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E.N. Suprun, S.V. Suprun, G.P. Evseeva, O.A. Lebedko EXOGENOUS FACTORS INFLUENCING THE COURSE OF BRONCHIAL ASTHMA

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This systematic literature review analyzes the environmental factors that affect the course of bronchial asthma. Based on 46 studies, a number of factors have been identified whose impact has been reliably confirmed, including sudden changes in daytime temperatures, vitamin D levels, micronutrient status, persistence of herpes-like viruses, and the specific sensitization spectrum of a particular region.

A comprehensive approach to the diagnosis, prevention, and treatment of bronchial asthma, taking these factors into account, will allow for personalized treatment of individual patients and improve its effectiveness.

Keywords: bronchial asthma, climate, vitamin D, viral infections, sensitization spectrum.

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Introduction. Bronchial asthma (BA) is one of the most common chronic diseases of the respiratory system in both adults and children. In recent decades, there has been an increase in asthma, and by now its incidence has reached 15-18% among the world's child population [21]. Russia as a whole [4] and Khabarovsk Krai [7], in particular, are no exception to this trend. Atopic inflammation, which, as a rule, underlies the pathogenesis of asthma in children, is primarily due to innate factors, however, the probability and duration of their implementation, as well as the course of the disease itself, can be significantly modi-

fied by a variety of exogenous influences [10, 17, 29].

The purpose of this review is to analyze environmental factors in asthma, their clinical implementation, and the possibility of selecting a therapy algorithm based on them. Based on a review of the literature data from PubMed, ScienceDirect, Google Scholar, Research Gate, and eLibrary databases.RU for the period 1997-2025. 192 publications were analyzed as a result of a search for the following keywords: "climatic effects in bronchial asthma", "vitamin D in bronchial asthma", "trace elements in bronchial asthma", "viruses in bronchial asthma",

"spectrum of sensitization in bronchial asthma", 46 of them were selected for detailed study and included in this a job.

Climatic factors. The most common factor affecting the human body, including asthma, is climate, with its most obvious manifestation being the temperature difference, seasonal and diurnal. The study of the effect of temperatures in patients with asthma has a long history, including numerous meta-analyses on this problem. For example, one of them studied more than 2,000 articles related to this topic in childhood. Of the 2,633 papers, the authors considered only 23 to meet the criteria for inclusion and exclusion. Fourteen studies reported inverse relationships, which showed that as children's temperature decreased, the number of asthma attacks increased. Nine studies have shown a link between hot weather and asthma attacks. Three studies reported an association between temperature changes and asthma attacks, while two studies found no association. Some studies have shown that an increase in the incidence of asthma in the age group of 5-14 years is associated with the beginning of the school year and, probably, with the spread of viral diseases, rather than with changes in temperature. Based on this, the authors draw a fairly obvious conclusion – extreme temperatures and their fluctuations are likely to cause an exacerbation of asthma in a child [43]. Another meta-analysis presented 19 sources that met the inclusion criteria, 13 papers quantified the effect of absolute temperature on the course of asthma in children, and six papers studied the effect of intraday or inter-day temperature fluctuations. All patients lived in urban areas. There was a discrepancy in the significance of the relationship between absolute temperature and asthma attacks, as well as in the form of this relationship (i.e. linear or nonlinear) and whether there were delayed temperature effects. More and more evidence indicates a non-linear relationship between absolute temperature values and asthma exacerbations in children [41]. Despite this, research in this area continues. Thus, in recent years, Iranian scientists have shown that changes in weather conditions, high relative humidity and cold weather can trigger asthma attacks, especially in young children, while the level of dust and thunderstorms did not significantly affect the frequency of asthma exacerbations in childhood [27]. In Poland, the study and determination of the relationship between the frequency of asthma exacerbation and the state of the environment was carried out in accordance with the UTCI bio-

meteorological index (Universal Thermal Climate Index). At UTCI values in the 5th grade range, describing thermoneutral conditions, asthma exacerbations were observed with an average frequency. A decrease in the UTCI value led to a decrease in the number of asthma exacerbations, while an increase increased their number [33].

The fact that such studies continue, despite the abundance of information obtained as part of previous work, is primarily due to the uniqueness of the climate in each area of residence. The southern part of the Russian Far East is located in a zone with a monsoon climate of temperate latitudes, characterized by harsh cold Siberian winters and hot, humid, tropically sultry summers. Pronounced diurnal changes in air temperature and pressure, characteristic of transitional seasons, lead to changes in the oxygen content in the air, having a negative impact on people with bronchopulmonary diseases, especially children [22]. In recent years, there has been an increase in both seasonal [8] and diurnal temperature differences [3].

In this regard, residents of the Amur region are particularly interested in the relationship between the frequency of asthma, exacerbations and sudden changes in ambient temperature.

