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# Primary Prevention of Allergic Diseases: Dreams or Reality?

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**Abstract**

Prevention is better than cure. Firstly, many regimes spend an enormous amount of money in order to treat their people who are suffering from different types of serious diseases. This article is an attempt to analyze of the existing international sources, which focuses on the primary prevention allergy. It is clear that the basis of such prevention is prophylaxes of the disease before it showed up. This is a very difficult question, because there are different points of view on the possibility of the prevention allergy today. The main purpose of this review is to summarize evidence base scientific data and researching results for the possibility of providing recommendations on primary prevention of childhood allergies. We would like to increase knowledge about the development of the allergic process, the ability to recognize and evaluate risk factors and all the factors of the next sensitization will enable us to better understand the tactics of prophylaxis allergic diseases.

**Keywords:** Primary prevention; Children; Allergic disease

## Introduction

The rapid growth of allergic pathology among children in the world and directly in Ukraine is a source of great concern for specialists. Now-a-days allergic diseases (AD) are an epidemic of the XXI century, and scientists are already waiting for a pandemic development allergy for the next 5-10 years [1-4]. International organizations dealing specifically with allergy and immunology update clinical and national guidelines, approval documents in various areas of allergy regularly [5,6]. Unfortunately, there are no any recommendations and opportunities on the primary allergy prophylaxis. The opportunities to research of the pregnant women and breastfeeding mothers are typically not available in connection with ethical reasons. However some evidence base surveys in this area is still ongoing, and for the last two decades there have been separate documents in several countries around the world. This is especially true for bronchial asthma (BA), allergic rhinitis (AR) and atopic dermatitis (AD) [7-9]. These documents are more detailed and informative, open source and evidence-based. We consider it necessary to attract the attention of the different specialists for the further researches that would help to answer questions and formulate certain recommendations for primary prevention of AD. All common strategies which focused on the primary prevention of allergy were aimed on identifying the main risk factors and preventing their possible effects on the development of the disease. In the modern studies, the issues of protection against possible allergens (AG) and early sensitization, immunomodulation and the development of tolerance to certain foods and inhaled hypertension are considered.

## Materials and Methods

### Sources of data and search strategy

A detailed series of searches for publications was carried out using several databases: PubMed, UpToDate, Medline, and Scopus. Seven groups of keywords with either Medical subjects areas (*MeSH) titles or All Fields were created using "OR" within the group and using the "AND" to join the four groups in PubMed, UpToDate, Medline and Scopus. The terms identifying Epigenetic and Genetic factors, Hygienic and Dietary Hypothesis, "Ecological" sensitization and oral tolerance, Pregnant and fetal system, Prebiotics and probiotics that associate with Allergy. In all cases, databases were searched from inception to March 2017.

## Definitions

### Allergy

As allergy is defined as an abnormally high or misguided reaction by the immune system to various foreign substances that are normally harmless, such as pollen, molds, animal proteins, dust mites, insect poisons, and foods. Symptoms may include sneezing, skin rashes, difficulty breathing, itching, watery eyes, and so forth. An allergen is a substance that triggers an allergic reaction.

### Primary prevention

The Primary Prevention is taken as a primordial prevention in order to avoid the danger of the disease. From a large view, everyone takes primary prevention to minimize the latent threatens of disease considering the national development. The aim of primary prevention is to prevent the disease effect on a human's body. All different health levels have also used effective methods such as regular medical examinations to everyone. All these work are important to prevent the disease before it occurs.

### Inclusion criteria

Original peer-reviewed articles were included which evaluated associations between influencing factors and allergic outcomes. With understanding of the interrelation of factor and lack of development allergy were considered for inclusion in our review.

### Exclusion criteria

Studies were excluded if they did not report any association between the impact factor and outcomes for children and adults participants, and the study no English translation was available.

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We used the Cochrane Risk of Bias tool to assess a randomized control trial.

