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The role of nutrition in childhood asthma

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Background: Asthma is a chronic respiratory disease with high prevalence in the Western world. The global burden of asthma continues to increase, especially in low- to middle-income countries due to urbanization. Childhood-onset asthma is typically related to allergy and is often preceded by frequent wheezing. Furthermore, atopic dermatitis, food allergy or allergic rhinitis are common predictors of childhood asthma, as depicted in "atopic march". Nevertheless, the pathogenesis of asthma consists of numerous factors, including hereditary and environmental components. Early exposure to tobacco smoke, pollution and respiratory infections has already been associated with the development of asthma. Current research aims to identify more modifiable risk factors linked with asthma to develop effective preventive guidelines. Researchers have studied the relationship of specific nutrients or other dietary factors with the risk of developing allergic diseases. These studies focus especially on the first 1000 days of life, including prenatal and postnatal phases.

Methods: Database search was performed in PubMed and relevant articles were selected from 2015 to present including a few older studies as well. Randomized controlled trials were prioritized. Search was limited to vitamin D, probiotics, fish oil and processed food. This review focuses on the preventive role of these nutrients related to childhood allergic symptoms, mainly asthma.

Results: 16 RCTs were included along with 9 cross-sectional or population-based original studies. Additionally, systematic reviews were used to compare the results. Vitamin D reduced the risk of asthma/wheeze in two studies at 1-3 years, but the effect was not sustained in longer follow-ups. Probiotics were associated with reduced risk of eczema but not with asthma or wheeze. Fish oil supplementation showed mixed results in prevention of childhood asthma or wheeze. Consumption of ultra-processed food increased the risk of childhood asthma or wheeze in majority of reviewed articles although one study reported contrasting results.

Conclusions: Currently there is no recommendations concerning dietary changes or supplements made solely for the prevention of childhood asthma. We identified that vitamin D supplementation during pregnancy or infancy might not be effective in long-term prevention of childhood asthma. Probiotics show potential in preventing atopic dermatitis but similar effect is not seen with asthma or wheezing illness. Fish oil supplementation with regular doses might not be effective in prevention of asthma or wheeze. High consumption of ultra-processed foods seems to be associated with childhood respiratory symptoms and asthma with one study reporting non-significant effect.

Key words: asthma, wheezing, children, prevention, Vitamin D, probiotics, fish oil, processed food.

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1 Introduction

Asthma is among the most common non-communicable diseases in the world affecting up to 18% of the population although there are high regional differences. It inflicts a considerable strain on healthcare, accounting for rising costs and leading to reduced quality of life. Total annual cost of asthma has reached 82 billion dollars in the US in 2013. Asthma is a chronic respiratory disease characterized by variable airflow limitation, subsequently causing shortness of breath and wheezing. Symptoms of asthma typically vary over time and in severity. Various environmental factors such as allergen exposure might trigger or worsen the clinical presentation of asthma. (GINA: main report 2022). The growing prevalence of asthma appears to be reaching a plateau phase, at least in high-income countries. Childhood-onset asthma is more often allergic by phenotype i.e., associated with parental history of allergic disease or atopy. However, there is also a greater chance of remission with up to 60% of children with asthma-like symptoms in early life (before age of 10) not affected in adulthood. The role of genetics appears to be highlighted for early-onset asthma versus adult-onset asthma. Yet there is a relationship with environmental factors such as habitat and exposure to infections or pollutants. (Porsbjerg et al. 2023.) Despite these known risk factors for asthma, the primary prevention has turned out to be challenging. There has been an emerging focus on nutritional factors during pregnancy and infancy to influence asthma development. Regardless of the available research there are no conclusive dietary guidelines that would have a certain effect on the development of allergic diseases. The role of dietary and nutritional factors thus needs further investigation to identify beneficial products as well as the optimal timing and quantity of administration (GINA: main report 2022).

This review aims to elaborate on the latest research related to the role of modifiable maternal and postnatal dietary factors in the development of early childhood asthma. The included nutrients were limited to vitamin D, probiotics, fish oil and processed food.

2 Methods

This literature review included practical work at Turku University Hospital (TYKS) as a part of Fish Oil and Probiotics in Pregnancy (FOPP) study from 2020 to 2022.

We were assigned to perform spirometry with bronchial dilation test to children of 5-6 years old as a part of planned visits to the hospital. Information about possible airway hyperresponsiveness is to be used in further studies. FOPP study aims to determine whether probiotics or fish oil supplements could affect the risk of gestational diabetes by lowering it. Furthermore, the researchers are keen to study the association of these supplements to a potential risk reduction in allergic diseases among children.

Database search was performed on the end of 2022 and updated in February 2023. Search was limited to PubMed archive only and studies published prior to 2015 were mostly excluded. Following search terms were used [(“Vitamin D*” OR “D vitamin*”) AND (child* OR preschool*) AND (asthma*), (“Probiotic*”) AND (child* OR preschool*) AND (asthma*), ("Fatty-acid*" OR "Fatty acid*" OR "Omega-3*" OR "Omega 3*" OR “Fish oil*”) AND (child* OR preschool*) AND (asthma*), ("Processed food*" OR “Ultra-processed food*” OR “Fast food*” OR “Junk food*”) AND (child* OR preschool*) AND (asthma*)]. Only articles written in English were included. Randomized controlled trials were prioritized.

Additionally, there were a couple of criteria for the included articles: 1) study focuses on the prevention or risk of asthma or other allergic disorders 2) study includes child population, preferably 0-6 years old.

