

KOZICZ, Michał Andrzej, KOŁODZIEJ, Magdalena, SAIUK, Nazarii, MĄDRY, Wojciech, MARCICKA, Justyna, MAZURKIEWICZ, Aleksandra, SALASA, Weronika, WOJCIECHOWSKA, Adriana, SEREDYŃSKI, Tomasz and MĘCZYŃSKA, Joanna. The Role of dietary supplements in the treatment of asthma - a narrative review. *Journal of Education, Health and Sport*. 2024;67:50812. eISSN 2391-8306.

<https://dx.doi.org/10.12775/JEHS.2024.67.50812>

<https://apcz.umk.pl/JEHS/article/view/50812>

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2024;

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 15.04.2024. Revised: 05.05.2024. Accepted: 09.05.2024. Published: 11.05.2024.

## **The role of dietary supplements in the treatment of asthma - a narrative review**

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## **Abstract**

**Introduction:** Asthma is a common inflammatory disease of airway affecting both adults and children. In a large number of cases asthma remains poorly controlled. There is a need to find an additional therapeutic demeanour alleviating symptoms and lowering the risk complications in a long-term. Recently, increasing number of studies has been examining dietary supplements in regards to their anti-inflammatory, immunomodulatory, anti-remodelling properties and their use in asthmatic patients.

**Aim of the Study:** The aim of the study was to collect and analyse current literature regarding influence of different dietary supplements on the course of asthma in both adults and children.

**Methods and Materials:** Extensive research was conducted using PubMed and Google Scholar, with the primary focus on literature from the past 5 years. Firstly, potential dietary supplements affecting course of asthma were collected. The names of the substances were juxtaposed with term “Asthma” to gather data regarding their effect on occurrence and control of asthma and potential mechanisms responsible for it. Additionally, references from selected articles were included in the analysis.

**Results:** Dietary supplements show promising results in decreasing asthma symptoms and lowering inflammation of airway. However, our study revealed that in current state of knowledge there is a deficit of studies performed on humans, especially large-scale, prospective studies that assess the efficacy of different doses of dietary supplements. Thus, further research of dietary supplements in asthma is needed, especially large-scale randomised controlled trials.

**Keywords:** Pulmonology; Asthma; Treatment; Dietary supplements; Food supplements

## **Introduction**

Asthma is a heterogenous, chronic inflammatory disease of the airway. Symptoms and their intensity vary over time and include cough, chest tightness, wheeze, shortness of breath as well as limitation of expiratory flow. It is also associated with airway hyperresponsiveness.<sup>1</sup> Number of people suffering from asthma in 2019 was 262 million, and it contributed to 461 000 deaths that year.<sup>2</sup>

Asthma occurs in different phenotypes. Most common is type 2 asthma. In this type inflammation is characterised by an increase in eosinophil count and Th<sub>2</sub> lymphocytes activity. Higher levels of cytokines such as interleukin (IL) 4, IL-5 and IL-13 produced by those cells

leads to cascade of reactions of the immune system. As a result mast cells are activated and lymphocytes B increase the production of immunoglobulin E (IgE).<sup>3,4</sup> Non-type-2 phenotype is characterised by increase in neutrophil caused by release of cytokines by Th<sub>1</sub> and Th<sub>17</sub> cells.<sup>4</sup>

Treatment of asthma includes inhaled corticosteroids and short-acting  $\beta$ 2-agonists for short-term relief. However, compliance to corticosteroid treatment is low, it was estimated that 22% to 63% of asthmatic patients stick to regular use of corticosteroids. In place of corticosteroids, short-acting  $\beta$ 2-agonists are often used too frequently. This adherence to symptomatic treatment and lack of anti-inflammatory drugs leads to worsening of chronic airway inflammation and may increase the risk of complications.<sup>5,6</sup> Despite treatment asthma remains uncontrolled in 25.3% of children, 22.3% of adolescents and 16.0% of adults.<sup>2</sup> European Food Safety Authority defines food supplements as concentrated sources of nutrients (i.e. mineral and vitamins) or other substances with a nutritional or physiological effect that are ingested. Examples of these substances are vitamins, minerals, amino acids, fatty acids, herbal extracts, plants. They have physiological effect on human body.<sup>7</sup> U.S. Food and Drug Administration (FDA) defines dietary supplements as products that are ingested in order to supplement the diet. They consist of “dietary ingredients”, such as: vitamins and minerals; herbs and other botanicals; amino acids. Dietary supplements must be labelled as such, or as supplements of dietary ingredients they include, for example “vitamin D supplement”. This category excludes drugs and substances that are tested as new drugs.<sup>8</sup>

The aim of this review is to provide an overview on last 5 years of findings concerning influence of dietary supplements on asthma management in both adults and children and to highlight possible mechanisms of occurring phenomena.

