of women living in the USA (follow-up period 2008–2012), where the odds ratio for new cases of bronchial asthma, adjusted by age, education, body mass index, consumption of dietary fiber, smoking, and occupational hazards, was 1.20 (95% CI: 0.99, 1.46) for an increase in PM2.5 concentrations by 3.6 μg/m^3 (interquartile range) [15].

In older age groups, a 2-year increase in PM2.5 by 10 μg/m^3 was associated with an increased risk of bronchial asthma by 2.24% (95% CI: 0.93%, 5.38%) in people aged >44 years [16], a 3-year increase in the average annual concentration of PM2.5 by 10 μg/m^3 led to an increase in the bronchial asthma incidence by 9% (95% CI: 4%, 14%) among elderly people (65+) [17]. Similar results were reported by [23] for low- and middle-income countries (China, India, Ghana, Mexico, Russia, and South Africa): 5.12% of the asthma cases in the study population over 50 years of age (95% CI: 1.44%, 9.23%) could be attributed to long-term exposure to PM2.5.

The phenotypic heterogeneity of bronchial asthma was investigated by a cluster analysis of well-characterized patients, grouping them into 4–5 phenotypic clusters, considering age, gender, lung function, medical aid need, and body mass index [24, 25]. To date, the T2 and non-T2 asthma endotypes, defined as "a disease subtype that is determined by a separate functional or pathological biological mechanism" [7], have been described. T2-endotype is characterized by a high level of type 2 inflammatory response in the airways [3, 7] and more severe course [6]. The molecular mechanisms of the non-T2-endotype are under investigation [3, 7, 26]. Considering different asthma phenotypes and endotypes when studying health effects of ambient particles was not regarded in previous epidemiological studies, but several authors hypothesized that the bronchial asthma linked to PM might be described as a separate phenotype, and its initial mechanisms could include damage to the airway epithelium, T2- as well as T17-mediated responses [27, 28].

The issue of the relationship between bronchial asthma and separate fractions of PM in the ambient air is insufficiently studied [2, 3]. There are also no convincing data on the effects of ambient particles with different chemical composition or origin. There is some information about the role of the oxidizing potential, which depends on the chemical composition of suspended particles. As discussed above, reactive oxygen species induced by particulate matter are regarded as an important mediator of their toxicity. The oxidation potential of PM2.5 taken from the atmospheric air of Paris was increased in the presence of metals such as copper and zinc, as well as polycyclic aromatic hydrocarbons and soluble organic compounds in PM [29]. The effects of fine particulate matter were enhanced by concomitant exposure to particulate matter and bacterial endotoxins in residential air: for emergency medical visits due to asthma exacerbations in the last 12 months, the odds ratio for comparing the subgroup with high exposures to PM2.5 and endotoxin and the subgroup with low levels of both pollutants was 5.01 (95% CI: 2.54, 9.87) [30]. Similar findings were shown in a recent Japanese study [31]. Combined exposure to PM10 and bacterial endotoxin near livestock farms was associated with the higher prevalence of bronchial asthma [32]. Thus, this line of research also deserves attention.

2. Material and methods

The research aim was to study the effect of fine particles in the ambient air on the formation, course, and underlying mechanisms of atopic allergic and eosinophilic non-allergic phenotypes of the T2-endotype of bronchial asthma in adults (18–65 years old).

The study included the following parts: (1) a case-control study, (2) a biomarker study as a part of the case-control study, (3) an epidemiological study of ecological type based on geoinformatics approach with a retrospective analysis of data on environmental pollution and population health.