## Results

### Epigenetic mechanisms

New ideas also relate to the significant influence of the epigenetic mechanisms on the development of AD in the future. Epigenetics may explain how genetic susceptibility and exposure to environmental factors interact in defining atopic disease phenotypes. Experimental data indicate that DNA methylation is a protective mechanism that suppresses a significant part of the genome of alien nature. DNA methylation in the cell controls all genetic processes: replication, reparation, recombination, transcription, inactivation of the X chromosome. It has a significant effect on the expression of genes and, ultimately, on the function of cells, tissues and the body as a whole. There is a direct relationship between the high level of DNA methylation and the number of repressed genes. Loss of ability to support DNA methylation can lead to immunodeficiency, the development of malignant tumors, and the formation of AD [10-12]. In addition to genetic susceptibility; environmental factors play an important role in the pathogenesis of asthma and allergy. Epigenetic factors may mediate at least some of these environmental effects [13,14]. Thus, we systematically examined whether environmental factors known to have an impact on asthma and allergy have also been reported to induce epigenetic changes in experimental settings [15]. The methyl-rich diet decreased transcriptional activity and mRNA expression of several genes, which was accompanied by DNA hyper methylation of the respective promoters [16-19].

### Hygienic hypothesis

It should be noted that in recent years the strategic direction, which is developing the primary prevention of allergy, has changed significantly. This, according to leading experts, should help to develop more effective preventive measures and change the epidemiological trend of the past decades [20-22]. Several hypothesis and ideas about mechanisms and risk factors of allergy have been proposed for the last decades. One of them is the hygienic hypothesis that was advanced by David Strachan in 1989. The hygiene hypothesis suggests that a newborn baby's immune system must be educated so it will function properly during infancy and the rest of life. One of the key elements of this education is a switch on T cells called TLR4. The bacterial protein LPS normally plays a key role by flipping that switch into the "on" position. The hygiene hypothesis has also been called the "biome depletion theory ". Scientists based this hypothesis in part on the observation that, before birth, the fetal immune system's "default setting" is suppressed to prevent it from rejecting maternal tissue. Such a low default setting is necessary before birth—when the mother is providing the fetus with her own antibodies. But in the period immediately after birth the child's own immune system must take over and learn how to fend for itself. The "hygiene hypothesis" is supported by epidemiologic studies demonstrating that allergic diseases and asthma are more likely to occur when the incidence and levels of endotoxin (bacterial lipopolysaccharide, or LPS) in the home are low. LPS is a bacterial molecule that stimulates and educates the immune system by triggering signals through a molecular "switch" called TLR4, which is found on certain immune system cells. Several studies have found that the risk of developing AD and BA in a big family is less compared with families with one child. Special mention should be given to works that deal with the so-called "sibling effect" [23-29]. The main idea is that in large families the hygiene is difficult, and the large microbial burden on the infant shifts its immune response towards the formation of anti-infective immunity. There are the great numbers of researches that explore the hygienic hypothesis, but not enough data that confirming their role in the development of AD [30,31]. There is very little information about the relationship of hygienic hypothesis with the mechanisms of food allergy. Despite this, the study conducted in Norway showed that birth by caesarean section was associated with a sevenfold increase in the risk of developing hypersensitivity reactions to eggs, fish, or nuts. In this study, the infants whose mothers were suffering from allergies, the sensitization to the chicken egg was established 4 times more often than among other children of the studied cohort. An analysis of 6 studies confirmed a certain effect of birth by cesarean section on an increased risk of food allergy [30-33]. One explanation is the babies who are born by Caesarean section are not exposed to their mothers' bacteria during birth, which is detrimental for development of the immune system. The other is that babies born by Caesarean section have more breathing problems after birth because they are less exposed to stress hormones and compression of the chest, since these mechanisms contribute to emptying the lungs of amniotic fluid. Maybe this can negatively affect lung function in the long term [34-36].