## **Vitamin D**

This fat-soluble vitamin can be found in foods such as oily fish, liver, shiitake mushrooms, egg yolk and organ meats.<sup>9</sup> However the main source of this compound in the human organism is endogenous synthesis in epidermal cells. This process requires UVB radiation. Unfortunately in many people exposure to sunlight is insufficient. In these people dietary sources become pivotal for preventing vitamin D insufficiency.<sup>10</sup> Vitamin D<sub>3</sub> is in fact an inactive hormone. In hepatic parenchyma it is converted into prohormone - 25-hydroxyvitamin D<sub>3</sub> (25OHD). 25OHD in the bloodstream is bound by the proteins and is the most stable vitamin D metabolite in human serum, with half-life of 2-3weeks.<sup>9</sup> It is the best indicator of the amount of vitamin D in patient’s body.<sup>11</sup> In the serum 1,25 dihydroxyvitamin

D (1,25(OH)<sub>2</sub>D) acts as a hormone regulating calcium-phosphate homeostasis, and comes from renal hydroxylation of 25OHD. Renal production of 1,25(OH)<sub>2</sub>D is regulated by hormones.<sup>12</sup> In addition to proximal tubular epithelial cells of kidneys, there are other cells in human body able to alpha-1 hydroxylate the 25OHD. Example of such cells are monocytes, macrophages, lymphocytes B and T. It indicates autocrine and paracrine function of active form of vitamin D. Vitamin D receptors (VDR) can be found in many types of cells responsible for immune reaction and pathophysiology of asthma for example lymphocytes, antigen presenting cells, mast cells and structural cells.<sup>13,14</sup> Conversion of 25OHD into 1,25(OH)<sub>2</sub>D by immune cells is contingent on the accessibility to the substrate of hydroxylation reaction rather than hormones, thus sufficient 25OHD serum concentration is needed for optimal paracrine 1,25(OH)<sub>2</sub>D production.<sup>15</sup> Immunomodulating and anti-inflammatory properties of vitamin D call attention of researchers to its application in the treatment of bronchial asthma.<sup>16,17</sup> Vitamin D deficiency is defined as serum level of 25OHD below 20ng/mL and insufficiency is serum level below 30ng/mL.<sup>10</sup>

In experimental studies vitamin D shown effect in decreasing activity of Th<sub>2</sub> and Th<sub>17</sub> cells, increasing the activity of regulatory T cells and in IL-10 production, what led to a belief that supplementation of vitamin D can lower the levels of IgE in asthmatic patients. However, such effect of vitamin D supplementation was not found by Rosser et al. in clinical trial.<sup>18</sup> Nevertheless, meta-analysis conducted by Wang et al. shown improvement in forced expiratory volume in 1 second/forced vital capacity (FEV<sub>1</sub>/FVC) and a decrease in IL-5 and IgE in the vitamin D supplementing group in comparison to placebo group. There was also positive effect on quality of life measured with St. George's Respiratory Questionnaire (SGRQ) score in the experimental group. Additionally, subgroup analysis shown increase in anti-inflammatory IL-10 in the previously vitamin D deficient people.<sup>19</sup> ACVID trial shown that the addition of vitamin D to standard treatment helped in acquiring better control of symptoms shown as increase in Asthma Control Test (ACT) score and improved quality of life in vitamin D deficient adults with asthma.<sup>20</sup> In meta-analysis done by Wang et al. supplementation of vitamin D was associated with FEV<sub>1</sub>% improvement (MD: 8.3 95%CI 5.95–10.64) in adult patients with air restriction (FEV<sub>1</sub>% < 80%) and vitamin D insufficiency. Vitamin D also proved to have a protective effect against asthma exacerbations – reduction in rate by 27% (RR: 0.73 95%CI (0.58–0.92)). However, subgroup analysis shown, that this effect is limited to patients with vitamin D insufficiency. These beneficial impacts were restricted to adults with stable asthma.<sup>21</sup>

