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Health risks of air pollution with fine particulate matter

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Abstract

The review presents up-to-date information on the health effects of ambient fine particulate matter, obtained in large cohort epidemiological studies, as well as in meta-analysis of pooled data. In addition, it summarizes the current data on the potential pathological mechanisms and existing monitoring systems. The literature search used the Scopus, PubMed, Russian Science Citation Index databases for 1990–2020. The results of epidemiological studies carried out in different countries indicate that fine particles in ambient air pose a serious threat to health. Scientific publications assessing the health impact of particulate matter show a wide range of adverse effects — from the increasing incidence of upper and lower respiratory tract diseases, including exacerbations of bronchial asthma, pneumonia, chronic obstructive pulmonary disease, to a high incidence of myocardial infarction, strokes, diabetes mellitus type 2, as well as an increase in overall mortality from natural causes, mainly mortality from respiratory diseases, cardiovascular and cerebrovascular diseases, lung cancer. The effects of short-term exposures are described in more detail, while the effects of long-term exposure to fine particles are not well understood. Potential mechanisms of the harmful effects of fine particulate matter include oxidative stress, inflammatory reactions, disorders of autonomic regulation and heart rhythm, fine particles translocation through the alveolar barrier into the vascular bed with endothelial damage and thrombus formation, and genotoxicity. Ambient fine particulate matter is a manageable risk factor, and reductions in air pollution will have a significant impact on public health outcomes.

Keywords: ambient air, public health, particulate matter, PM2.5, PM10, morbidity, mortality, health risks.

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Introduction. Air pollution with particulate matter (PM) is a serious global problem. PM is defined as "a widespread air pollutant comprising a mixture of solid and liquid particles in the air in suspension" [1] and "a complex mixture of extremely small particles and liquid droplets, consisting of acids, organic chemicals, metals, and soil or dust particles" [2]. Particles can be either directly emitted into the atmospheric air (primary particles) or formed in the atmosphere from gaseous precursors (secondary particles).

The most widespread chemical components of PM are sulfates, nitrates, ammonium ions, other inorganic ions such as sodium, potassium, calcium, magnesium, and chloride, as well as organic and elemental carbon, and mineral particles, including those containing silicon compounds, particle-bound water, metals (including iron, copper, zinc, manganese, cadmium, nickel, titanium, and vanadium), and polycyclic aromatic hydrocarbons [1]. PM also contains biological components such as allergens and microorganisms [1].

Indicators that are commonly used to characterize PM content in the air and are important for health include the mass concentrations of all airborne particles, mass concentrations of particles with a diameter of less than 10 μm (PM10), and particles with a diameter of less than 2.5 μm (PM2.5). The ratio of the amount or mass of particles of various sizes in the air is determined by a complex set of factors and can vary over a very wide range. There is no single conversion factor between PM2.5 and PM10 as well as other aerosol size fractions. According to the Regional Office for Europe of the World Health Organization, in some European urban settlements, the weight of PM2.5 is 50%–70% of the mass of PM10 in the air [1]. As part of the PM2.5 fraction, ultrafine particles with a diameter of less than 0.1 μm are also identified [3].

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PM represents a mixture of physical and chemical characteristics depending on the location, meteorological parameters, and many other factors. This mixture has components with significantly different mechanisms of action. According to individual authors, on the example of some European countries, secondary inorganic aerosol (ammonium ions, nitrates, and sulfates) prevails in the total PM fraction [4], amounting to 465% ± 13% for PM10 and 56% ± 6% for PM2.5. Finely dispersed secondary organic aerosol from biogenic precursors (e.g., biogenic terpenes) predominates in the organic fraction of PM aerosols in summer; organic carbon also provides a large contribution [4]. In winter, secondary organic aerosol is formed as a result of the oxidation of gaseous precursors of anthropogenic origin, mainly the products of fossil fuel combustion [4].

According to another study, PM2.5 has seven most common chemical components, which in total account for at least 79%–85% of the mass of PM2.5, namely, ammonium ions, elemental and organic carbon, nitrates, silicon, sodium, and sulfates [5]. Strong seasonal and geographical fluctuations in the chemical composition of PM2.5 were revealed.

The main sources of PM [1] are internal combustion engines (both diesel and gasoline), combustible solid fuels (coal, brown coal, heavy oil, and biomass), industrial enterprises (construction, mining, production of cement, ceramics and bricks, smelting production, etc.), and erosion of the road surface because of traffic and abrasion of brake pads and tires.