### Dietary hypothesis

The dietary hypotheses that were studied in the last three decades have considerable importance at the mechanisms of sensitization in infants and the further development of AD. The basis of these hypotheses is to determine the possible relationship between the diet and the development of allergies. Unfortunately, in recent years, our diet has undergone major changes, which could not but affect the changes in the nature of the immune response to new nutritional ingredients. Some studies have taken into account the content of macro and micronutrients in foods of different nations, dietary benefits, both national and geographical, depending on the prevalence of allergies and asthma in different parts of the world. There are three main dietary hypotheses [37-39]. The first hypothesis concerns the changes in the introduction of fat in the diet of children. Its essence is to increase the number of children with allergies by reducing the consumption of animal fats, primarily fish oil, and the corresponding increase in the use of margarine and vegetable oils [40-43]. Very interesting and well-studied is the antioxidant hypothesis. Separate data based on observational studies suggest that the use of a pregnant Mediterranean diet containing a large amount of fresh fruit and vegetables is associated with lower levels of development in this region of asthma and other clinical manifestations of pollen sensitization. In support of this hypothesis, there is evidence of an increase in the prevalence of AD, and especially BA, in the UK, which is associated with a decrease in the consumption of fresh fruits and vegetables in the so-called Western diet. The idea is that certain antioxidants such as vitamin C and beta-carotene, which are contained in vegetables and fruits, can have an anti-inflammatory protective effect on the development of asthma. However, there is no biological explanation as to how this could affect the decrease of specific IgE sensitivity to food [44-46]. And the last dietetic hypothesis is the hypothesis of vitamin D, which is one of the most interesting. It is perceived as advanced in explaining the increase in the incidence of asthma and AD in recent years. There are two points of view on the role of vitamin D: the first – "excess vitamin D" – suggests that increasing the content of vitamin D in the diet leads to an increased risk of developing an allergy. The second option – "vitamin D deficiency" – offers the opposite concept. We should be considered that vitamin D is associated with intrauterine development and the formation of the fetal immune system. Data from

epidemiological studies show that more vitamin D intake by pregnant women reduces the risk of developing asthma by 40% in their children aged 3 to 5 years. These studies have shown that vitamin D deficiency is associated with overweight, belonging to the African-American race (especially in the central cities of the cities), and recent immigrants from countries oriented to the West have thus become epidemiologic examples where they are observed. It has also been shown that ensuring adequate vitamin D in the mother's diet during pregnancy can significantly reduce the prevalence of asthma among young children. There are immunological arguments that can be given to support both points of view. Vitamin D has been shown to *in vitro* inhibit the rapid increase in the number of T cells and secretion of Th1: IL-2, IFN-gamma, and IL-12 cytokines. At the same time, there is evidence that vitamin D supports the development of T-regulatory cells both *in vitro* and in natural conditions, and this may reduce the likelihood of the development of allergic inflammation [47-49].

## "Ecological" sensitization and oral tolerance

The effect of the so-called "ecological" sensitization and oral tolerance on the development of allergic pathology is the next issue, which is very carefully considered and researched in the world. There is currently no conclusive evidence that preventing contact with allergens in children under four months of age reduces the likelihood of developing an allergy. According to research findings, the consistent elimination of food allergens during pregnancy, breastfeeding and early childhood is not able to reduce the long-term IgE-mediated food allergy in children. It can be assumed that measures to reduce the exposure of the allergen could be inadequate in many studies, and the prescribed diets were not sufficiently weighed and rigorous, and increased sensitivity to food allergens may occur not only as a result of their direct intake, but also formed with other methods of receipt allergens in the baby's body. But today, the anti-allergy paradigm is revised, and early "oral" allergens are more likely to prevent the development of allergy, rather than cause it (Figure 1). There are several mechanisms discussed as possible risk factors (deficiency of secretory IgA), which, according to some researchers, lead to the implementation of allergic predisposition [50-52]. Their contribution to the development of atopic disease is still under discussion.

The explanation for the concept of environmental food exposure is supported by many research studies in rats and they show that sensitization to the antigen can actually occur only after skin effects. There are, for example, studies in which food allergen-specific T cells have been isolated from damaged skin in patients with AD. This study found that local effects of peanut oil in the form of peanut butter on infant skin resulted in an increased risk of peanut allergy after reaching the age of 5 years. At the same time, many studies indicate that it is

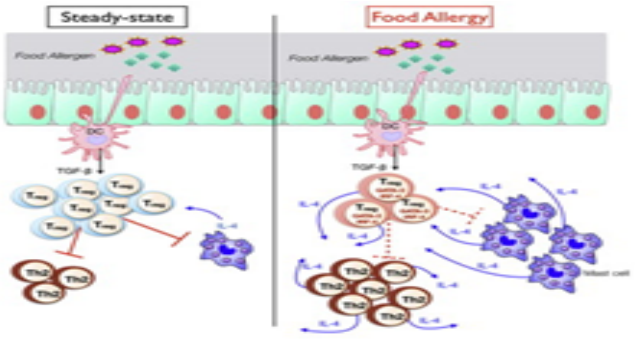


**Figure 1:** Formation of oral tolerance.

the oral induction of tolerance, and not the dietary elimination of hypertension, to prevent the development of food allergy. And the early introduction of allergenic products into the infant's diet (in the first 6 months of life) may reduce the development of food allergy through induction of oral tolerance [45,39]. In 2015, the results of a randomized controlled study (Study Early about Peanut Allergies study) were published, in which half of the babies of peanuts were excluded from the diet and the other half received it. The study showed that the early introduction of peanut infant formula (in the form of a paste) significantly reduced the frequency of food allergy development for peanuts compared to the cohort of children who did not receive it.