VDKA Randomised Controlled Trial (RCT) did not show any difference in the time to severe asthma exacerbation between vitamin D and placebo groups of children aged 6-16 with severe asthma and vitamin D levels below 30ng/mL.<sup>22</sup> Kumar et al. found no protective effect of vitamin D supplementation in preventing moderate to severe asthma exacerbations requiring systematic corticosteroids in children. However, low quality of included trials and poor representation of 25OHD deficient children precludes drawing a conclusion on role of vitamin D in this group of patients.<sup>23</sup> In meta-analysis done by Li et al. vitamin D supplementation did not decrease the risk of asthma exacerbation in children compared to placebo, however they found, that it reduces the risk in the subgroup of children with baseline 25OHD levels below 10ng/ml in comparison to placebo (RR=0.48, 95%CI:0.28 to 0.83, p=0.009). This indicates that vitamin D supplementation helps decrease asthma exacerbation risk in children with vitamin D deficiency.<sup>24</sup>

It stands in opposition to findings of meta-analysis done by Hao et al.. They found no positive effect of vitamin D supplementation in controlling asthma in children. Moreover, they report that vitamin D supplementation may impair patients' lung function- reduce FEV1 and FVC% in comparison to placebo groups.<sup>25</sup>

Although clinical trials do not show this effect clearly in patients, vitamin D, through VDRs, influences the smooth muscle cells and inhibits their contraction and remodelling. It reduces VEGF-induced ADAM33 and cyclin D1 expression, decreases smooth muscle cells reaction to acetylcholine, induces phosphorylation of retinoblastoma protein and checkpoint kinase 1 leading to a decrease in smooth muscle cell proliferation. Vitamin D is also lowering the production of IL-6 and IL-8 involved in bronchial inflammation by reducing the activation of NF-κB. It also regulates function and proliferation of bronchial fibroblasts and decreases collagen production. Additionally, vitamin D regulates immune responses in the airway. It promotes defence against respiratory pathogens, what can lead to a decrease in the number of pathogen induced asthma exacerbations.<sup>26</sup>

Overall, most findings seem to be contradictory and more high quality clinical trials are necessary to further explore potential benefits derived from supplementation of vitamin D in patients with asthma. However supplementation of vitamin D in patients with its deficiency is a low-risk, low-cost and potentially beneficial action.

### **Vitamin C**

Ascorbic acid (vitamin C) is a molecule with antioxidative properties. It incapacitates free radicals directly by donating electrons and indirectly by reactivating other molecules

involved in scavenging free radicals as vitamin E and glutathione. It mitigates damage done by free radicals to cells. It also acts as a cofactor of many enzymes.<sup>27</sup> Vitamin C is an immunomodulating agent- it inhibits NF- $\kappa$ B-mediated inflammation.<sup>28</sup> By reducing the amount of reactive oxygen species (ROS), vitamin C shown an effect in suppressing oxidative stress-mediated MAPK signalling and reduced NF- $\kappa$ B and AP-1 in response to dust mite. This shows a promising role of ascorbic acid in preventing asthma exacerbations induced by allergens.<sup>29</sup>

Study by Tecklenburg et al. shows no difference in baseline lung function, however after-exercise drop in FEV<sub>1</sub> was about 56% lower in vitamin C group than in placebo group. Post-exercise urinary concentration of inflammatory mediators (LTC<sub>4</sub>-E<sub>4</sub> and PGF<sub>2</sub>) was significantly lower in the vitamin C group. Levels of fractional exhaled nitric oxide (FENO) were reduced by ascorbic acid supplementation in a similar way.<sup>30</sup> This shows that ascorbic acid may play an important role as an addition to classical therapy, especially in reducing asthma symptoms related to physical activity.

Statistical analysis done by Hemilä et al. shows that supplementation of vitamin C reduces the risk of exacerbations caused by common cold and reduces bronchial hypersensitivity to histamine.<sup>31</sup> This indicates usefulness of vitamin C in preventing infection-related asthma exacerbations.