Agriculture is the main source of ammonium ions. A study of sources of PM2.5 in urban and rural areas of the Midwest (USA) revealed that for each site, 7–9 possible contamination factors were identified, namely, secondary sulfates (which accounted for 29%–30% of PM2.5), secondary nitrates (17%–24%), combustion products of biomass (9%–21%), gasoline (6%–16%), and diesel fuel (3%–9%), as well as dust (6%–11%), industrial emissions (0.4%–5%), and reagents for anti-icing treatment of road surfaces (2%–6%). The contribution of gasoline engines to air pollution with PM2.5 was 1.14 times and that of diesel engines was 2.3 times higher in urban than in rural areas [6].

The important role of anthropogenic sources of PM in the atmospheric air was confirmed by data on the determination of air pollution in 50 large cities of the world during the quarantine measures introduced in 2020 because of the new coronavirus infection. Particularly, in the three most polluted capitals, Dhaka, Kampala, and Delhi, during the lockdown period, the PM2.5 concentrations decreased by 14%, 35%, and 40%, respectively [7].

The results of epidemiological studies conducted in different countries indicate that PM poses a serious threat to health. Scientific publications evaluating the effect of PM on health demonstrate a wide range of adverse effects, from an increase in the incidence of upper and lower respiratory tract diseases [8], including exacerbations of bronchial asthma [9], pneumonia [8], and chronic obstructive pulmonary disease (COPD) [10], to a high incidence of coronary disorders (myocardial infarction and acute and subacute forms of ischemic heart disease) [11] and stroke [12] and increased rates of mortality from respiratory diseases, cardiovascular and cerebrovascular diseases [13–17], and lung cancer [18]. The effects of short-term exposure are described in more detail, while the effects of long-term exposure to PM remain underinvestigated.

An important circumstance that determines the particular urgency of the problem is that the PM content in the air is a manageable risk factor, and a decrease in pollution levels will have a significant effect on public health indicators.

This study aimed to analyze and provide generalize information on the effects of atmospheric air pollution with fine PM on the population health, obtained in the course of major cohort epidemiological studies and during meta-analyses of pooled samples. Modern information on the alleged mechanisms of the pathological action of PM and data on existing monitoring systems are also presented. In preparing the review, relevant literatures from Scopus, PubMed, and Russian Science Citation Index databases were searched for the period from 1990 to 2021.

PM and mortality. In the early 1990s, Dockery et al. [13, 19] in the pioneering Harvard Six Cities Study showed that long-term exposure to PM increases the overall mortality rate from natural causes and mortality from cardiovascular diseases and lung cancer. A prospective monitoring participated by 8,111 people aged 25–74 years started in 1975–1977, included three control points (1989–1991 [13], 1998 [20], and 2009 [21]), and became the most important milestone in the study of the effect of PM on health. Among other things, the study revealed that atmospheric air pollution with PM is a manageable risk factor, since the decrease in the average annual concentrations of PM2.5 between the periods of 1979–1989 and 1990–1998 led to a significant reduction in mortality from all natural causes with relative risk of 0.73 [95% confidence interval (CI) 0.57–0.95] [20].

The Global Burden of Disease Study 2015 revealed that PM2.5 exposure resulted in 4.2 million deaths and 103.1 million Disability Adjusted Life Years (DALYs) per year worldwide, which accoun-

ted for 7.6% of the total number of deaths and 4.2% of DALYs [22].

Atmospheric air pollution with PM is relevant for developing Asian countries. India and China, the two largest Asian countries, have the worst air quality in the world [23].

A systematic review and meta-analysis of 59 studies on PM pollution in 127 major cities in mainland China [24] showed that with a short-term increase in PM10 concentration of 10 μg/m^3, the daily mortality rate from all natural causes increased by 0.36% (95% CI 0.26%–0.46%), from cardiovascular diseases increased by 0.36% (95% CI 0.24%–0.49%), and from respiratory diseases increased by 0.42% (95% CI 0.28%–0.55%). With an increase in PM2.5 concentration of 10 μg/m^3, the daily mortality rate from all natural causes increased by 0.4% (95% CI 0.35–0.91%), from cardiovascular diseases increased by 0.63% (95% CI 0.35%–0.91%), and from respiratory diseases increased by 0.75% (95% CI 0.39%–1.11%). In assessing chronic exposure to PM10, each increase in PM10 concentration of 10 μg/m^3 led to an increase in mortality risk by 23%–67%.

In the European Cohort Study of Air Pollution Effects (ESCAPE), a large prospective study, based on data from 22 European cohorts (total study population, n = 367,251; mean follow-up period, 13.9 years) [16], a significantly increased risk factor of 1.07 was registered for PM2.5 (95% CI 1.02–1.13), which meant an increase in overall mortality of 7% with an increase in the average annual concentration of PM2.5 of 5 μg/m^3. The risk ratio for PM2.5 remained significantly elevated even though the analysis was limited to participants exposed to PM at concentrations below the EU annual average limit values, with a risk ratio of 1.06 (95% CI 1.00–1.12) at PM2.5 concentrations of <25 μg/m^3 and 1.07 (95% CI 1.01–1.13) at PM2.5 concentrations of <20 μg/m^3.