## Genetic factors

Today nobody has any doubts that genetic factors are the main and most important risk factors for the development of allergic diseases [53-57]. The presence in the family of atopic disease is considered to be the genetic factor of predisposition to the development of a child with IgE-induced hypersensitivity and is a prerequisite for the inclusion of a newborn in a "high risk" group. The first study to prove the inheritance of BA and AR was conducted by Cooke et al. in 1916. The fundamental work emphasized the family's "accumulation" of atopy and its inheritance. It is convincingly shown that the development of asthma in children occurs under the influence of the interaction of a number of genetic and environmental factors. The 2007 International Advanced Study on Asthma and Allergy in Childhood, conducted in 2007, showed that. BA and atopy, despite their causative relationships, are still separate categories and can be inherited in different ways [58,59]. All researchers are unanimous in that prevention is recommended for high-risk children from early childhood. The child falls into such a group at the presence of a burdened allergic anamnesis (presence of one or more relatives of asthma, AR, and/or food allergy). In children with a history of allergic allergy (sick parents or siblings), in comparison with children without burdened allergic anamnesis, the development of allergic diseases is noted in 50-80% and 20% of cases, respectively. The history of allergic illness of a relative of the first degree of kinship at present is the only useful indicator of the increased risk of developing an allergic illness in a child [47]. It has been established that in the presence of atopic disease in one of the parents the probability of developing an allergy in a child is about 30%, in both parents – 60%-70%. The most reproducible results of research in genetic associations include the following five areas of the human genome: 5q31-32, 6p21, 11q12-13, 16p11-12 and 20p13. Only recently, as a result of a general study of the association of the genome, a new high-probability development BA (ORMDL3) was identified. ORMDL3 is considered the main determinant of the development of asthma in childhood. Perhaps even a few loci, affect the propensity to develop asthma in childhood. Thus, the genes located on the chromosome 5q (ADRB2, IL13 and IL4), and not just the ORMDL3 mentioned above (chromosome 17), are likely to be determinants of childhood asthma [60]. However family inheritance of asthma and allergic diseases implies that genetic factors are important in the pathogenesis of allergy, but reliable genetic markers of IgE sensitization or specific allergic diseases have not yet been identified. Although a certain number of "candidate" genes have already been identified, none of the pathogenesis of the disease has yet been confirmed. An increase in the incidence of allergic diseases indicates that it is the environmental factors that influence the manifestation of genetic predisposition [56].

## Pregnant and fetal system

And one of the most important issues that directly concern the implementation of primary prevention methods is the possible effect

of the allergen on the "pregnant and fetal" system. Pregnancy is a condition characterized by physiological immunosuppression, which is accompanied by suppression of proinflammatory responses of the body, which ensures the safety of implantation of the embryo. Implantation and development of the embryo in the uterine cavity is a complex, multistage process that is regulated by a multitude of neuro-immune-endocrine humoral factors. 1 One of the most important mechanisms that ensure the preservation of the fetus is the systemic immunity of the mother [61]. In the gestation period there is a decrease in the function of the cellular immunity with the restructuring of the immunoregulatory linkage of T-lymphocytes in the direction of increasing the number of T-suppressors, and this suppression persists from the 8th to the 32nd week of gestation. Cancellation of suppressive effects of T-cells begins with the 37th week and is accompanied by an increase in the helper effect before childbirth.50 Naturally, during pregnancy, the woman is in contact with various substances, including those with potential allergens (AG), the processes of their biotransformation, as xenobiotics in pregnant women are reduced and tend to cumulating. The above factors become more unfavorable in diseases of the liver, kidneys, and women with a burdened allergic heredity or with already formed AD. There are two ways of switching hypertension from mother to fetus, through the amnious and through the placenta. The presence of inhalation and food in the amniotic fluid of the fetus is detected from the 16th week of gestation, and in the circulation of the fetus, from the 37th week. There are two mechanisms of protection against the harmful effects of xenobiotics-placental, which provides immunological balance at the expense of steroids and placental lactogen, and liver, due to the detoxification function of the liver. A prolonged exposure to hypertension in the mother may lead to the formation of a fetal IgE-dependent response, and in the future-AD. At the pathological course of pregnancy, favorable conditions are created to increase the permeability of the fetoplacental barrier for hypertension and infectious antigens, which contributes to intrauterine sensitization of the fetus. Important risk factors for the development of atopy are the influence of allergens during pregnancy, mother's age and delivery by cesarean section. Since the course of the pregnancy itself introduces certain limitations for the development of the functions of the immune system of the child, the period from the middle of pregnancy to the age of two years of the child, one of the most responsible periods, and a subject of special concern for the development of immunopathological conditions, including allergic diseases, including asthma. Several prenatal perinatal risk factors have been identified that contribute to the development of immunotoxicological reactions [62]. Among these factors, which are mediated by immune disorders and increase the risk of developing allergic diseases, include: active and passive smoking, the influence of particulates of exhaust gases of diesel engines, connected with automobile movement, influence of heavy metals, antibiotics, hormonal and endocrine disorders and alcohol [63].