In more recent study done by Siripornpanich et al., around 40% of children with persistent asthma exhibited vitamin C deficiency despite its recommended intake. It may be due to its higher utilization to combat free radicals. Lower vitamin C level was correlated with worse asthma control, higher incidence of severe asthma and eosinophilic airway inflammation as well as higher plasma PGF<sub>2</sub> $\alpha$  concentration.<sup>32</sup> On the other hand, observational study analysing the National Health and Nutrition Examination Survey (NHANES) did not found a correlation between serum vitamin C levels and risk of asthma in adults.<sup>33</sup>

Supplementation of anti-oxidative substances such as vitamin C can be useful as an adjunct therapy of asthma, especially in regard to allergen-induced and exercise induced worsening of symptoms and in paediatric asthma.

## **Vitamin E**

Vitamin E is a family of substances:  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherol and  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocotrienol. These lipid-soluble substances are produced by plants, and ingested by animals with plant lipids. Rich sources of vitamin E are seeds, vegetable oils and nuts.<sup>34</sup> Most

abundant isoform of vitamin E is  $\alpha$ -tocopherol, followed by  $\gamma$ -tocopherol, which tissue concentration in humans is ten times smaller. Tocopherols and tocotrienols counteract oxidative damage done by ROS to fatty acids in the cell membrane. They all share the same property of scavenging free radicals, but besides that, their biological activity differs.  $\alpha$ -tocopherol affects cell cycle, influences gene transcription and signal transduction.<sup>35</sup>

$\alpha$ -tocopherol affects the immune system, mainly by influencing T cells. By preventing membrane lipids peroxidation, it alters its integrity. This influences surface proteins' activity. It is also shown that its anti-inflammatory properties include suppression of PGE<sub>2</sub> and pro-inflammatory cytokines: TNF- $\alpha$ , IL-1 $\beta$  and IL-6. It promotes Th<sub>1</sub> response.<sup>36</sup>  $\alpha$ -tocopherol has anti-inflammatory properties, prevents bronchial hyperresponsiveness, and decreases eosinophil and leukocyte recruitment to lungs in mice models of asthma.<sup>37</sup>

$\gamma$ -tocopherol on the other hand, exacerbates allergic inflammation, promotes bronchial hyperresponsiveness and increases eosinophil and leukocyte recruitment. Studies also proved, that  $\gamma$ -tocopherol increases disease severity in lungs when tested on animal asthma models.<sup>29</sup>

These opposite effects of two most abundant isoforms of vitamin E have been also observed in human cohort of the Shanghai Women's Asthma and Allergy Study. It shows that plasma level of  $\alpha$ -tocopherol is negatively correlated with asthma risk, whereas higher  $\gamma$ -tocopherol plasma concentration is correlated with higher asthma risk.<sup>38</sup> Contrary to these findings, in trial conducted by Burbank et al., 14 days supplementation of 1200 mg of  $\gamma$ -tocopherol reduced sputum eosinophilia and mucins. It also lowered LPS-induced neutrophilia in comparison to placebo.<sup>39</sup> This suggests that precision in studying different molecules of vitamin E is needed, and isoforms ought to be researched separately in regards to their heterogenous bioactivity.<sup>36</sup>

## **Vitamin A**

Vitamin A is a fat-soluble substance found in orange-colored vegetables, milk products, liver and fish. In fact, plants contain provitamin A- carotenes, whereas animal products provide us with retinoids- retinol and retinyl esters. These substances are crucial for regeneration of visual pigment, cellular differentiation, regulating metabolism, immune competency and maintaining proper state of mucosal membranes. Vitamin A is stored in liver and adipose tissue.<sup>40</sup>

Vitamin A undergoes irreversible transformation to retinoic acid (RA). It interacts with transcription factors such as retinoic acid receptors or retinoid X receptors and these ligand-receptor complexes regulate transcription of genes.<sup>41</sup>