Epidemiological studies have also suggested a relationship between stroke mortality rate and long-term exposure to air pollution with PM. A meta-analysis of 20 studies, including 14 cohort studies and six studies that used data from medical registries, involving more than 10 million people, showed that the pooled risk coefficient of stroke mortality was 1.080 (95% CI 0.992–1.177) with an increase in the average annual PM10 concentration for every 10 μg/m^3 [12]. The role of PM2.5 was demonstrated in a subsample that included only Europe and North America, as the risk factor for death from stroke was 1.125 (95% CI 1.007–1.256) with an increase in the average annual concentration of PM2.5 for every 5 μg/m^3 [12].

The combined effect of high temperatures and air pollution, taking into account the consequences of abnormally hot weather in the summer of 2010 in Moscow, unprecedented in the entire history of meteorological measurements in the city, caused a significant increase in deaths of Moscow residents. Thus, the relative increase in mortality from all natural causes for every 10 μg/m^3 increase in daily average concentrations of total PM amounted to 0.47% (95% CI 0.31–0.63) [25].

Based on the data of the Russian meteorological service on the content of total PM in the atmospheric air of Russian cities, using calculated coefficients for PM10 and PM2.5 (based on the assumptions made by the authors of the study that the share of PM10 fraction in total PM is approximately 55% and PM2.5 amount to approximately 65% in PM10 fraction), the additional mortality rates of the population in 219 Russian cities were determined, amounting to 67.9 thousand cases per year when exposed to PM10 and 88.2 thousand cases per year taking into account the effect of PM2.5 [26].

PM and cardiovascular diseases. Recently, the number of studies on the effect of PM on indicators of cardiovascular morbidity has increased. In 2007, one of the first prospective studies on this problem (Women's Health Initiative study) showed that long-term exposure to PM not only increases overall and cardiovascular mortality rates, but had been demonstrated at the time by the Harvard Six Cities Study [13, 20] to also increase the risk of non-fatal heart diseases. An increase in the average annual concentration of PM2.5 of 10 μg/m^3 was associated with an increase in the risk of cardiovascular events such as coronary heart disease, myocardial infarction, stroke, and other cerebrovascular diseases by 24% with a hazard ratio of 1.24 (95% CI 1.09–1.41) [27, 28].

In a later prospective follow-up of 11 European cohorts from the ESCAPE study, with an increase in the average annual concentration of PM2.5 of 5 μg/m^3, the risk of myocardial infarction and unstable angina pectoris increased by 13% (adjusted for sociodemographic and behavioral co-founders, hazard ratio 1.13; 95% CI 0.98–1.3) and by 12% with an increase in the average annual concentration of PM10 of 10 μg/m^3 (hazard ratio 1.12; 95% CI 1.01–1.25) [11]. Moreover, the concentrations of finely dispersed PM were lower than the standards established in Europe.

The effect of polluted air on the heart failure rate was also confirmed; thus, the risk coefficient, adjusted for gender, age, body mass index, and concentration of the secondary pollutant (nitrogen oxides) was 1.15 (95% CI 1.02–1.30) [29].

In the above meta-analysis [12], the pooled risk factor for new stroke cases was 1.064 (95% CI 1.021–1.109) for an increase in PM2.5 of 5 μg/m^3

in a subsample of only Europe and North America. A meta-analysis did not reveal a significant association of long-term exposure to PM2.5 or PM10 with arterial hypertension; however, for short-term exposures, the generalized relative risks were significantly increased, i.e., the relative risk was 1.10 (95% CI 1.06–1.13) for PM2.5 and 1.06 (95% CI 1.02–1.10) for PM10 [30]. The stratified analysis showed stronger associations for men, Asians, North Americans, and regions with higher levels of air pollution.

The mechanisms by which PM damages the cardiovascular system are not fully understood. Nowadays, several pathogenetic processes have been proposed, which may be responsible for adverse cardiovascular outcomes associated with PM exposure, namely, oxidative stress and release of mediators in the lung tissue, followed by systemic inflammation, impaired autonomic regulation and heart rhythm, passage of particles through the alveolar barrier into the vascular bed with damage to the endothelium, appearance of atherosclerotic plaques, and thrombogenesis [31, 32].