3 Review of the literature

3.1 Vitamin D

Growing evidence in recent studies indicates a connection between vitamin D deficiency and childhood asthma. Vitamin D (VD) is believed to be one of the contributing factors in asthma pathogenesis by means of regulatory immune responses and airway smooth muscle remodeling. It might also influence the development and maturation of the lungs. (Salmanpour et al. 2022.) The most commonly used biomarker indicating the overall VD status is 25-hydroxyvitamin D_3 [25(OH)D]. Vitamin D deficiency is an emerging health issue due to the decreased sun exposure and low dietary intake. (Ali et al. 2017.) The main results of this chapter are depicted in table 1.

The Vitamin D Antenatal Asthma Reduction Trial (VDAART) was a fairly large multicentre study that aimed to determine the preventive effect of prenatal VD supplementation regarding asthma or recurrent wheeze of their offspring (Litonjua et al. 2016). The study randomized 881 pregnant women to receive higher and lower doses of VD supplements (4400 IU/day and 400 IU/day respectively). Results showed a 6.1% absolute reduction of asthma or recurrent wheeze by the age of 3 years (HR, 0.8; 95% CI, 0.6-1.0). However, it failed to achieve statistical significance even though it was borderline (p=0.051).

There were many limitations to this study which encouraged investigators to make secondary analyses. The data was gathered via parental report, since asthma diagnosis in early life is challenging. Followed children were at high risk of developing allergic diseases and thus generalizing these results should be made with caution. In addition, 25% of the women in the intervention group did not achieve the target level of 75 nmol/L of 25(OH)D by the end of pregnancy. Investigators were not able to make any recommendations based on this study. The timing of VD administration might need to happen in early pregnancy (before 4th week). Also, the dose may have been too scarce. Postnatal VD supplementation should be considered since the blood level of 25(OH)D was similar between groups of children at 1 year.

Wolsk et al (2017) performed their trial using the same VDAART-data and found that women with initial 25(OH)D level of 75 nmol/L or greater on entry together with randomization to the intervention group (4400 IU/day) had the lowest risk of offspring asthma or wheeze (OR, 0.42; 95% CI, 0.19-0.91) at 3 years. The protective effect of their offspring was even bigger with women that

had their initial 25(OH)D levels measured 100 nmol/L or greater (OR, 0.13; 95% CI, 0.02-0.99). However, the population for this group was very small.

Based on the results, investigators concluded that VD supplementation early or even before pregnancy could be beneficial since mothers with high preintervention 25(OH)D blood levels and continued supplementation had the lowest risks in offspring asthma/wheeze by 3 years.

Litonjua et al conducted a 6-year follow-up of a VDAART study (Litonjua et al. 2020). This was of high clinical relevance, since asthma diagnosis can be more difficult to make at a younger age. The results were underwhelming as no protective effect was achieved by the age of 6 years with prenatal vitamin D supplementation. Secondary outcomes also failed to show significant results between groups. Similar 6-year follow-up (Brustad et al. 2019) of a randomized controlled trial found no evidence of in utero VD supplementation via mother reducing child's asthma risk (OR, 0.87; 95% CI, 0.59-1.28). Furthermore, a significant effect on persistent wheeze was not found even at the age of 3 in the same birth cohort (Chawes et al. 2016) although there were fewer events of troublesome lung symptoms in the intervention group. Investigators also noticed an up-regulation of airway immune profile at early infancy which is of unknown importance since the results were not positive in the subsequent 6-year follow-up.

These studies indicate that maternal vitamin D supplementation solely during pregnancy might not be effective in preventing the development of asthma/recurrent wheeze in offspring by the age of 6 years. A more multifaceted approach might be needed to prolong the protective effect to mid childhood or school age. Vitamin D supplementation alone might have a positive effect on certain childhood wheeze or asthma phenotypes. Future studies should combine prenatal and postnatal supplementation since the positive rise of blood 25(OH)D levels during pregnancy was not sustained.

A study with black preterm infants aimed to assess the effectiveness of postnatal vitamin D supplementation in reducing recurrent wheeze by 12 months of age (Hibbs et al. 2018). There was a positive association compared to diet-limited supplementation (RR, 0.66; 95% CI, 0.47-0.94). However further research and longer follow-up is needed to make any recommendations.

Another study including only postnatal vitamin D supplementation was carried out in Finland (Rosendahl et al. 2019). Infants were administered 1200 IU or 400 IU of daily VD as of 2 weeks of

birth until 12 months of age. Thereafter information about allergic diseases via questionnaires and study diaries as well as serum samples for IgE-measurement were gathered. No difference on food or aeroallergen sensitization was found between groups. Likewise, there was a similar rate of wheezing illness or hospitalization due to bronchiolitis/wheezing between groups. Only 1 child had diagnosed asthma by 12 months of age. Moreover, a higher cord blood 25(OH)D level at birth correlated with increased risk of food sensitization.

The mother-child pairs of this study were mostly VD sufficient during pregnancy and birth. Therefore, results demonstrate the lacking effect of vitamin D supplementation in this population. Information about allergic diseases was based on parental report which is a potential limitation. In addition, the follow-up time was narrowed to 12 months, thus there were only 1 case of diagnosed asthma. Nonetheless, early wheezing illness could act as a predictor to later development of asthma. Study does not support the role of vitamin D in the primary prevention of allergic diseases in early childhood.