## Prebiotics and probiotics

The potential of the use of prebiotics and probiotics in the primary prevention of allergic diseases in children is given a lot of attention [64-68]. Microflora appears on the mucous membranes of the respiratory, gastrointestinal and urogenital tract from the first minutes of the birth of the child and is an active participant in his life. Its average weight in an adult is up to 1 kg, which can be compared with the weight of some internal organs. Intestinal microflora participates in the processes of digestion, synthesis of vitamins and amino acids. One of the main functions of normal microflora-protective, as affecting the immune system, bacteria give it a regulatory effect. Reducing the amount of normal microflora can increase the risk of developing inflammatory processes. Recently, more and more research has been devoted to the role of microflora in the development of allergic diseases in children. During the first week after birth, the flora of the gastrointestinal tract (GI) is represented by various microorganisms – *Streptococci, Clostridia, Neisseria, Staphylococci*, and others. By the end of the first week of life in the gastrointestinal tract are dominated by *Bifidobacteria* – anaerobic gram-positive sticks that do not form spores [69-72]. Along with *bifidobacteria* in young children in the intestine there are *lactobacilli* – aerotolerant gram-positive non-spore-forming sticks. In the newborn period, their number may vary. However, in 30% of healthy newborns, lactobacillus is not detected. According to research results Ahrne et al. (2005), lactobacillus was not detected in 26% of cases, 37% had only one species, in 26%, 2 species and only 11% of children were found three or more species. With age, the number of species of lactobacillus increases, the number of *bifidobacteria* gradually decreases, and the number of E. coli remains stable. *Enterobacteria* are aerobic gram-negative, non-porous, mobile bacteria. Non-pathogenic intestinal sticks are localized in the colon and begin to dominate the structure of the intestinal microflora for up to seven years. In the intestine also detected obligate anaerobic gram-negative sticks that do not form spores. These are so-called *bacteroids*, the function of which has not been studied. It is known, in particular, that the number of *bacteroids* in the intestine may increase with some diseases, for example, with BP. A number of other types of bacteria –*Peptostreptokokki, Fusobacteria, Eubacteria, Catenobacteria, Vijonella* are involved in the proteolysis of milk proteins and fermentation of carbohydrates. With excessive growth and changes in the ecological niche, they can exhibit pathogenic properties. To date, the most studied immunobiological properties of *Bifidobacteria, Lactobacilli and E. coli*. Since the significance of the effect of normal microflora on the development of atopy does not cause doubt, it is necessary to find out what factors can affect its condition in children, especially young children [73-78]. An important factor that affects the attachment of normal microflora is the degree of childbirth at birth, type of birth, and the presence of breastfeeding. Breast milk, in addition to nutrients, contains substances that improve the growth and normal state of normal microflora. These include triglycerides, polyunsaturated fatty acids, glycans, antimicrobial peptides, lactalbumin, secretory immunoglobulin A, and others. Polyunsaturated fatty acids (PZH), triglycerides and lactoferrin, when ingested in the stomach, have an inhibitory effect on pathogenic microorganisms. These substances can act in the form of whole molecules, as well as in the allocation of their individual components, which appear under the influence of lipases. The breast milk contains a large number of antimicrobial peptides, which are excreted when digesting milk in the stomach of the baby. Antimicrobial activity of peptides of milk depends on the state of the mucous membrane of the gastrointestinal tract of the child. Thus, some proteins have an inhibitory effect on the growth of microbes in the absence of inflammation on the mucous membrane, while others are active only in the presence of inflammation. Typically, breast milk peptides become active only when they reach the stomach of the baby. A great variety is characterized by oligosaccharides of breast milk. Their concentration varies depending on the individual characteristics of the mother and the duration of lactation. In milk, oligosaccharides are present in the form of free structures and in conjugated form. Free oligosaccharides are involved in the metabolism of *bifidobacteria* and contribute to their reproduction in the intestines of humans, that is, they play a prebiotic effect. In addition, both free and related oligosaccharides directly interact with receptors of immune compromised cells. Oligosaccharides, in contact with molecules of cellular adhesion and Toll-like receptors, can provide regulatory effects