In double-blind, randomized, crossover studies where participants alternately inhaled filtered air, high-concentration PM2.5 air (150 μg/m^3), ozone-enriched air, and air containing both PM2.5 and ozone, the diastolic blood pressure increased and heart rate variability decreased, dependent on the presence of only PM2.5. The authors suggested the role of such a pathogenetic mechanism as reflex (in response to irritation of the nerve endings in the epithelium of the respiratory tract) changes in autonomic regulation [33].

The Multiethnic Study of Atherosclerosis and Air Pollution (MESA Air), a major prospective study conducted in the USA, showed that long-term exposure to even low PM2.5 concentrations (average annual concentrations < 25 μg/m^3) led to the development of persistent endothelial dysfunction, and flow-mediated dilatation (vascular stress test) during ultrasound examination of the carotid arteries decreased with an increase in the average annual concentration of PM2.5 [34].

Toxicological studies with atherosclerosis simulation on apolipoprotein E knockout mice revealed that 6-month exposure to PM2.5 at a concentration corresponding to a contamination level of 15.2 μg/m^3 increased the formation of atherosclerotic plaques, altered vasomotor tone, and induced vascular inflammation [35]. Patients who are obese and diabetic were at a higher risk of developing adverse cardiovascular effects associated with PM2.5 exposure [36].

PM and COPD, bronchitis, pneumonia, and coronavirus disease 2019 (COVID-19). The airways are directly exposed to the external environment and are more vulnerable to pollutants than other body systems. Epidemiological and experimental studies have shown a close relationship between air pollution and respiratory diseases, including COPD [10, 37].

COPD is a heterogeneous disease characterized by persistent respiratory symptoms and impaired respiratory function. Morbidity and mortality from COPD are increasing every year, which leads to serious economic and social consequences. The Global Burden of Disease Study estimates that COPD has affected 174 million people globally [38]. According to the World Health Organization prognosis, COPD was to become the third leading cause of death and the fifth leading cause of disease burden worldwide in 2020 [39].

A meta-analysis showed that the generalized estimates of the relative risks of COPD were 1.006 (95% CI 1.004–1.008) and 1.008 (95% CI 1.004–1.011) for every 10 μg/m^3 PM2.5 and PM10, respectively [10]. The role of PM in the development of COPD was slightly lower than that of pollutant such as nitric oxide.

The development of oxidative stress is considered a presumptive pathogenetic mechanism of COPD under the influence of PM [40]. An increase in the production of reactive oxygen species is directly related to the oxidation of proteins, deoxyribonucleic acids (DNA), and lipids, which can directly damage the lungs or various cellular reactions because of the generation of highly reactive secondary metabolic formations [41]. Reactive oxygen species can change the extracellular matrix remodeling, induce apoptosis; disrupt cell proliferation, state of the surfactant, and antiproteinase defense; and prevent the restoration of alveoli and immune defense mechanisms in the lungs. Reactive oxygen species can also increase inflammation and induce DNA damage [42–44].

For both PM2.5 and PM10 fractions of PM, in a cohort study (n = 47,357; mean follow-up period, 5.7 years), the association of long-term exposure with the occurrence of new cases of chronic bronchitis was not proved [45]. The prevalence of chronic bronchitis was higher in the presence of PM10, and for nonsmokers, it was higher in the presence of PM2.5. Short-term exposure to PM (PM10 and PM2.5) can increase the frequency of hospitalizations for pneumonia, primarily among children, with generalized meta-relative risks of 1.02 (95% CI 1.01–1.02) and 1.02 (95% CI 1.01–1.03), respectively [46].

During the COVID-19 pandemic, it has been hypothesized that air pollution from a combination of factors such as local climate, industrializa-

tion level, and regional topography may facilitate the transmission of SARS-CoV-2 and worsen the course of COVID-19. In particular, a study conducted in Milan during the initial period of the pandemic revealed a correlation between the average daily ground level concentrations of PM and the number of new cases of COVID-19 [47]. From January 1 to April 30, 2020, for the Milan metropolitan area, very high values of the average daily concentrations of PM2.5 (87.1 ± 39.6 μg/m^3) and PM10 (35.9 ± 18.5 μg/m^3) were registered, exceeding the standard levels of 25 and 40 μg/m^3, respectively. The temporal dynamics of the daily average PM2.5 and PM10 concentrations, as well as the maximum daily PM10 concentrations, correlated with the daily number of new confirmed cases of COVID-19.