Table 1. Vitamin D supplementation in prevention of childhood allergic outcomes.

Reference (year)	Country	N	Age	Intervention	Outcome	Design	Effect of VD	Conclusion
Brustad et al (2019)	Denmark	545	6 years	2800 IU/day vs. 400 IU/day	Asthma	RCT	aOR 1.21 (95% CI, 0.63-2.32)	No effect on asthma
Chawes et al (2016)	Denmark	581	3 years	2800 IU/day vs. 400 IU/day	Persistent wheeze	RCT	HR 0.76 (95% CI, 0.52-1.12)	No effect on persistent wheeze
Hibbs et al (2018)	United States	300	12 months	400 IU/day vs diet-limited	Recurrent wheezing	RCT	RR 0.66 (95% CI, 0.47-0.94)	Reduced risk of recurrent wheezing
Litonjua et al (2020)	United States	707	6 years	4400 IU/day vs. 400 IU/day	Asthma or recurrent wheeze	RCT	Effect (95% CI): 3.5 (-2.5-9.5)	No effect on asthma or recurrent wheeze
Litonjua et al (2016)	United States	806	3 years	4400 IU/day vs. 400 IU/day	Asthma or recurrent wheeze	RCT	HR 0.8 (95% CI, 0.6-1.0)	Borderline reduction of asthma or recurrent wheeze
Rosendahl et al (2019)	Finland	975	12 months	1200 IU/day vs. 400 IU/day	IgE sensitization to food or aeroallergen (1), Allergic disease and symptoms (2)	RCT	Wheezing illness: 0.94 (95% CI, 0.58-1.50)	No effect on allergic diseases or sensitization
Wolsk et al (2017)	United States	806	3 years	4400 IU/day vs. 400 IU/day	Association of 25(OH)D levels in pregnancy with the risk of asthma or recurrent wheeze	RCT	OR 0.42 (95% CI, 0.19-0.91)	Baseline 25(OH)D ≥75 nmol/L together with treatment reduced the risk of asthma/recurrent wheeze

IU/day = International units/day (1 μg = 40 IU), IgE = Immunoglobulin E, aOR = Adjusted odds ratio, HR = Hazard ratio, RR = Relative risk ratio, 25(OH)D = 25-hydroxyvitamin D_3, VD = Vitamin D, RCT = Randomized controlled trial

3.2 Probiotics

Probiotics are dietary supplements which show numerous beneficial health effects to the host when consumed in adequate amounts. Probiotics consist of live microorganisms capable of enriching gut microflora and strengthening the immune system through various mechanisms. (Sharifi-Rad et al. 2020.) Researchers have hypothesized the possible preventive effect of oral probiotic supplementation on pediatric asthma. Results have been mixed and currently there is no recommendation to use probiotics in primary prevention of childhood asthma. (Trambusti et al. 2020, GINA: main report 2022). Previous research has been largely inspired by the "hygiene hypothesis" which suggests that early life exposure to microbes might modulate and enhance the immune system leading to reduced risk of allergic diseases (Colquitt et al. 2022). Furthermore, a connection between the GI tract and lungs has been identified, termed gut-lung axis. Despite their anatomical separation, disturbances in the gut microflora might play a role in the development of asthma while the mechanisms of this relationship are not fully understood. (Hu et al. 2021.)

Probiotic interventions have shown promise in reducing the risk of infant eczema and atopic dermatitis, although there are also contrasting results. Investigators have not found a significant effect with probiotic supplementation on the incidence of childhood asthma. (Colquitt et al. 2022). However, eczema is strongly associated with later development of asthma and rhinitis according to "atopic march" and thus these studies are of high clinical relevance (von Kobyletzki et al. 2012). Kalliomäki et al (2001) were among the first to discover a preventive effect on atopic eczema by administrating *Lactobacillus GG* to mothers and infants at high risk of developing atopic diseases. At 2 years of age the risk of eczema was cut down by half among infants who were given probiotics (RR, 0.51; 95% CI, 0.32-0.84). Main results of the reviewed studies are depicted in table 2.

Wickens et al (2012) have followed a high-risk birth cohort for several years and found that maternal and postnatal probiotic supplementation (*Lactobacillus rhamnosus* HN001) reduces the risk of eczema at the ages of 2 and 4 years when compared to placebo [(HR, 0.51; 95% CI, 0.30-0.85) and (HR, 0.57; 95% CI, 0.39-0.83) respectively]. There was also a significant reduction of rhinoconjunctivitis at 4 years of follow-up but not for wheeze even though the trend was protective (HR, 0.79; 95% CI, 0.59-1.07). Fecal sample analyses show that a long-term colonization of the bowel with probiotic strains is not likely since the detection of current strains was lower in both intervention groups compared to placebo at 4 years. However, investigators could not exclude any immunomodulatory effects that might persist and help to prevent allergic diseases.

Authors also report some limitations. There is a possibility of misclassification regarding allergic rhinitis and asthma. Some of the transient wheezers may have been wrongfully placed to asthma-category. In addition, bias as a result of unblinding could not be excluded due to the positive results of the prior study against eczema at 2 years. However, care was taken to minimize this effect. This is among the few studies that show a prolonged protective effect of probiotic supplementation against the development of allergic diseases. Even so, further research is needed to confirm these results.