For the case-control study, patients with bronchial asthma were selected while seeking medical help ("cases"), and the comparison group was selected from among those who did not suffer from bronchial asthma ("controls"). The groups were formed based on inclusion/exclusion criteria and comparison criteria, supplemented by the collection of information about potential confounders. The probable T2-endotype of bronchial asthma was determined by the absolute number of eosinophils in the blood (≥150 cells/μl). A total of 156 patients with bronchial asthma were examined, of which 82 patients were selected in the "cases" group (40 patients with an allergic phenotype, 42 patients with an eosinophilic non-allergic phenotype of bronchial asthma). The inclusion criteria for the "cases" group were: (1) age from 18 to 65 years; (2) an established clinical diagnosis of an allergic or non-allergic phenotype of the T2-endotype of bronchial asthma; (3) informed consent to participate in the study. The exclusion criterion for the group of "cases" was the allergen-specific immunotherapy or biological therapy at the time of examination, or information in the medical records about the use of such therapy earlier. The comparison group (48 people) was selected according to the following comparison criteria: (1) compliance of the distribution of "controls" with the distribution of "cases" by sex, age (in the range up to 10 years), body mass index (up to 23.9; 24–29.9; 30 and more kg/m^2), level of education (secondary; college; high); (2) exclusion of the diagnosis of bronchial asthma and other chronic respiratory diseases; (3) informed consent to participate in the study. For individuals included in the study, the average and maximal annual concentrations of PM2.5 and PM10 fractions averaged over the period 2014–2020 were determined, considering measurements at monitoring points closest to the areas of residence. For measurements, the DustTrak™ II Aerosol Monitor 8530 (TSI Inc., USA) was used. Additionally, in the areas of residence, ambient air sampling was carried out by the 8-stage impactor MOUDI 100NR (TSI, USA) to study the elemental composition of the aerosol (SEM, energy dispersive spectroscopy) and the contamination by bacterial endotoxin (kinetic LAL test). Besides, air samples were taken for microbiological examination by classical cultural methods and using MALDI-TOF spectrometry. Using the multiple logistic regression, adjusted odds ratios were calculated with 95% confidence intervals for allergic and eosinophilic non-allergic phenotypes of bronchial asthma in comparison with the comparison group, depending on the levels of exposure variables characterizing air pollution with particulate matter.

For the biomarker study, as a part of the case-control study, 61 patients with T2-endotype of BA were examined (34 patients with an allergic phenotype, 27 patients with a non-allergic phenotype of the disease). The comparison group consisted of 30 people without symptoms of asthma and other allergic diseases who were matched by gender, age, body mass index (BMI), profession (position). All patients with BA and persons from the comparison group underwent blood sampling to determine biological markers of various types of inflammation: alarmins (TSLP, IL-33, IL-25), T2-cytokines (IL-4, IL-5, IL-13), DPP4, and also—in order to clarify the involvement of non-T2-mechanisms—IL-6, TGF-beta1, IL-17A, IL-1beta; multiplex analysis using xMAP Luminex technology was applied. The blood serum level of periostin was determined by ELISA. The study design was supplemented by whole blood sampling from the same study participants and subsequent analysis of the expression of genes encoding certain cytokines: IL-4, IL-5, IL-6, TGF-beta1, IL-17A, IL-1beta, IL-25, IL-33. In the biomarker study, the calculated masses of aerosol particles deposited in different parts of the lungs were used as additional exposure characteristics. To estimate the masses of aerosol particles deposited in the lungs, an original method to reconstruct the aerosol particle size distribution function using actual PM2.5 and

PM10 concentrations under the assumption of a lognormal distribution characteristic of atmospheric aerosols was developed. To assess the relationship between serum levels of cytokines and concentrations of PM2.5 and PM10 fractions, multiple linear regression was used, gender, age, body mass index (BMI) being included as confounders in the regression models. In addition, a data aggregation method based on the principal component analysis was applied.

To study the relationship between ambient air pollution with particulate matter and bronchial asthma in adults (18–65 years old), a retrospective analysis of the incidence of bronchial asthma (ICD-10 codes J45.0, J45.1, J45.8) for 2014–2020 was carried out. BA incidence was determined for the population of Kazan in and for persons living in the areas at up to 1 km from the monitoring points as well. The database of social and hygienic monitoring and the regional medical information system "Electronic Health of the Republic of Tatarstan" were used. The absolute risks of bronchial asthma in adults (18–65 years old), as well as the absolute risks of BA phenotypes, were calculated. Using linear mixed models based on the Poisson or the negative binomial distribution, the dependences of the absolute risks of BA phenotypes on the PM fraction concentrations were studied.

3. Results and discussions

3.1 Case-control and biomarker studies on the effect of fine particles in the ambient air on atopic allergic and eosinophilic non-allergic phenotypes of the T2-endotype of bronchial asthma in adults

The results of the "case-control" study [33] indicate the role of fine particulate matter in the ambient air in the development of bronchial asthma in adults (18–65 years old), and also suggest the involvement of various underlying mechanisms in the formation of the clinical picture of eosinophilic non-allergic and allergic phenotypes of bronchial asthma: in non-allergic asthma —the reaction of the epithelium to the deposition of particles in the respiratory tract, and in allergic asthma—a reaction to the composition of the aerosol. An increased risk of the eosinophilic non-allergic phenotype of bronchial asthma and its more severe course were noted at higher average annual concentrations of the PM2.5 fraction averaged over 2014–2020. The concentration of bacterial endotoxin had a statistically significant effect on the odds of developing an BA allergic phenotype and was associated with a more severe course of the disease; the odds of an allergic phenotype also increased with an increase of carbon in the composition of the aerosol.