RA signalling is active in adult lungs and plays a role in airway homeostasis. Its disruption leads to airway smooth muscle (ASM) hypertrophy, hyperreactivity and an increase in collagen production by increasing TGF- $\beta$  signalling. These findings show that deficiency in vitamin A can lead to airway hyperreactivity and remodelling.<sup>41</sup> Another study shows, that the RA metabolism in asthmatic lungs is altered. RA synthesis in ASM is reduced and RA signalling lowered. It also indicates that increase in RA signalling leads to a reduction in ASM mass, which can attenuate airway remodelling.<sup>42</sup> Heine et al. showed that 9-cis retinoic acid (9cRA), a bioactive vitamin A metabolite, modulates response of B cells by decreasing the production of specific IgE and promoting specific IgA production in response to OVA-sensitization. An increase in IL-10 was also observed.<sup>43</sup> It shifts the balance towards Treg response and promotes resolution of airway inflammation.<sup>44</sup>

Study performed by Feng et al. shows that supplementation of vitamin A reduces inflammatory responses in mouse model of asthma. They observed a decrease in eosinophil peroxidase activity and total IgE, LTB<sub>4</sub>, Cys-LT, IL4, IL-5, IL-17, and IL-33 levels.<sup>45</sup> Tian et al. demonstrated that neonatal pneumonia decreases vitamin A levels in murine model. They also proved that supplementation with all-trans retinoic acid (ATRA) after this infection decreases Th<sub>2</sub> and Th<sub>17</sub> production, but promotes Treg and Th<sub>1</sub> production in OVA-induced allergic airway disease (AAD). This intervention also lowered an influx of immune cells into the airway and airway hyperreactivity. This implies, that supplementation with vitamin A can prevent progression of asthma triggered by infections.<sup>46</sup>

In meta-analysis done by Hu et al. there was no association between vitamin A intake and asthma risk in children, nor between serum vitamin A levels and asthma risk. However, this study showed that asthmatic patients have lower serum vitamin A levels than healthy group. It remains unclear, whether low vitamin A level is a cause of asthma, or an effect of higher utilization due to inflammation process in asthma.<sup>47</sup>

Pang et al. showed that reduction of retinol levels in asthmatic patients is significantly more specific to patients with eosinophilic asthma. This shows that retinol deficiency plays a greater part in the pathogenesis of eosinophilic asthma than in non-eosinophilic asthma.<sup>48</sup> It has been proven that serum levels of vitamin A are positively correlated with lung function and quality of life in paediatric patients with stable asthma.<sup>49</sup> In a study performed on British children around 7 year old, higher vitamin A, but not  $\beta$ -carotene was associated with higher

FEV<sub>1</sub> and FEF<sub>25-75%</sub> and lower incidence of asthma, especially in children without paternal history of atopy.<sup>50</sup>

Data from Korea National Health and Nutrition Examination Survey (KNHANES) shows no link between vitamin A intake and asthma prevalence.<sup>51</sup> However, those findings might not be accurate due to the nature of population-based cross-sectional survey study.

### **Curcumin**

Curcumin is a polyphenolic constituent of turmeric- a spice derived from *Curcuma longa*. This substance has been present in traditional eastern medicine for a long time. In recent years it was studied in regard to its antioxidant and anti-inflammatory properties. It acts by inhibiting activation of NF-κB and AP-1, suppressing production of proinflammatory cytokines IL-1β and IL-8, as well as scavenging NO free radicals and inhibiting iNOS.<sup>52</sup> It has been shown that curcumin reduces bronchial hyperreactivity and airway constriction in allergen induced asthma in guinea pig model.<sup>52</sup>

Study performed by Zhu et al. confirms anti-inflammatory effect of curcumin in mouse model of allergen induced asthma. In this study curcumin had an effect of reducing hypersecretion, activity of NF-κB and lowering levels of proinflammatory cytokines (TNF-α, IL-4, IL-5, and IL-13) both in vitro and in vivo.<sup>53</sup> Study analysing *C. longa* extract's influence on asthma model in rats also proved its antioxidant, anti-inflammatory and immunomodulating properties. It was shown that *C. longa* extract helped maintaining balance between Th<sub>1</sub> and Th<sub>2</sub> lymphocyte response.<sup>54</sup>

Study conducted by Wiczfinska et al. presented promising effects of curcumin on remodelling process. Curcumin lowered expression of MMP9, TGF-β and collagen I genes in fibroblasts in vivo. These genes are associated with remodelling process.<sup>55</sup>

There are plans to conduct clinical trials in order to evaluate effect of using curcumin in asthmatic patients.<sup>56</sup> Such studies would prove useful in assessing measurable effects of supplementing curcumin and its influence on asthma control in humans.