A Finnish trial is in line with previous study. The risk of infant eczema during 2 years of follow-up was reduced with both probiotic combinations compared to placebo when administered only to the mothers. Supplementation was not associated with risk reduction of atopic sensitization. There were no adverse effects in the intervention groups and GI symptoms during trial did not differ between the study groups. (Rautava et al. 2012.)

Probiotic supplementation was given to sensitized mothers with either prior history or active allergic disease leading to a higher risk of allergy or atopy in their children. This was made purposefully but limits the use of applying these results to the general population. Furthermore, a longer follow-up might help to show a definite preventive effect versus the postponement of atopic march.

A 6-year follow-up of a Norwegian ProPact study demonstrated a protective trend concerning atopic dermatitis with children whose mothers were in the probiotic group (Simpson et al. 2015). The result was statistically significant in complete case analysis (OR, 0.48; 95% CI, 0.25-0.92). However, the prevalence of asthma (OR, 3.25; 95% CI, 0.33-31.6) or wheeze (OR, 0.85; 95% CI, 0.52-1.38) were not reduced by the maternal probiotic supplementation. There was a marked loss to follow-up which could affect the reliability of this study. However, it is one of the few studies to include unselected women from the general population.

Cabana et al (2017) conducted a study using only postnatal probiotic administration in the US. High-risk infants received daily capsules of *Lactobacillus rhamnosus* GG + 225 mg of inulin (intervention group) or 325 mg of inulin (placebo) which were dissolved in pumped breast milk, formula or water. Investigators aimed to show a preventive effect towards childhood eczema and asthma with probiotic supplementation during the first 6 months of life. Results were

underwhelming since no significant effect was detected. At 5 years the cumulative incidence of asthma was 9.7% in the probiotic group and 17.4% in the placebo group (HR, 0.88; 95% CI, 0.41-1.87). Regarding to “atopic march” earlier eczema diagnosis was linked to greater risk of asthma (HR, 3.64; 95% CI, 1.66-7.96).

A larger sample size might have been needed to yield a distinguishable difference in the incidence of asthma. Moreover, there was a high breastfeeding rate and lower than average percentage of infants born via cesarean section. Study adds to the evidence that not all children with high risk of developing allergic diseases benefit from probiotic supplementation. Furthermore, supplementation during late pregnancy might be necessary to produce a protective effect.

The optimal timing of administering probiotics is still disputed. Most studies include prenatal or postnatal supplementation or both with infants receiving their supplements no later than 6 months of age. A randomized controlled trial (Schmidt et al. 2019) studied the effect of probiotic supplementation in the later stage of infancy (mean age 10.1 months). 285 children were randomized in two groups making sure to even the baseline characteristics. Probiotic group received a combination of *Lactobacillus rhamnosus* and *Bifidobacterium animalis subsp lactis* while the placebo group received maltodextrin. Parents were unselected regarding prior asthma history. The results were gathered after 6 months of follow-up (mean age 16.1 months). A significantly lower proportion of children developed eczema in the probiotic group compared to placebo (RR, 0.37; 95% CI, 0.14-0.98). There was no difference between groups concerning the incidence of other allergic diseases. However, such diseases e.g. asthma tend to have a later onset and thus a longer follow-up might be needed.

Table 2. Probiotics in prevention of childhood allergic outcomes.

Reference (year)	**Country**	**N**	**Age**	**Intervention**	**Outcome**	**Design**	**Effect of Probiotic**	**Conclusion**
Cabana et al (2017)	United States	184	5 years	*Lactobacillus rhamnosus* GG vs. placebo	Eczema (1) Asthma and allergic rhinitis (2)	RCT	HR 0.95 (95% CI, 0.59-1.53) 0.88 (95% CI, 0.41-1.87)	No effect on eczema or asthma/allergic rhinitis
Rautava et al (2012)	Finland	205	2 years	*L. rhamnosus* + *Bifidobacterium longum* OR *L. paracasei* + *B. longum* vs. placebo	Eczema	RCT	OR 0.17 (95% CI, 0.08-0.35) 0.16 (95% CI, 0.08-0.35)	Reduced risk of eczema No effect on atopic sensitization
Schmidt et al (2019)	Denmark	290	16 mths	*L. rhamnosus* + *B. animalis subsp* vs. placebo	Eczema (1) Asthma or other allergic disease (2)	RCT	RR 0.37 (95% CI, 0.14-0.98)	Reduced risk of eczema No effect on asthma or other allergic disease
Simpson et al (2015)	Norway	163	6 years	*L. rhamnosus* + *L. paracasei* + *B. animalis subsp* vs. placebo	Atopic dermatitis, Asthma, Allergic rhinoconjunctivitis	RCT	Complete case analysis: OR 0.48 (95% CI, 0.25-0.98)	Reduced risk of atopic dermatitis in complete case analysis No effect on other outcomes
Wickens et al (2012)	Australia & New Zealand	425	4 years	*L. rhamnosus* vs. placebo	Eczema (1) Wheeze, SCORAD ≥ 10, Sensitization (2)	RCT	HR 0.57 (95% CI, 0.39-0.83)	Reduced risk of eczema extends to 4 years, less rhinoconjunctivitis, no effect on wheeze

HR = Hazard ratio, OR = Odds ratio, RR = Relative risk ratio, mths = months, RCT = Randomized controlled trial

3.3 Fish oil

It has been suggested that fish oil supplementation during pregnancy or in early infancy might reduce the risk for allergic diseases such as childhood asthma. Due to the increasing incidence of asthma or wheeze preventive research in this field has potentially great clinical significance. Previous trials have not shown consistent correlation between maternal fish oil supplementation and reduced risk of asthma or wheeze among their offspring. (Wu et al. 2022, Yang et al. 2013.) Fatty acids can be divided into three categories: saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) with health benefits increasing in respective order. Current research is focused on N-3 PUFAs such as linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). N-3 PUFA is more commonly known as omega-3 fatty acids. The protective effect of PUFA against asthma in prenatal period and early life is believed to happen through multiple immunomodulatory and anti-inflammatory pathways. (Xu et al. 2021.) Main findings considering fish oil are compiled in table 3.