on the immune response. A large number of clinical studies have shown the protective effect of oligosaccharides on infectious processes, and some work suggests that this action may also be relevant to preventing the development of atopic diseases. Protective action on the mucous membrane of the gastrointestinal tract of the child is provided and glycans-complex carbohydrate structures, presented in the form of glycoproteins, glycolipids, mucin and glucosoamino glycans. In breast milk, they are about 1%. In its structure, glycans are reminiscent of receptors, expressed on epithelial cells, which are interacting with pathogenic bacteria. In recent years, it has been established that the majority of lymphocytes in female milk are CD3+, CD8+-cells that belong to the T-cell component of mucosal immunity in the mother. These cells are involved in the formation of the phenomenon of immunological tolerance, and also are components of antiviral and antitumor immunity. Of great importance is the content of breast cancer in the tumor-necrotic factor (TNF), which among other effects is to regulate. In recent years, the number of double-blind, placebo-controlled studies on the effectiveness of using probiotics for the prevention of allergic diseases in young children has increased significantly. Probiotics may be those most effective for both prophylaxis and allergy treatment, which, to a lesser extent, can stimulate the production of proinflammatory cytokines. These probiotic cultures include *B. bifidum, B. infantis, B. longum*. It is also possible that *bifidobacteria*, which are inherent in early childhood, can suppress histamine products and the expression of histamine H1 receptors, as has been shown in the experimental work of Japanese researchers. Although the mechanism is still unclear, it is anticipated that early and more extensive colonization with symbionts of microbial flora in healthy infants can support oral tolerance and reduce the risk of developing allergic diseases. Kalliomaki et al. demonstrated that the appointment of probiotics (in the final weeks of pregnancy and the first 6 months of life) protected against the development of blood pressure at the age of one year and four years. Unfortunately so far, little is known about the influence of probiotics on the prevention of food allergies. Thus, when discussing research on probiotics for the prevention and treatment of allergies, it can be noted that when choosing a probiotic, great importance is the relevance of the child's age and the type of *bifidus* and *lactobacilli*. Unlike probiotics, most prebiotics are used as dietary supplements; in biscuits, porridges, chocolate, pasty and dairy products. Prebiotics include oligosaccharides of breast milk and oligosaccharides that are derived from other sources [79-81]. Technologically, oligosaccharides are obtained from natural sources: they can be synthesized from monomers or obtained by hydrolysis of polymers. These studies are more closely related to artificial mixtures, their possible preventive action in the development of allergies.

### Future step

This views considering the issue of primary prevention of allergic diseases in children, it is not possible to avoid the problem of environmental pollution of the environment. The rapid increase in the prevalence of allergic diseases in developed countries of the world over the past decades can partly be explained by the impact of environmental pollutants. Indeed, air pollution is a growing health problem. Recommendations based on controlled trials can be started from a position adopted by all professionals without exception – all babies need a clean environment for normal development! Although today we have information that reveals some of the causes of the formation of atopy, mechanisms and development in childhood, and factors contributing to the progression of the disease [82-90]. But there are only isolated recommendations that we can use to carry out the primary prevention of allergic diseases. The main ones require an active participation of society, and not only the interaction of parents and professionals. And the rapid increase in the incidence of allergic diseases continues.