### **Omega-3 polyunsaturated fatty acids (n-3 PUFA)**

Docosahexaenoic acid (DHA), alpha linolenic acid (ALA) and eicosapentaenoic acid (EPA) are examples of omega-3 polyunsaturated fatty acids (n-3 PUFA). Main dietary source of these compounds are fish oils. N-3 PUFA have anti-inflammatory properties. They suppress production of omega-6 derived inflammatory mediators, such as cysteinyl leukotrienes and prostaglandin D<sub>2</sub>. N-3 PUFA are also precursors of anti-inflammatory substances such as resolvins, protectins, and maresins, which promote resolution of

inflammation.<sup>57</sup>

Beneficial effect of omega-3 fatty acids is also mediated by free fatty acid receptor 4 (FFA4). This n-3 PUFA sensing receptor can be found in monocytes, macrophages, eosinophils and dendritic cells. It prevents mast cell degranulation, and activation of dendritic cells. This leads to attenuation of inflammation, lower mucin secretion, reduction of both pro-inflammatory cytokines (IL-4, IL-5, IL-13, IFN- $\gamma$ , and IL-17A) and number of immune cells (eosinophils and lymphocytes) in bronchoalveolar lavage fluid.<sup>58</sup> There are reports of omega-3 acids supplementation in mice leading to increased airway reactivity. This phenomenon is a result of interaction with sphingolipid metabolism, and is not associated with inflammation.<sup>59</sup>

In the study done by Stoodley et al. on 255 adults with asthma and 137 without it, erythrocyte n-3 PUFA concentration was expressed as the omega-3 index (O3I)- sum of mass percentages of eicosapentaenoic acid and docosahexaenoic acid. They found that higher O3I was associated with lesser severity of illness, lower inhaled corticosteroids intake and in obese patients- lower CRP and better lung function.<sup>60</sup>

Cross-sectional study performed by Adams et al. on adults working in fish processing factory showed that blood levels of n-6 fatty acids such as linoleic acid, dihomo-gamma-linolenic acid and arachidonic acid were correlated with non-specific bronchial hyperresponsiveness (NSBH), while n-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) were associated with lower risk of NSBH.<sup>61</sup> Another study links higher intake of omega-6 fatty acids with greater asthma severity and worse lung function in children, as well as augmented symptoms occurring due to exposure to particulate matter(PM), both  $\leq 2.5 \mu\text{m}$  and  $\text{PM} \leq 10 \mu\text{m}$ . This study did not find protective traits of omega-3 intake in regards of baseline lung function and asthma severity, however it proved the role of omega-3 fatty acids in mitigating effects of exposure to PM.<sup>57</sup> It indicates that correcting balance between omega-3 and omega-6 fatty acids can protect children from exacerbations caused by air pollution with PM.

Limiting intake of omega-6 and supplementing omega-3 fatty acids in diet of 10 adult patients with aspirin exacerbated respiratory disease lead to reduction of urinary levels of LTE4 and PGD-M. Improvement of clinicals symptoms was observed, however there was no improvement in pulmonary function tests.<sup>62</sup>

On the other hand, there are reports of increased oxidative stress due to exposure to O<sub>3</sub> in epithelial cells supplemented with omega-3 fatty acids. This phenomenon occurs due to

susceptibility of polyunsaturated fatty acids to peroxidation. Products of this reaction may play a role in systemic inflammation caused by O<sub>3</sub>.<sup>63</sup> Cohort study performed by Ekström et al. showed, that in children and adolescents, higher plasma concentration of omega-3, as well as omega-6 fatty acids was associated with decreased risk of asthma at the age of 24. Contrary to that, self-proclaimed higher intake of omega-6 was associated with higher risk of asthma.<sup>64</sup>