A randomized controlled trial published by Bisgaard et al in 2016 showed promising results. 736 pregnant women were randomized to two groups from which the intervention group received a high-dose N-3 LCPUFA supplement. Fish oil supplementation started at week 24 of pregnancy and lasted until 1 week post-delivery. Primary endpoint was persistent wheeze or asthma and there were also secondary endpoints such as eczema. Results showed the strongest preventive effect among those children whose mothers had the lowest preintervention EPA and DHA blood levels (HR 0.46; 95% CI, 0.25-0.83). A statistically significant risk reduction was seen also in the whole treatment group versus control group.

To conclude, the maternal fish oil supplementation was associated with lower prevalence of asthma or persistent wheeze in their offspring. The effect was sustained through 2 and 5 years of age. Considering the high baseline intake of N-3 LCPUFA among the Danish population the effect of supplementation might be even greater in other populations.

More recent study elaborated on the connection between maternal fish oil supplementation and childhood asthma by considering the maternal PUFA status and personal asthma history as well as child sex (Rosa et al. 2020). They found that higher maternal N-6 PUFA levels during pregnancy correlated with higher risk of asthma in their offspring through the ages of 4 to 6. This effect was even more pronounced with children whose mothers had personal asthma history. In additional

analysis investigators also found a significant interaction which indicated that male children with asthmatic mothers and a higher N-6/N-3 PUFA ratio in pregnancy had the highest risk regarding all outcomes. Findings suggest that prenatal PUFA status can affect the development of asthma in their children although changes are related to sex. Still, further evidence is needed to identify those who benefit from long-chain PUFA intervention.

In contrast, a 6-year follow-up study published in 2016 did not show a reduced risk of IgE-associated allergic disease among 6 years old children with a familial risk of allergy (Best et al. 2016). Mothers received fish oil supplementation during pregnancy and their children were assessed for any allergic symptoms and IgE-sensitization specified by the investigators. As said, there was no association of prenatal PUFA supplement and reduced incidence of allergic disease with sensitization (wheeze with sensitization: RR 1.24; 95% CI, 0.83-1.85).

Investigators noticed a larger proportion of mothers who sought unblinding in the intervention group versus control group (15.2% versus 9.9% respectively) which could be a potential limitation of this study. Moreover, the breastfeeding rate was initially higher after birth in the intervention group versus control group (96% versus 91% respectively).

A long-term follow-up study with preterm infants was conducted in Australia (Gunaratne et al. 2019). Trial included 657 infants born before 33 weeks of gestation. Lactating mothers were given fish oil supplements to raise the breast milk PUFA content. High-DHA group achieved significantly higher DHA concentration compared to standard-DHA group and this translated correspondingly to the plasma DHA content of their offspring. Supplementation lasted until infants were 40 weeks of postmenstrual age. Analysis was based on a parental report via validated questionnaire for allergic symptoms at 7 years of corrected age. There was no significant reduction of any measured symptoms when high- and standard-DHA groups were compared (wheeze: RR 1.10; 95% CI, 0.73-1.65). The findings do not promote the supplementation of preterm infants with fish oil to prevent allergic diseases.

A large, pooled analysis of 18 European and US birth cohorts intended to find a connection between dietary fish and seafood intake during pregnancy and childhood respiratory symptoms (wheeze, asthma, allergic rhinitis). Results were underwhelming since the evidence was not supportive towards a protective effect. (Stratakis et al. 2017.) This led the investigators to think that the simultaneous exposure to pollutants might neutralize the beneficial effects of seafood. Further

research is needed to distinguish the effects of different fish types. In addition to this the possible exposure to toxicants while consuming seafood should be considered and measured as well.
The evidence from this multicohort study does not support the increase of fish intake during pregnancy in order to reduce respiratory outcomes such as asthma in their children. However, there are some studies that suggest a healthy diet including regular fish components during early childhood might reduce the risk of allergic disease (Øien et al. 2019, Lee-Sarwar et al. 2019).

Table 3. Fish oil supplementation in prevention of childhood allergic outcomes.