The medians of the average and maximal annual concentrations of PM2.5 fraction averaged over the period 2014–2020 in the areas of residence of patients with bronchial asthma exceeded the maximum allowable levels applied in the Russian Federation (25 and 160 μg/m^3) by 1.2 and 1.1 times, respectively. For the PM10 fraction, the average annual concentration exceeded the maximum allowable level (40 μg/m^3) by 2.3 times, and the maximal annual concentration exceeded the maximum allowable level (300 μg/m^3) by 1.2 times. In the comparison group, the levels of fine PM fractions did not exceed exposure limits, except for the maximum annual concentrations. The chemical composition of the fine PM fractions was represented mainly by carbon (from 36.9–100%) with minor metallic impurities. Contamination with bacterial lipopolysaccharides ranged from 0.0139 to 0.0694 EU/m^3. Microbiological examination of ambient air samples (in the areas of residence of 45 patients with

bronchial asthma and 45 persons from the comparison group) showed the growth of bacteria and fungi. Differences in pollution levels between both groups of patients and the comparison group were statistically significant, indicating a higher level of pollution by fine particles, as well as a higher content of carbon and bacterial endotoxin in the areas of residence of patients with bronchial asthma; no differences were found in the total number of microbes.

The study showed the important role of the PM2.5 fraction for patients with eosinophilic non-allergic phenotype of bronchial asthma (**Table 1**): the risk of this bronchial phenotype in adults statistically significantly increases with an increment of the average annual concentration averaged over the period 2014–2020 by 10 μg/m^3—the odds ratio adjusted by confounders (heredity for asthma, age, concentration of bacterial endotoxin

Exposure parameter	Adjusted odds ratios (95% confidence intervals)	
	Non-allergic bronchial asthma	Allergic bronchial asthma
PM2.5 average annual concentration averaged over 2014–2020 years. (monitoring data for residential address); increment – 1 μg/m^3.	4.76 (95% CI: 1.67, 24.40)[1]	OR 4.52 (95% CI 0.91, 55.68)[3]
PM2.5 maximal annual concentration averaged over 2014–2020 yrs. (monitoring data for residential address), increment – 10 μg/m^3.	1.17 (95% CI: 1.00, 1.42)[2]	1.13 (95% CI: 0.88, 1.58)[3]
PM10 average annual concentration averaged over 2014–2020 years. (monitoring data for residential address), increment – 1 μg/m^3.	1.71 (95% CI: 1.23, 2.92)[1]	1.84 (95% CI: 0.95, 5.27)[3]
PM10 maximal annual concentration averaged over 2014–2020 years. (monitoring data for residential address), increment – 10 μg/m^3.	1.12 (95% CI: 1.02, 1.25)[2]	1.11 (95% CI: 0.95, 1.35)[3]
Fraction of carbon in the aerosol composition. Size fraction <3.2 μm (impactor. Measured at the address of residence), increment – 1%.	1.16 (95% CI: 0.98, 1.47)[2]	1.45 (95% CI: 1.02, 2.52)[3]
Bacterial endotoxin in the size fraction <3.2 μm (impactor. Measured at the address of residence), increment – 0.01 EU/m^3.	2.03 (95% CI: 0.81, 6.47)[2]	1.12 (95% CI: 0.94, 1.42)[3]
Bacterial endotoxin in the size fraction 3.2–18 μm (impactor, measured at the address of residence), increment – 0.01 EU/m^3.	3.19 (95% CI: 1.61, 8.51)[2]	1.32 (95% CI: 1.08, 2.00)[3]
Passive smoking, increment – 1 hour/week.	1.90 (95% CI: 0.69, 8.68)[2]	3.24 (95% CI: 1.28, 14.79)[2]

[1]*Confounders: age, heredity for BA, the concentration of bacterial endotoxin in the size fraction <3.2 μm.*
[2]*Confounders: age, heredity for BA.*
[3]*Confounders: heredity for BA, passive smoking.*

Table 1.
Effect of air pollution with particulate matter on the risk of non-allergic and allergic phenotypes of bronchial asthma (case–control study).