Vitamin D. Another regional feature of the environmental impact on the body is the level of sunlight and the ability to perceive it by humans in connection with other climatic features. The Amur region is one of the leaders among the regions of Russia in terms of formal indicators of insolation, the number of sunny days for our region exceeds 300 per year. However, a rather harsh climate with large temperature fluctuations, up to extreme ones, does not allow us to take full advantage of this advantage, so the level of vitamin D in the population is quite low. According to studies conducted in 2020, vitamin D deficiency was detected in almost half of the children's population of our region [2, 6]. Meanwhile, the role of this vitamin in the pathogenesis of asthma is well known. Recent Iranian studies have shown that vitamin D levels in patients with asthma are lower than in the control group and decrease with increasing severity of the disease [38]. Similar results were obtained by Indian researchers in the same year [35]. Several earlier epidemiological and *in vivo* studies also found an association between low vitamin D levels in blood serum and increased inflammation, decreased lung function, increased exacerbations, and general deterioration in patients with

asthma [12, 23, 37]. Later, a meta-analysis confirmed a significant decrease in objective indicators, such as FEV1, and the appearance of signs of obstruction with low vitamin D levels in children and adults with asthma [30]. A number of scientific papers using meta-analysis methods show the effectiveness of vitamin D in the complex therapy of asthma. Thus, 483 unique studies were studied in one of them, eight of which were randomized and controlled (1,078 people in total) according to a certain methodology, taking into account the adjusted incidence ratio [aIRR]. It was found that vitamin D intake reduced the frequency of asthma, exacerbations in all observed patients requiring treatment with systemic corticosteroids (aIRR – 0.74, 95% CI 0.56-0.97; $p=0.03$; 955 patients in seven studies; high-quality evidence). An analysis of the frequency of exacerbations in participants treated with systemic corticosteroids showed that protective effects of therapy were observed in patients with baseline levels of 25(OH)D is less than 25 nmol/L (aIRR – 0.33, 0.11-0.98; $p=0.046$; 92 participants in three studies; average quality data), but not found in patients with a higher baseline content of 25(OH)D (aIRR – 0.77, 0.58-1.03; $p=0.08$; 764 people in six studies; evidence of average quality; $p=0.25$). A two-stage meta-analysis revealed no signs of heterogeneity of the effect ($I^2=0.0$, $p=0.56$) [47]. One of the Russian studies shows some elements of the therapeutic effects of vitamin D when it is included in the complex therapy of asthma. Vitamin D promotes positive changes in the cytokine network during treatment, which is associated with its ability to regulate Th2 functions and, as a result, reduce the synthesis of IL13 and 17, which are involved in the pathogenesis of allergies [1].

Thus, the detection of vitamin D levels in children of the Amur region suffering from asthma and confirmation of its effect on the course of the disease is of great scientific and practical interest and may have high clinical significance.

Trace elements. The ratio and quantity of trace elements in the human body also has regional characteristics and largely depends on the biogeochemical characteristics of the region. The effect of a number of trace elements on the course of asthma is known [49], but various studies lead to ambiguous results when trying to determine the degree and direction of changes. According to the Iranian authors, the average serum levels of Zn and Se in patients with asthma were lower than in conditionally healthy people in the control group, and the concentration

of Cu in the blood serum of patients was slightly higher than in the control group [46]. In recent work, Turkish scientists have noted a decrease in the level of Zn in the blood of children with asthma compared with healthy ones [48], earlier studies revealed a significant decrease in the level of Cr, Se, Zn in the blood serum of children with asthma, compared with healthy ones, and the level of Cu in their blood serum was significantly higher, than in the control [36], which coincided with the data of the Iranian authors [46]. Studies by Indian scientists have also confirmed significantly lower levels of Zn and higher levels of Cu in patients with asthma, compared with healthy ones [13]. A study by Egyptian authors published in 2022 confirmed a significant ($p<0.008$) decrease in serum levels of Zn and Mg in patients with asthma, while serum levels of Fe and Cu were significantly ($p <0.016$) higher than in people without this disease.. At the same time, there were no significant differences in the content of these trace elements in the blood serum, depending on the severity of asthma, or its control [45]. On the other hand, according to one of the studies using meta-analysis methods, which included 34 sources, there were no significant differences in the level of Zn and Se between asthma and the control group, but they were found in the level of Cu, and the degree of these differences is not the same for humanity in general and for Mongoloids, in particular, it was revealed There is a significant difference in Mg levels, which has no ethnic differences [40]. A later meta-analysis involving 66 sources revealed that patients with asthma have significantly lower levels of Zn ($SMD = -0.32$; 95% CI $-0.48, -0.17$; $I^2 = 90.9\%$) and Se ($SMD = -0.32$; 95% CI $-0.48, -0.17$; $I^2 = 90.9\%$) in blood serum compared with healthy individuals [15].