Reference (year)	**Country**	**N**	**Age**	**Intervention**	**Outcome**	**Design**	**Effect of fish oil**	**Conclusion**
Best et al (2016)	Australia & New Zealand	706	6 years	DHA (800 mg/d) + EPA (100 mg/d) vs. placebo	Allergic disease with sensitization	RCT	Asthma: RR 1.01 (95% CI, 0.75-1.37)	No effect on allergic diseases
Bisgaard et al (2016)	Denmark	695	3-5 years	DHA + EPA (2,4 g/d) vs. placebo	Persistent wheeze or asthma	RCT	HR 0.69 (95% CI, 0.49-0.97)	Reduced risk of persistent wheeze or asthma
Gunaratne et al (2019)	Australia	569	7 years	Mothers: DHA + EPA (900+195 mg/d) Infants: DHA (50 mg/kg/d) vs. placebo	Wheeze and rhinitis	RCT	RR 1.10 (95% CI, 0.73-1.65)	No effect on any outcomes
Rosa et al (2020)	United States	1019	4-6 years	Association between prenatal PUFA status and offspring wheeze/asthma	Asthma and wheeze	Cross-sectional study	N-6 PUFA IQR diff. Ever asthma: RR 1.21 (95% CI, 1.01-1.46)	Higher prenatal N-6 PUFA increased the risks of all respiratory outcomes among children with asthmatic mothers
Stratakis et al (2017)	EU & US	60774	0-8 years	Association of fish intake during pregnancy and offspring allergic symptoms	Allergic symptoms	Pooled analysis of 18 birth cohorts	Asthma risk at preschool age: RR 1.02 (95% CI, 0.97-1.07)	No effect on any outcomes

DHA = Docosahexaenoic acid, EPA = Eicosapentaenoic acid, PUFA = Polyunsaturated fatty acid, RR = Relative risk ratio, HR = Hazard ratio, IQR diff. = Interquartile difference, mg/d = milligrams per day, g/d = grams per day, RCT = Randomized controlled trial

3.4 Processed food

Worldwide dietary patterns, especially in the western countries are changing rapidly. Ultra-processed foods (UPF) including different types of fast food are already eaten in such quantities that make up more than half of the dietary energy consumed in the US and UK. (de Oliveira et al. 2022.) UPFs consist of numerous ingredients that are known dietary risk factors, such as saturated fat and high amounts of added sugar and sodium. This kind of nutrition is a well-defined contributor to the incidence of several non-communicable diseases and responsible for diet-related deaths and other disabilities. (Elizabeth et al. 2020.) NOVA food classification categorizes different types of foods to 4 groups. The first group is made of unprocessed or minimally processed foods with no added substances to the original product. However, it allows basic processing of food such as boiling or drying. Ultra-processed foods belong to the fourth group. UPFs usually require multiple industrial processes and contain high levels of added salt and sugar as well as ingredients not used in household kitchens and additives. UPFs include e.g. soft drinks, pastries, pasta, pizza and burgers. (Monteiro et al. 2019.) This part of the review will be focusing on the possible association between dietary intake and allergic outcomes, mainly childhood asthma or wheeze. Results of the reviewed studies are compiled in table 4.

A population-based study in the US studied the prenatal exposure to fast food (von Ehrenstein et al. 2015). The maternal diet was analyzed via questionnaires soon after birth. Using the ISAAC core questions, the symptoms among offspring was assessed at 3.5 years of age. Fast food consumption during pregnancy correlated to the risk of current or severe asthma among children dose-dependently reaching statistical significance in “every day” vs. “never” comparison (RR, 4.46; 95% CI, 1.36-14.60 and RR, 4.34; 95% CI, 1.22-15.43 respectively).

Recently published observational study using a US cohort of 2736 children (6-19 years) aimed to find connections between UPF intake and allergic symptoms (Kong et al. 2022). UPF intake was classified to 4 quartiles. Investigators found a coherent association between UPF consumption and current asthma among children. The highest risk was in the fourth quartile (OR, 1.76; 95% CI, 1.1-2.82). However, there was also a significant reduction of IgE-sensitization with children consuming more UPFs (Q4: OR, 0.66; 95% CI, 0.49-0.89). This might be due to the lower protein (allergen) content characterizing UPFs.

A similar cross-sectional study was also performed in Spain but with a younger population (~5 years). Participants were divided into 2 groups based on their median UPF consumption (N=513). Data was self-reported by parents using wheezing illness as an end point. High consumption of UPFs increased the risk of primary outcome by 87% (OR, 1.87; 95% CI, 1.01-3.45) after multivariate analysis. This also raised the probability of asthma but was not statistically significant. (Moreno-Galarraga et al. 2021.)

There is also some evidence of other modifying factors affecting diet-induced allergic symptoms such as gender and geographical location. A large multicentre study in France showed that allergic symptoms were much more prevalent in male children. (Saadeh et al. 2015.) It offered more comprehensive dietary assessment and IgE-sensitization with skin-prick test and bronchial hyper-responsiveness using pre- and post-exercise PEF was also measured. Fast food consumption was associated with asthma among IgE-sensitized children (OR, 2.39; 95% CI, 1.47-3.93).

A statewide study using 56312 surveys was carried out in California. It aimed to explore the prevalence of asthma among children aged 2-11 years in respect to different types of foods and sociodemographic factors. (Reis et al. 2020.) Higher consumption of soft drinks (3 or more/day), french fries (2 or more servings/day) and fast food (2 or more times/week) was linked with increased asthma prevalence (fast food: OR, 1.21; 95% CI, 1.02-1.45). Consumption of fruit seemed to be protective of childhood asthma when comparing those children eating zero fruits per day versus 4 or more fruits per day (16,6% versus 13,9% respectively).

In contrast Machado Azeredo et al (2020) provided opposing evidence using the data from 2004 Pelotas birth cohort. UPF consumption during childhood (6 years) or school age (11 years) was not associated with asthma at 11-year follow-up. The subanalysis of different UPF items did not offer any associations either. There was however a positive connection between childhood obesity and asthma in adolescence (OR, 1.77; 95% CI, 1.20-2.60).