### **Probiotics**

WHO defines probiotics as live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. Mainly, the genera *Lactobacillus* and *Bifidobacterium* are used in those supplements.<sup>65</sup> Microorganisms stay in mutualistic relationship with human body. They influence immune system of the gut in the first place, but thanks to gut-lung axis their beneficial effect is present in the respiratory system as well. Proper composition of microorganisms plays a role in maturation of immune system in children and helps in maintaining balance between pro and anti-inflammatory factors. Imbalance in amount and activity of immune cells influenced by gut microbiota is one of the factors in pathogenesis of asthma. Both gut and lung dysbiosis occur in asthma. Probiotics modify bacterial dysbiosis and thus help in reducing lung inflammation.<sup>47-49</sup>

Meta-analysis conducted by Xie et al. explored the beneficial role of various probiotics in asthma. After taking probiotics, FeNO, asthma symptoms and risk of acute episodes of asthma were lower. Degree of asthma control measured with Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT) was higher in experimental group. No significant difference between placebo and probiotics group in regard to lung function indicators (FEV<sub>1</sub> and FEV<sub>1</sub>/FVC%) was found.<sup>66</sup> These results suggest that intake of probiotics can mitigate inflammation in lungs and alleviate symptoms of asthma. No protective effect of supplementing probiotics was displayed in infants in regards to asthma.<sup>67-69</sup>

Randomised Control Trial enrolling children with a mean age of 10.1 months did not show protective influence of probiotic supplementation against asthma. The experimental group received daily sachets of 1.0 g maltodextrin supplemented with *Lactobacillus rhamnosus* (LGG) in combination with *Bifidobacterium animalis* subsp. *lactis* (BB-12), each in a dose of 10<sup>9</sup> colony forming units (CFU), for 6 months.<sup>70</sup> Nevertheless, a different RCT comprising of 160 asthmatic children in the age of 6 to 18 years did prove beneficial effects of probiotic supplementation. Participants were administrated

placebo or *Lactobacillus paracasei* GMNL133 (LP), *Lactobacillus fermentum* GM-090 (LF), or their mixture (LP + LF). All three experimental groups exhibited improvement in asthma severity and C-ACT scores. Only in the LP + LF group IgE levels decreased and peak expiratory flow rate (PEFR) increased significantly. Best outcomes were achieved in LP + LF group, presumably because of dose-dependent effect or synergy between strains.<sup>71</sup> Similarly, promising results were achieved in PROPAM study. 422 children with mean age of 7 years partook in this RCT. Experimental group was administrated a mixture of *Ligilactobacillus salivarius* LS01 ( $1 \times 10^9$  live cells) and *Bifidobacterium breve* B632 ( $1 \times 10^9$  live cells) 2 times a day for 8 weeks, then once a day for following 8 weeks. This intervention led to reduction of asthma exacerbation probability in comparison to placebo group (OR = 3:17). Moreover, patients in placebo group were at a greater risk of having two exacerbations than patients in experimental group (OR = 3:65).<sup>72</sup> Trial assessing influence of an addition of *Bifidobacterium lactis* Probio-M8 to asthma treatment found, that in comparison to standard treatment + placebo, supplementation with this probiotic helped to increase ACT score and decrease FeNO as well as CaNO (alveolar nitric oxide concentration). It also helped to maintain a stable gut microbiota diversity. There was no beneficial effect on lung activity (measured with PEF, PEV<sub>1</sub> and FVC), serum IgE levels nor peripheral eosinophil count found in said trial.<sup>73</sup>

## **Conclusion**

Asthma poses a serious health problem in the world. Many people suffer from it, despite being diagnosed and treated. Poor asthma control calls for additional health interventions. One of which can be supplementing the diet with substances that can affect course of this disease. Although many dietary supplements have been proven to have anti-inflammatory, immunomodulating and anti-remodelling properties in vitro and in animal models, there is not enough publications tracing such effects in patients. Notably, there is a shortage of high quality studies. Many findings are contradictory. There is also a gap in the state of knowledge regarding optimal doses of dietary supplements in treatment of asthma. Therefore, conducting further research, with a particular emphasis on large-scale RCTs, is crucial for resolving the dubiety over the role which dietary supplements can play in the treatment of asthmatic patients.

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### **Funding statement**

The study did not receive special funding.

### **Informed Consent Statement**

Not applicable

### **Acknowledgments**

Not applicable

### **Conflict of Interest Statement**

The authors report no conflict of interest

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