## Discussion

A publication by David Strachan in The BMJ in 1989 described the idea that a loss of species diversity from the ecosystem of the human body could lead to allergic disease (BMJ 1989; 299:1259-60). This is a first study to show that newborn baby's immune system must be educated so it will function properly during infancy and the rest of life. Strachan's view can be accurately described as "biome depletion," an evolutionary distortions that works together with other distortions (for example, inflammatory diets and vitamin D deficiency) to undermine immune function in industrialized societies. Today a lot of controversial data has been accumulated in order to completely refute or support the dietary hypothesis of food sensitization development. However, a serious "intervention" study with the early introduction of fish in the diet of children showed no increase in the prevalence of allergy to fish and citrus compared with the group in which fish and citrus from the diet were excluded. The study also showed a decrease in the levels of specific IgE to all food groups, not just fish. This suggests that expanding the diet will allow for a non-specific immune effect or a nonspecific hyposensitization effect on a few foods. The coming back to the "biome depletion", Strachan articulated that viral infections, particularly of the respiratory tract, are important precipitants of the expression of atopy. They could, however, be explained if allergic diseases were prevented by infection in early childhood. We defined David Strachan he identified a loss of species diversity from the ecosystem of the human body as a problem. We defined that some epidemiologic studies demonstrating that allergic diseases and asthma are more likely to occur when the incidence and levels of endotoxin (bacterial lipopolysaccharide, or LPS) in the home are low. LPS is a bacterial molecule that stimulates and educates the immune system by triggering signals through a molecular "switch" called TLR4, which is found on certain immune system cells. Furthermore, we ensured the robustness of our finding using the imputing dataset for dealing with missing data. In the contrast, there is very little information about the relationship of hygienic hypothesis with the mechanisms of food allergy. Despite this, the study conducted in Norway showed that birth by caesarean section was associated with a sevenfold increase in the risk of developing hypersensitivity reactions to eggs, fish, or nuts. In this study, the infants whose mothers were suffering from allergies, the sensitization to the chicken egg was established 4 times more often than among other children of the studied cohort. The effect of these associations should be investigated in future researches. And also largely unexploded and very interesting fact that we would like to hear more often is progesterone support during pregnancy and allergy in child.

And one of the most important issues that directly concern the implementation of primary prevention methods is the possible effect of the allergen on the "pregnant and fetal" system. Our analyzed of databases showed that exposure to prenatal maternal psychosocial stress was associated with increased risk, albeit modestly, of asthma and allergy in the offspring. The pronounced risk during the third trimester may represent cumulative stress exposure throughout pregnancy rather than trimester-specific effect. These findings may represent a causal effect or a result of inherent biases in studies. And we agree with researches which studied associations between prenatal and postnatal tobacco smoke exposure timing and the cumulative incidence of

early onset eczema types in infancy. Tobacco smoke exposure during the third trimester of pregnancy was found to be associated with a higher cumulative incidence of AD/E, especially in all infants and those without parental allergic diseases. And very interesting fact about a critical "window of opportunity" of tobacco smoke exposure for eczema in early infancy may be the third trimester of pregnancy. We hope that a further prospective cohort study investigating whether smoking-induced epigenetic changes in fetal and neonatal T cells cause susceptibility to AD in early infancy may provide evidence for new prophylactic programs for AD.

Area of functional genetic polymorphism which can determine differences in the sensitivity to environmental factors, emphasizing the complexity of the interactions "gene-external environment" is still underdeveloped. Investigating the interaction between different genes, as well as between genes and the environment ("gene gene", "gene-environment") allows us to conclude that the prevention of allergic diseases should be directed to separate genetically sensitive areas ("profile of the gene") and ecological influencing factors.

The analysis of the studies that concern the microbiome has shown today they are the most often investigated and their results are extremely contradictory. No doubt, microbiota has significant prevention role in AD. We had to investigate this issue in this study. However, we are sure that this problem requires further researches and reviews.

## Conclusion

Therefore, since most primary prophylaxis of allergy is still in need of further study, their solution should be one of the main strategic objectives of allergy. At the same time personalized medicine, which involves tailoring health care to each person's unique genetic makeup, has the potential to transform how we diagnose, prevent and treat disease. After all, no two people are alike. Mapping a person's unique susceptibility to disease and targeting the right treatment has deservedly been welcomed as a new power to heal.

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