According to other researchers, the association between long-term exposure to PM2.5 at the place of residence and hospitalization for COVID-19 was dependent on the presence of pre-existing asthma or COPD [48]. In patients with COVID-19 and asthma or COPD, the risks for hospitalization increased by 62% or more, with a 10-year average PM2.5 increase of 1 μg/m^3 (odds ratio 1.62; 95% CI 1.00–2.64) and by 65% with an increase in 10-year maximum PM2.5 levels of 1 μg/m^3 (odds ratio 1.65; 95% CI 1.16–2.35). Among patients with COVID-19 without asthma or COPD, PM2.5 exposure was not associated with more frequent hospitalizations.

In a Chinese study, after adjusting for mobility of people and socioeconomic factors, the number of COVID-19 cases increased by 32.3% (95% CI 22.5%–42.4%) and 14.2% (95% CI 7.9%–20.5%) with an increase in the average annual concentrations of PM2.5 and PM10 for every 10 μg/m^3, respectively; however, when the data were stratified by population size, the association became insignificant [49]. PM2.5 can carry the SARS-CoV-2 virus on its surface [50].

The authors of the review on atmospheric air pollution and COVID-19 [51] noted that studies on this subject have some issues, such as the use of different research methods, incomplete accounting of potential co-founders, and underestimation of official data on morbidity and, to a lesser extent, mortality, which present the real situation incompletely. More research is required to strengthen the scientific evidence for the role of PM2.5 and PM10 (as well as NO_2) in the spread of COVID-19 and the resulting mortality.

PM and bronchial asthma and allergies. Bronchial asthma is a serious chronic disease of children and adults worldwide, and its prevalence has been growing over the past few decades [52]. This disease is one of the significant causes for temporary disability, hospitalization, and visits to emergency departments.

Currently, bronchial asthma is considered "a heterogeneous disease, which, as a rule, is characterized by the presence of chronic inflammation of the airways. It is determined by a history of respiratory symptoms such as sibilant rales, dyspnea, chest congestion and coughing, the severity of which changes over time, as well as variable limitation of the expiratory air flow rate" [53, p. 20]. Bronchial asthma is "a disease which development is based on various processes." The known variants of the combination of demographic, clinical, and/or pathophysiological characteristics are often called "bronchial asthma phenotypes" [53, p. 20].

Several studies have shown that air pollution with PM increases the risk of bronchial asthma exacerbations and frequency of hospitalizations [54–56] and worsens the quality of life of patients with asthma [57].

A meta-analysis of 41 studies showed that air pollution from transport increased the risk of asthma in children aged 0–18 years by 3% for every 1 μg/m^3 PM2.5 concentration increase (pooled odds ratio 1.03; 95% CI 1.01–1.05) and by 5% for every 2 μg/m^3 PM10 (pooled odds ratio 1.05; 95% CI 1.02–1.08) [58]. A later meta-analysis of 13 studies showed that air pollution with PM2.5 from transport increases the risk of asthma in children aged 0–18 years (pooled odds ratio 1.07; 95% CI 1.00–1.13) [59]. In a meta-analysis of four cohort studies, an increase in PM2.5 concentration of 10 μg/m^3 increased the risk of bronchial asthma in children by 34% (odds ratio 1.34; 95% CI 0.96–1.86) [60]. There is epidemiological evidence of a decrease in the incidence of new cases of bronchial asthma among children with a decrease in environmental pollution with PM [61].

However, the question of the etiological role of PM in the atmospheric air in the emergence of new cases of bronchial asthma in adults remains open, research is still insufficient, and existing data are contradictory.

The Adventist Health and Smog (AHSMOG) study, the earliest identified study reporting an association between long-term exposure to air pollution and the incidence of bronchial asthma evaluated a cohort of nonsmoking Seventh-day Adventists in California, USA [62]. The participants were enrolled in 1977, at age 25–87 years, with repeated studies in 1987 and 1992. The models took into account co-founders such as gender, age, education, smoking, and gaseous pollutants (ozone and sulfur dioxide). No association was found between new cases of bronchial asthma and the presence of PM10 in the ambient air.

The Study of Air Pollution and Lung Disease in Adults (SAPALDIA), a Swiss cohort study with an 11-year follow-up period, established that the incidence of bronchial asthma among nonsmokers 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, and this dependence did not change when taking into account the differences in education and occupational exposure, secondhand smoking, presence of asthma or allergies in parents, presence of other pollutants, proximity to roads with heavy traffic, and functional state of the lungs [63].

A meta-analysis of the incidence of bronchial asthma among the adult population in six prospective cohorts followed-up within the ESCAPE study for 10 years in eight European countries (participants, n = 17,909) 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) by 10 μg/m^3 and 5 μg/m^3, respectively. The model included co-founders such as gender, age, education, body mass index, smoking, and clinical aspects [64].