in the fraction with a particle size of less than 3.2 μg) was 4.76 (95% CI: 1.67, 24.40); odds ratios characterizing the effect of the PM10 fraction were below 2.0. No statistically significant relationship was found for the allergic phenotype of bronchial asthma and mass concentrations of fine particles in the ambient air. At the same time, the role of bacterial and chemical air pollution in allergic asthma formation was shown: the adjusted odds ratio for an increment of passive smoking duration by 1 hour was 3.24 (95% CI: 1.28, 14.79); for an increment of bacterial endotoxin found in the fraction with deposition in the tracheobronchial region of the respiratory system (3.2–18 μm) by 0.01 EU/m3–1.32 (95% CI: 1.08, 2.00); for an increment of carbon in the chemical composition of the aerosol by 1%—1.45 (95% CI: 1.02, 2.52).

Eosinophilic non-allergic bronchial asthma was better controlled at lower average annual concentrations of the PM2.5 fraction (**Figure** 1), while in the case of allergic asthma, bacterial contamination of the aerosol mattered (**Figure 2**), which may

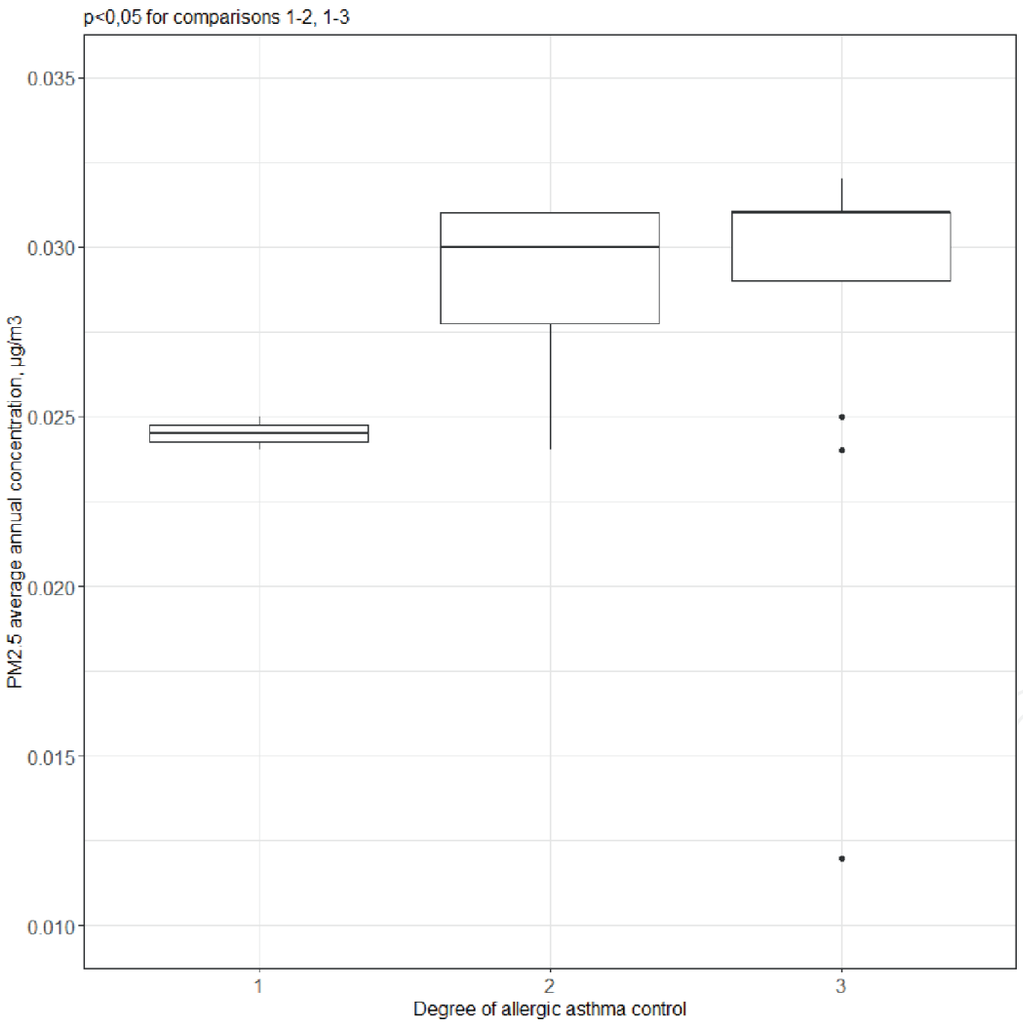

Figure 1.
*PM2.5 average annual concentration (monitoring data for residential zones averaged over the period 2014–2020 in the city of Kazan) for patients with non-allergic and allergic bronchial asthma, depending on the degree of bronchial asthma control. Model 1: PM2.5Avr (mg/m³) ~ b1i * Degree of control of non-allergic asthma (1 – controlled, 2 – partially controlled, 3 – uncontrolled, Asthma Control Test) + b2 * Age (years) + b3 * Heredity for asthma (no/yes) + b4 * BMI (kg/m²); b1,1–2 = 0.012, p = 0.09, b1,1–3 = 0.013, p = 0.02. Model 2: PM2.5Avr (mg/m³) ~ b1i * Degree of control of allergic asthma (1 – controlled, 2 – partially controlled, 3 – uncontrolled) + b2 * Age (number of years) + b3 * Heredity for asthma (no/yes) + b4 * BMI (kg/m²) + b5 * Passive smoking (hours/week); p > 0.1 for coefficients b1(1–2) and b1(1–3).*