Limitations of these studies begin from the cross-sectional designs which restricts the investigators from making causal relationships. The results are based on self-reported data since there is a risk of information bias. Finally, UPF classification in study surveys did not always match with NOVA grouping. The evidence suggests a relationship with higher UPF consumption and allergic diseases, but further research is needed to make recommendations.

Table 4. Ultra-processed foods in prevention of childhood allergic outcomes.

Reference (year)	Country	N	Age	UPF report	Outcome	Design	Effect of UPF	Conclusion
Azeredo et al (2020)	Brazil	2190	6-11 years	FFQ	Wheeze and asthma in the past 12 months	Observational cohort study	OR 0.84 (95% CI, 0.58-1.21)	No effect on asthma or wheeze
Moreno-Galarraga et al (2021)	Spain	513	5 years	FFQ	Wheezing or asthma or bronchitis/recurrent wheezing	Observational cohort study	OR 1.87 (95% CI, 1.01-3.45)	Increased risk of wheezing illness and bronchitis/recurrent wheezing No effect on asthma
Kong et al (2022)	US	2736	6-19 years	24 h-diet recall	Hay fever, allergy, rash, sneeze, wheeze, eczema and active asthma	Observational cohort study	Asthma Q4 vs. Q1 OR 1.76 (95% CI, 1.1-2.82)	Increased risk of asthma, more eczema in girls, less sensitization
Reis et al (2020)	US	56312	2-11 years	Other	Asthma	Observational cohort study	Fast food & Asthma OR 1.21 (95% CI, 1.02-1.45)	Consuming more soda, french fries and fast food increased the risk of asthma
Saadeh et al (2015)	France	7432	9-11 years	FFQ	Wheeze, asthma, allergic rhinitis and atopic eczema	Cross-sectional study	Fast food & Asthma OR 2.39 (95% CI, 1.47-3.93)	Fast food and butter intake increased the risk of asthma among atopic children
von Ehrenstein (2015)	US	1201	3.5 years	Other	Asthma, wheeze, rhinitis	Population-based study	Current asthma: RR 4.46 (95% CI, 1.36-14.60)	Increased risk of current and severe asthma with the highest consumption of fast food

UPF = Ultra-processed food, OR = Odds ratio, RR = Relative risk ratio, FFQ = Food frequency questionnaire

4 Discussion

Main findings of this review are 1) Vitamin D supplementation during pregnancy or infancy might not be effective in the prevention of childhood asthma or other allergic diseases 2) Probiotics appear to reduce the risk of atopic eczema but may not be effective in preventing asthma 3) Fish oil supplementation show conflicted results in reducing childhood wheeze or asthma and preventive effect cannot be excluded 4) Processed food consumption appears to be related to increased risk of childhood asthma but further research is needed to confirm this relationship.

Vitamin D has been identified as a potential nutrient affecting the development of childhood allergic diseases, including asthma. Vitamin D status can be assessed readily by measuring serum 25-hydroxyvitamin D_3. Moreover, it is easily modifiable by various interventions, such as oral supplementation, dietary changes or even by increasing sun exposure. There is some evidence connecting low vitamin D levels among children (Rajabbik et al. 2014) or during pregnancy (Wei et al. 2016) to the development of asthma or eczema. However, the available data remains insufficient to implement clinical guidance.

This literature review included seven randomized controlled trials studying the association of vitamin D supplementation and respiratory outcomes in childhood (Table 1). Of these studies, five used maternal VD supplementation only (Brustad et al. 2019, Chawes et al. 2016, Litonjua et al. 2016, Litonjua et al. 2020, Wolsk et al. 2017). Scholars found an inverse relationship between high maternal 25(OH)D level and risk of asthma/recurrent wheeze among offspring (Wolsk et al. 2017). In addition, single RCT reported a borderline protective effect with VD supplementation on recurrent wheezing (Litonjua et al. 2016). However, the positive effects were not sustained in longer follow-ups (Brustad et al. 2019, Litonjua et al. 2020). Other studies declared non-significant results. Two studies used early postnatal vitamin D supplementation (Hibbs et al. 2018, Rosendahl et al. 2019). Hibbs et al (2018) reported reduced risk of persistent wheezing by 12 months among preterm infants (RR, 0.66; 95% CI, 0.47-0-94). Other study did not manage to show differences between groups, hence the information about postnatal supplementation remains conflicted.

Recent meta-analysis and systematic review support the findings of these RCTs included. Luo et al (2022) summarizes that vitamin D supplementation had no effect on childhood asthma or wheeze (RR, 0.98; 95% CI, 0.82-1.18). Subgroup analysis regarding different time periods of VD

administration (prenatal/postnatal/prenatal and postnatal) did not show marked effect. Results were similar considering eczema, allergic rhinitis, respiratory infections and food allergy. Systematic review by Yepes-Nuñez et al (2018) does not support the use of vitamin D in the primary prevention of allergic diseases during different periods of pregnancy or childhood. Overall, the available information regarding primary prevention of asthma by means of vitamin D supplementation remains limited and further studies are needed.

Probiotics are believed to promote the normal gut microflora. An altered state between the microorganisms of the gut has been linked to the progress of allergic diseases. The colonization of the bowel of the developing infant is assumed to take place in the early stages of growth, possibly already during pregnancy. (Sestito et al. 2020.) Available evidence suggests a reduced risk of atopic dermatitis (eczema) but no effect on allergic respiratory outcomes. Clinical guidelines regarding probiotic supplementation in the primary prevention of childhood asthma do not exist.