Similar results were obtained in a cohort of women living in the USA (follow-up period 2008–2012), where an increase in PM2.5 concentration of 3.6 μg/m^3 (interquartile range), (corrected co-founders were age, education, body mass index, consumption of dietary fiber, smoking, and occupational hazards), the odds ratio was 1.20 (95% CI 0.99–1.46) for new cases of bronchial asthma [42]. In older age groups, the relationship between long-term exposure to PM and new cases of bronchial asthma was significant.

In a monitoring that covered 117 regions of Canada from 2007 to 2014, 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. In addition to PM2.5 concentrations, the models included variables such as gender, age, latitude and longitude, share of clean energy, and volume of fuel sales [65].

In a study conducted in Korea among the elderly people (aged > 65 years), an increase in the average annual concentration of PM2.5 of 10 μg/m^3 over a 3-year period led to an increase in the incidence of bronchial asthma by 9% (hazard ratio 1.09; 95% CI 1.04–1.14). Statistical models included variables of age, gender, characteristics of the area of residence, and household income [66].

The severity of bronchial asthma varies between patients. The phenotypic heterogeneity of this disease was investigated by a cluster analysis of a large number of well-characterized patients, which allowed grouping them into 4–5 phenotypic clusters, taking into account age, gender, lung function, medical aid appealability, and body mass index [67, 68].

The identification of the heterogeneous structure of bronchial asthma raised the question of whether this heterogeneity could be due to certain cellular and molecular mechanisms. As a result, the study suggested that bronchial asthma endotypes (endotype is understood as "a disease subtype that is determined by a separate functional or pathological biological mechanism" [69]) explain better its characteristics compared with phenotypes.

The term "endotype" was proposed in 2008 as a conceptual basis for new ideas about the molecular heterogeneity of bronchial asthma [69]; to date, the T2 endotype of bronchial asthma has been described, characterized by a high level of type 2 inflammatory response in the airways [54, 69].

The type 1 and 2 response paradigm describes immune responses that are regulated by different subpopulations of T lymphocytes (Th1 and Th2) [Error: No source of cross-reference found]. Th1 cells secrete interleukin-2, interferon-γ, and lymphotoxin α and stimulate type 1 immune response, which is characterized by pronounced phagocytic activity. By contrast, Th2 cells secrete predominantly interleukins-4, -5, and -13 and stimulate the type 2 immune response, characterized by high antibody titers and eosinophilia. Type 2 immune responses in the airways are mediated by eosinophils, mast cells, basophils, Th2 cells, and congenital type 2 lymphoid cells (ILC2), as well as B cells producing immunoglobulin (Ig) class E.

A study established that the reaction of the airway epithelium (with the participation of TSLP, interleukins-25 and -33) leads to an increase in the production of type 2 cytokines, which start to control a cascade of subsequent events, including IgE-caused hypersensitivity to aeroallergens, activation of the airway epithelium, chemoattraction of mast cells, eosinophils, and basophils, and remodeling of the epithelium and subepithelial matrix [69].

The molecular mechanisms of the non-T2 endotype of bronchial asthma are underinvestigated. Such patients are likely to belong to several separate endotypes of the disease [69], and in addition to the type 2 inflammatory response, the formation of a Th17-dependent lymphocytic response and the involvement of the inflammasome mechanism of inflammation are possible [41, 54].

Bronchial asthma caused by exposure to airborne PM can be described as a separate phenotype, and its pathogenesis is different from the pathogenesis of allergic bronchial asthma and involves the mechanisms of both acquired and innate immunity [9, 54]. In allergic eosinophilic asthma,

Th2 lymphocytes and mast cells induce eosinophilic airway inflammation in an allergen-specific IgE-dependent manner [70].

Upon PM inhalation, the initial mechanisms include damage to the airway epithelium, activation of Toll- and NOD-like receptors and epithelial growth factor receptor, and triggering of oxidative stress, followed by the activation of transcriptional nuclear factor κB and the expression of proinflammatory cytokines. The latter include both cytokines involved in the implementation of innate immunity (interleukins-1β, -6, and -8) through the activation of macrophages and neutrophils, and epithelial cytokines TSLP, interleukins-33 and -25 with the subsequent triggering of T2-mediated responses through dendritic cells migrating to mediastinal lymphatic pathway, and activation of ILC2 cells.

T2-mediated immune response induces a change in the Ig class in B cells from IgM to IgE; hypersecretion of interleukins-4, -5, and -13, which leads to eosinophilia; adhesion of eosinophils to the vascular endothelium; increased epithelial permeability and mast cell survival; increased production of mucus by goblet cells; and airway remodeling [54, 70]. It is also necessary to investigate the possible formation of the Th17-lymphocytic response [54, 70] and the NLRP3 inflammasome mechanism of inflammation [41].