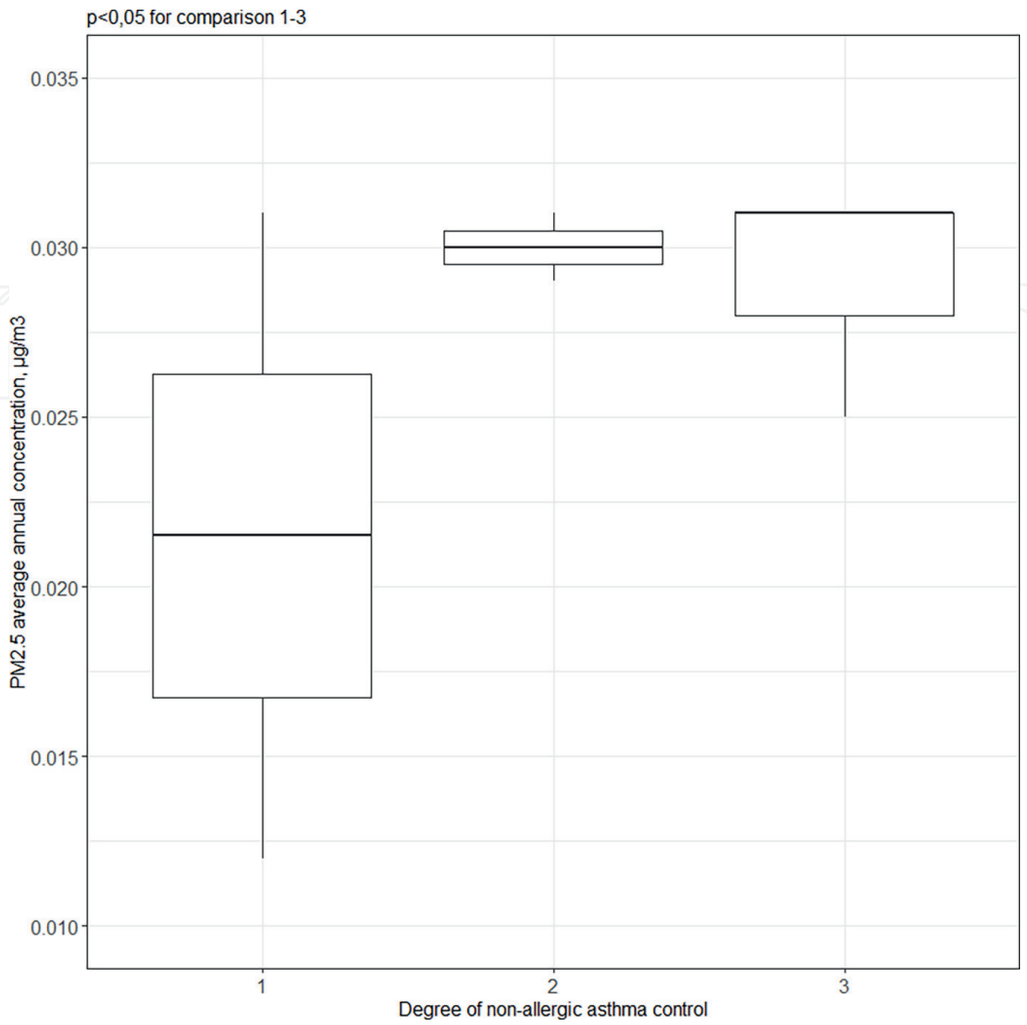

Figure 2.
*Bacterial endotoxin (BE) in the 3.2–18 μm size fraction of ambient particles at the residential zones of patients with non-allergic and allergic bronchial asthma, depending on the degree of disease control. Model 1: BE (EU/m³) ~ b1i * degree of control of non-allergic asthma (1 – controlled, 2 – partially controlled, 3 – uncontrolled) + b2 * age (years) + b3 * heredity for asthma (no/yes) + b4 * BMI (kg/m²); p > 0.1 for coefficients b1,1–2 and b1,1–3. Model 2: BE (EU/m³) ~ b1i * degree of control of allergic asthma (1 – controlled, 2 – partially controlled, 3 – uncontrolled) + b2 * age (years) + b3 * heredity for asthma (no/yes) + b4 * BMI (kg/m²); b1(1–2) = 0.020, p = 0.04, b1(1–3) = 0.027, p = 0.01.*

indicate the importance of various physicochemical characteristics of the suspended solids aerosol in pathogenesis and influence on the clinical course of different phenotypes of the T2-endotype of bronchial asthma.

The data obtained indicate the presence of eosinophilic inflammation in patients of both groups (allergic and eosinophilic non-allergic bronchial asthma) [34]. For patients with eosinophilic non-allergic asthma, an increase in the production of epithelial cytokines IL-33 and IL-25 (alarmins), as well as IL-13 and DPP4, being depended on average annual concentrations of PM2.5 and PM10 averaged over the period 2014–2020. For patients with allergic asthma, similar dependencies were not found. Despite the presence of common signs of T2-type eosinophilic inflammation, the immune patterns of atopic allergic and eosinophilic non-allergic phenotypes of bronchial asthma differed significantly: with a comparable high level of the absolute number of eosinophils in the blood, patients with an allergic phenotype showed pronounced features of the T2-endotype, while with a non-allergic phenotype, there

was a lower intensity of T2-type inflammation (IL-4) and an increased expression of genes of cytokines associated with a T17-type response (IL-6, TGF-beta1), being related to the mass of the deposited aerosol. These findings are important for the choice of therapy in different phenotypes of bronchial asthma.

3.2 Ambient particulate matter and bronchial asthma: Results of the epidemiological study based on a geospatial approach