Thus, it is obvious that the nature of the effect of trace elements on the pathogenesis of asthma is closely related to the biogeochemical characteristics of the patient's area of residence, therefore, studies characterizing this problem in a particular region are of particular interest.

Viral infections. The role of viral infection in asthma has long been known, reflected in international conciliation documents, including the latest editions of GINA [21]. New generalizing works on this problem appear periodically [34]. However, the influence of pneumotropic persistent viruses of the herpes group, such as Ebstein-Barr virus (EBV) and human herpes virus type 6, on the development and course of asthma is of particular interest. They persist for a long time,

often for life, in the bronchial mucosa and inevitably take part in the pathomorphosis of asthma [5]. There was a significant difference in the interleukin profile in children with asthma infected with and without herpes viruses, in particular, higher levels of TNF α , IL1, 2, 4, 10 and lower levels of IL6 and 8 [9]. Studies have shown a high incidence of EBV in children with asthma, [28], and the frequency of virus DNA isolation in the bronchial epithelium of patients with asthma, has been confirmed in comparison with the population without this disease, which indicates its active reproduction in the target organ, the bronchi. A positive relationship has been established between the activation of EBV and the level of ID in children with asthma, [18]. The role of human herpes virus type 6 in the pathogenesis of asthma is much less reflected in the available literature, there are only isolated articles on this topic, which put forward the thesis of the protective role of the persistence of this virus. In an experiment on mice, it was shown that exposure to type 6 herpes significantly inhibited the production of IL4, 5, and 3 in the lavage fluid and in lung tissue exposed to the virus in asthma [19].

The spectrum of sensitization. Asthma in children is primarily an atopic disease, therefore, sensitization to specific allergens underlies its pathogenesis. The influence of the sensitization spectrum on the course of asthma and its controllability is of great interest. The most common allergen in asthma is the house dust mite, this is a well-known fact, confirmed by the consent documents, including all editions of GINA [21]. In children with asthma, it is registered with a frequency of about 90%, which is why the fact of sensitization to it cannot have a significant effect on the nature of the course of asthma. The house dust mite is an obligate human saprophyte, therefore, the very fact of its presence in the inhaled air cannot act as a relevant predictor for the likelihood of developing asthma. In this regard, more attention is being paid to studying the frequency of occurrence and significance of other respiratory allergens in the development of asthma. For example, fungal spores have been shown to increase the likelihood of developing asthma in both children and adults. [20, 24, 26, 32]. It has long been known that sensitization to fungal spores causes a more severe course of asthma compared to other allergens [42]. More recent studies have shown that not only sensitization to mold, but also to pet hair, cockroaches, and weeds, in particular ragweed, causes a more severe course of asth-

ma than to other allergens, primarily the house dust mite [25]. A clear association has been found between the concentration of fungal spores in the environment and an increase in clinical asthma-like symptoms in children [14]. Recent studies have confirmed that the concentration of fungal spores in house dust affects not only the severity, but also the controllability of asthma, [31]. Pathogenetic animal models have demonstrated that it is fungal sensitization that causes the most pronounced eosinophilic infiltration of the bronchial mucosa [44].

It is obvious that pollen inhalation leads to asthma exacerbation in patients sensitized by it, including children [16]. This is confirmed by a meta-analysis published in 2020, which shows the effect of pollen concentration on the frequency and severity of asthma, exacerbations [39]. When studying the effect of sensitization to weed pollen, it was found that in people with sensitivity to this allergen, the bronchial wall is somewhat thinner than in patients sensitive to house dust mites, which is probably due to a shorter total exposure time during the year [11].

Thus, we see that differences in the severity and pathogenesis of asthma are caused by sensitization to those allergens that depend on the patient's place of residence and, to some extent, his socio-economic conditions, which is why local studies of these factors in specific regions are of great interest. The area near the Amur River is regularly flooded, resulting in conditions favorable for the uncontrolled spread of fungal allergens outside and inside, in humid and poorly ventilated homes. The catastrophic flood in August-September 2013 was unprecedentedly powerful and protracted, with enormous economic damage. Assessing its consequences in terms of changing the spectrum of sensitization in patients with asthma is important for pediatric allergy and pediatrics in general. In addition, the Amur region is characterized by a wide variety of vegetation, including wind-pollinated, which has been increasing in recent years due to the invasion of species not native to the area, such as ragweed, therefore, an assessment of the impact of the sensitization spectrum on asthma in children of the Amur region is necessary and interesting from a scientific and practical point of view.

Conclusion. From the above, it is obvious that the pathogenesis, course, and, accordingly, severity and susceptibility to therapy are influenced by many multidirectional endogenous and exogenous factors. They form a unique mosaic for each patient. A sufficiently deep study of

them opens up prospects for personalizing the diagnosis, prevention, and therapy of asthma.

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