Growing evidence shows that DNA methylation may be significant in asthma development. In particular, exposure to air pollutants leads to changes in DNA methylation at the cytosine-guanine dinucleotide (CpG sites) [70]. The issue of the relationship between bronchial asthma and the role of individual fractions of PM in the atmospheric air is no less complicated [54, 55].

Studies have shown that PM2.5 may be associated with atopic dermatitis in children, adolescents, and young adults, and the meta-relative risks calculated from a subsample of people aged 2–30 years were 1.05 (95% CI 0.95–1.16) for PM2.5 and 0.96 (95% CI 0.83–1.11) for PM10 [71]. Fine particles inhaled from the environment, due to their intrinsic electrostatic properties and porous surfaces, form complexes with free airborne allergens (e.g., animal dander, dust, mold, and pollen). PM can interact with these allergens to promote sensitization by altering the allergenic properties of airborne allergens [72, 73].

PM and cancer, reproductive disorders, sleep disorders, diabetes mellitus, and other diseases. In 2013, PM in the atmospheric air was recognized by the International Agency for Research on Cancer as a group I carcinogen [18]. This conclusion was based on long-term (since the mid-1970s) data on the relationship between PM2.5 and PM10 with the risk of lung cancer [18, 74, 75].

A more recent meta-analysis of 18 studies examined the association of PM2.5 and PM10 with lung cancer incidence and mortality and provided risk estimates for an increase in exposure to PM by 10 μg/m^3 [76]. The meta-relative risk of lung cancer associated with PM2.5 was 1.09 (95% CI 1.04–1.14). The meta-relative risk of lung cancer associated with PM10 was similar, but less precise, namely, 1.08 (95% CI 1.00–1.17). The meta-estimates were resistant to the influence of potential co-founders and use of various exposure characteristics.

Analysis of smoking status showed that the PM2.5-associated risk of lung cancer was highest in former smokers, which amounted to 1.44 (95% CI 1.04–2.01), followed by 1.18 (95% CI 1.00–1.39) for never-smokers, and then 1.06 (95% CI 0.97–1.15) for current smokers. Risks were analyzed separately for the two most common histological subtypes of lung cancer, adenocarcinoma, and squamous cell carcinoma. The meta-estimates of the relative risk of adenocarcinoma associated with PM2.5 and PM10 were 1.40 (95% CI 1.07–1.83) and 1.29 (95% CI 1.02–1.63), respectively, for squamous cell carcinoma, the risk also increased, but not significant and amounted to 1.11 (95% CI 0.72–1.72)].

In a new meta-analysis of 17 studies analyzing the association between PM2.5 exposure and lung cancer morbidity and mortality rates, the meta-estimate of the risk of PM2.5-associated lung cancer was 1.11 for mortality (95% CI 1.05–1.18) and 1.08 (95% CI 1.03–1.12) for morbidity [77].

The mechanisms of the carcinogenic effect of PM remain unexplored. Direct cytotoxicity caused by oxidative stress, oxidative damage to DNA, mutagenicity, micronucleus formation, and stimulation of proinflammatory factors have been suggested [75]. Several researchers point out that the carcinogenicity of PM may be associated not with their direct action but with the absorption of polycyclic aromatic hydrocarbons and heavy metals on their surface [75].

Evidence shows the effect of PM2.5 on the incidence of premature births. Thus, in the ESCAPE study (14 cohorts from eight European countries), an increase in this indicator was noted by 1.18 with an increase in the concentration of PM2.5 for every 5 μg/m^3 (95% CI 1.06–1.33) [78]. A decrease in the body weight of a newborn by 6.6 g was revealed with an increase in the concentration of PM10 for every 7.8 μg/m^3 [79].

Recent studies have associated ambient air pollution with sleep disorders [43]. Data from a prospective cohort study conducted from 2015 to 2018 in

Ningbo (China, 38,775 participants) were used. The risk ratios for sleep disorders associated with an increase in PM2.5, PM10, and NO_2 by the interquartile range, calculated using proportional Cox models, were 1.14 (95% CI 1.03–1.25), 1.13 (95% CI 1.01–1.27), and 1.13 (95% CI 1.04–1.23), respectively.

A systematic review and meta-analysis of studies on the association of airborne PM with the incidence of type 2 diabetes mellitus (30 articles) showed that longer exposure to PM2.5 was associated with a higher incidence of type 2 diabetes mellitus (coefficient risk 1.10; 95% CI 1.04–1.16) for 10 μg/m^3 increase in PM2.5 concentration. Moreover, no significant relationship was found between the incidence of type 2 diabetes mellitus and PM10, as well as nitrogen dioxide [44].