In the epidemiological study based on a geospatial approach [35], a statistically significant increase in the incidence of bronchial asthma was revealed with an increase of 0.09 per 100 annually (growth rate of 17.6% per year). The increase in the incidence of bronchial asthma was observed mainly due to the non-allergic phenotype—by 0.011 per 100 population annually, and the mixed phenotype—by 0.034 per 100 population annually; the increase in the incidence of allergic asthma (by 0.028 per 100 population annually) did not reach statistical significance. An increase in the maximal annual concentrations of PM2.5 by 10 μg/m^3 increased the absolute risk of non-allergic bronchial asthma by 0.066 per 100 people aged 18–65 years ($p < 0.05$). For other phenotypes of bronchial asthma (allergic asthma, mixed asthma), no statistically significant relationships with mass concentrations and deposited doses were found.

4. Conclusions

As a result of the described studies, the role of ambient fine particles in the development of the eosinophilic non-allergic phenotype of bronchial asthma in adults (18–65 years old) has been proven. The hypothesis about different underlying mechanisms in response to exposure to particulate matter for various phenotypes of bronchial asthma was confirmed. Differences in the immune patterns of the allergic and eosinophilic non-allergic phenotypes of bronchial asthma were established. With a comparable high level of the absolute number of eosinophils in the blood, pronounced features of the T2-endotype were observed in patients with an allergic phenotype. With a non-allergic phenotype, there was a lesser intensity of T2-type inflammation, as well as increased expression of genes of T17-type cytokines, being related to the mass of the deposited aerosol. It has been shown that the estimation of bacterial endotoxin concentrations could be recommended as the most preferable method to characterize the microbiological contamination of atmospheric aerosol in epidemiological studies. Approaches to decision-making in the development of population programs for the prevention of bronchial asthma and in the selection of personalized recommendations for patients with different phenotypes of bronchial asthma were determined. Currently, the treatment of bronchial asthma is based on the use of drugs that can suppress the activity of certain cytokines. The data obtained in the study might become a starting point for the development of new personalized approaches to the treatment and secondary prevention of bronchial asthma associated with air pollution by fine aerosols.

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Conflict of interest

The authors declare no conflict of interest.

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