This literature review included five randomized controlled trials studying the connection between probiotic supplementation and childhood allergic disorders (Table 2). Two studies administrated the probiotic supplementation only to the mother (Rautava et al. 2012, Simpson et al. 2015). Supplementation began in the late pregnancy and lasted until 2-3 months postpartum. Both reported less eczema among children with mother receiving probiotics at 2 and 6 years of follow-up respectively. However, there was no effect on other allergic outcomes, including asthma. Another two studies included only postnatal supplementation (Cabana et al. 2017, Schmidt et al. 2019). Cabana et al (2017) began the supplementation immediately after birth lasting a total of 6 months while Schmidt et al (2019) administered the probiotic in later infancy (10 months of age) with the same total treatment duration. Results were mixed, since early probiotic supplementation did not reduce eczema or asthma at 2 years of age. In contrast, Schmidt and co-workers (2019) reported a preventive effect on eczema (at 16 months of age). Other outcomes were non-significant, including asthma. One randomized controlled trial combined prenatal and postnatal probiotic supplementation (Wickens et al. 2012) continuing from 35 weeks of pregnancy until 6 months of lactation. Infant received the probiotic until 2 years of age. In line with previous studies, there was a significant reduction in the prevalence of eczema by the age of 4 years. Additionally, there was less rhinoconjunctivitis among children taking probiotics. Positive trend was also seen regarding wheeze (HR 0.79; 95% CI, 0.59-1.07). In conclusion, early probiotic supplementation seems to have a strong potential in preventing childhood eczema, especially in high-risk population as described in recent meta-analyses (Colquitt et al. 2022, Zuccotti et al. 2015). Similar effect is not found with

wheezing or asthma. However, these results might have later implications, considering the function of atopic dermatitis as the earliest form of "atopic march". Studies with a larger population and a longer follow-up are needed to provide clinical guidelines.

Adequate fish oil consumption has been hypothesized to help prevent allergic diseases in childhood. Fish oil contains mainly polyunsaturated fatty acids (PUFA), which are an essential part of cell membranes and lipid tissues. Omega-3 PUFAs may also contribute to anti-inflammatory response by decreasing the production of cytokines, thus leading to possible preventive effects considering the development of allergic disorders. (Xu et al. 2021.)

This literature review included three randomized controlled trials, one large pooled analysis and one birth cohort study (Table 3). Investigators aimed to show less frequent cases of asthma or other allergic diseases by administrating fish oil supplements to study participants. Two randomized controlled trials with high-risk infants gave fish oil capsules to pregnant women for the duration of third trimester (Best et al. 2016 and Bisgaard et al. 2016). Infants did not receive any supplementation. Best et al (2016) reported no difference between study groups on any IgE-associated allergic disease (eczema, wheeze, rhinitis) at 6 years of age (aRR, 1.04; 95% CI, 0.82-1.33). Results were similar when compared to prior 3-year follow up (Palmer et al. 2013). In contrast, Bisgaard et al (2016) managed to show significant reduction of recurrent wheeze or asthma with children between the ages of 3 and 5 (HR, 0.69; 95% CI, 0.49-0-97). There were also less lower respiratory tract infections among children with supplemented mothers (HR, 0.75; 95% CI, 0.58-0.98). One RCT involved preterm infants, who were given a high-dose DHA supplementation until 40 weeks of postmenstrual age. Allergic symptoms did not differ between groups at 7 years of age. Rosa et al (2020) connected high N-6 PUFA serum levels and male sex to increased risk of asthma among children with asthmatic mothers. Omega-3 PUFAs indicated a protective effect in quartile analyses (Q4 vs. Q1: RR, 0.59; 95% CI, 0.33-1.03). A large, pooled analysis (Stratakis et al. 2017) did not support the association of maternal seafood consumption and reduced risk of childhood allergic symptoms. A recent meta-analysis (Wu et al. 2022) does not show an overall reduction of asthma or wheeze with maternal fish oil supplementation (OR, 0.91; 95% CI, 0.72-1.14). However, in subgroup analysis it seemed to have a slight effect on decreasing clinically diagnosed asthma (OR, 0.56; 95% CI, 0.35-0.91). Moreover, high-dose (≥ 1200 mg/day) supplementation was associated with risk reduction of asthma or wheeze. Results indicate the need for further research especially with high-dose fish oil although the safety of administering such doses should be assessed concurrently.

Rapidly increasing consumption of ultra-processed foods might be linked to the global asthma "epidemic". This literature review included six observational studies analyzing the consumption of UPF and subsequent asthma-related symptoms among children (Table 4). Single population-based study analyzed the prenatal exposure to fast food consumption showing a dose-dependent relationship (von Ehrenstein et al. 2015), while the others studied the association of childhood UPF consumption and allergic symptoms. Four cross-sectional studies connected the regular consumption of UPFs to increased risk of asthma or wheezing (Moreno-Galarraga et al. 2021, Kong et al. 2022, Reis et al. 2020, Saadeh et al. 2015). Figures are depicted in table 4. There was on study with a contrasting view (Azeredo et al. 2020). In conclusion, the reviewed evidence suggests that the consumption of ultra-processed foods, including different types of fast food might be a potential target for preventive measures regarding childhood asthma-related symptoms. For now, the clinical guidelines are limited to national nutrition recommendations although decreasing fast food intake should be advocated. Further research is needed to provide specific guidelines considering ultra-processed foods and subsequent allergic outcomes.

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