Influence of the PM chemical composition. Currently, there are no convincing data on the difference in effects when exposed to particles with different chemical composition or different sources of origin. There is some information about the role of oxidative potential, which depends on the chemical composition of PM. As discussed above, PM-induced reactive oxygen species are considered an important mediator of their toxicity. The oxidizing potential of PM2.5 sampled from the atmospheric air of Paris was increased in the presence of metals such as copper and zinc in PM, as well as polycyclic aromatic hydrocarbons and soluble organic compounds [80].

A study investigated the oxidation potential of finely dispersed PM2.5 in the atmospheric air of a number of Canadian cities [81] and revealed that the oxidative potential correlated positively with the content of soot and a number of metals (copper, iron, manganese, and titanium) in PM. The solubility of metals and, accordingly, the oxidation potential increased with a decrease in the hydrogen index (pH) of the aerosol and the formation of metal ligands with organic compounds.

The effects of fine PM were enhanced by the simultaneous exposure to PM and bacterial endotoxins in the air of residential premises, and in relation to emergency medical care calls because of exacerbations of bronchial asthma in the last 12 months, the odds ratio for comparing the subgroup with high PM2.5 and endotoxin levels and the subgroup with low levels of both pollutants was 5.01 (95% CI 2.54–9.87). When assessing the effect of each factor separately (only high concentrations of PM2.5 or bacterial endotoxin), the odds ratios were slightly higher than 1.0 and not significant [82].

A similar assumption (increased risks under conditions of joint exposure to PM10 and bacterial endotoxin) was also made in a study of the effect of air pollution near livestock farms on the prevalence of serologically confirmed atopy and bronchial asthma [83]. A recent Japanese study confirmed that the simultaneous presence of endotoxin and both types of PM (less than 2.5 μm and more than 2.5 μm) led to an increase in the number of weekly emergency visits for medical care due to exacerbations of bronchial asthma [84]. Thus, this line of research also deserves attention.

Monitoring of PM in the ambient air. PM in the atmospheric air is monitored by many states, primarily in Europe, North America, Asia, and Australia that provide information for the population in real time [85]. For epidemiological cohort studies (European project ESCAPE), the land use regression models was developed, which enabled calculation of individual concentrations at the place of residence of thousands of study participants [86]. The regression models that enabled to predict individual concentrations were created based on geoinformation data on traffic intensity, population density, land use aspects, geographical altitude, and pollution levels at monitoring points.

In the Russian Federation, information on actual exposures and effect of PM on public health is extremely limited. The WAQ Index W.A.Q database contains data only for some Russian cities (Moscow, Saratov, Krasnoyarsk, Novokuznetsk, Irkutsk, and Tomsk) [85]. Private initiatives also exist, for example, the IQAir project [87] with a wider representation of Russian cities or the Russian platform CityAir which is being developed by Skolkovo [88].

Despite the availability of data on monitoring the content of PM in the atmospheric air in several cities of the Russian Federation, this information is not systematized. A significant part of Russian scientific publications on this issue is based on review [26]. The largest number of Russian publications on the content of PM in ambient air and its risks to public health refer to studies conducted in Moscow [89].

In recent years, publications have appeared on the presence of finely dispersed PM in the atmospheric air near highways in Perm [90] and in the air of Vladivostok [91, 92], Yakutsk [93], and Krasnoyarsk [94]. The federal project "Clean Air" should also be noted, which includes regular monitoring of atmospheric air pollution, including PM, in 12 cities of the Russian Federation [95].

Limitations of many Russian studies were incomplete data on the fractional composition of PM [89, 91, 93], a small number of monitoring points [90, 91, 94], and the lack of data on the relationship between the concentration of PM in the air and indicators of public health [90, 91, 93].

In a few Russian studies that have analyzed the effect of PM on the health of the population [89,

94], the research methodology assumed the use of only one exposure parameter, i.e., the average daily concentrations; for diseases with pathogenesis that involves allergic reactions or an irritating type of action, high peak levels of pollution; and for diseases with a long latency period, averaged long-term concentrations, which may be of noninferior importance. The new exposure parameters, such as the mass of PM fractions deposited in the lungs, are almost not used, while separate works in this topic have started to appear [96, 97]. These studies are based on calculated data, and their reliability still needs to be further evaluated. In addition, a serious Russian problem is the lack of synchronization between big databases collected as part of the social, hygienic, and environmental monitoring and medical databases.

Conclusion. Therefore, the pronounced damage to public health associated with the presence of PM in the ambient air of populated areas requires targeted actions to minimize the risk from this group of pollutants and to continue investigations on the toxicity of fine PM and their role in the pathogenesis of various diseases.

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