

## S3 Guideline Allergy Prevention\*

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### Key words

allergy – evidence – S3  
Guideline – primary  
prevention – revision

**Abstract.** **Background:** The persistently high prevalence of allergic diseases in Western industrial nations and the limited possibilities of causal therapy make evidence-based recommendations for primary prevention necessary. **Methods:** The recommendations of the S3 Guideline Allergy Prevention, published in its last version in 2014, were revised and consented on the basis of a current systematic literature search. The evidence search was conducted for the period 06/2013 – 11/2020 in the electronic databases Cochrane and MEDLINE, as well as in the reference lists of current reviews and through references from experts. The literature found was screened in two filtering processes, first by title and abstract, and the remaining papers were screened in the full text for relevance. The studies included were sorted by level of evidence, and the study quality was indicated in terms of potential bias (low/high). The revised recommendations were formally agreed and consented upon with the participation of representatives of the relevant professional societies and (self-help) organizations (nominal group process). Of 5,681 hits, 286 studies were included and assessed. **Results:** Recommendations on maternal nutrition during pregnancy and breastfeeding as well

as on infant nutrition in the first months of life again play an important role in the updated guideline: Many of the previous recommendations were confirmed by the current data. It was specified that breastfeeding should be exclusive for the first 4 – 6 months after birth, if possible, and that breastfeeding should continue with the introduction of complementary foods. A new recommendation is that supplementary feeding of cow's milk-based infant formula should be avoided in the first days of life if the mother wishes to breastfeed. Furthermore, it was found that the evidence for a clear recommendation for hydrolyzed infant formula in non-breastfed infants at risk of atopic diseases is currently insufficient. It is therefore recommended to check whether an infant formula with proven efficacy, demonstrated in allergy prevention studies, is available until the introduction of complementary feeding. Finally, based on the EAACI guideline, recommendations were made for the prevention of hen's egg allergy by introducing and regularly giving thoroughly heated (e.g., baked or hard-boiled) but not "raw" hen's egg (also no scrambled egg) with the complementary food. The recommendation to introduce peanut in complementary feeding was formulated cautiously for the German-

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speaking countries: In families with regular peanut consumption, the regular administration of peanut-containing foods in age-appropriate form (e.g., peanut butter) with the complementary diet can be considered for the primary prevention of peanut allergy in infants with atopic dermatitis (AD). Before introduction, a clinically relevant peanut allergy must be ruled out, especially in infants with moderate to severe AD. There is still insufficient evidence for an allergy-preventive efficacy of prebiotics or probiotics, vitamin D, or other vitamins in the form of supplements so that recommendations against their supplementation were adopted for the first time in the current guideline. Biodiversity plays an important role in the development of immunological tolerance to environmental and food allergens: there is clear evidence that growing up on a farm is associated with a lower risk of developing asthma and allergic diseases. This is associated with early non-specific immune stimulation due to, among other things, the greater microbial biodiversity of house dust in this habitat. This aspect is also reflected in the recommendations on animal husbandry, on which a differentiated statement was made: In families without a recognizable increased allergy risk, pet keeping with cats or dogs should not generally be restricted. Families with an increased allergy risk or with children with already existing AD should not acquire a new cat – in contrast, however, dog ownership should not be discouraged. Interventions to reduce exposure to dust mite allergens in the home, such as the use of mite allergen-proof mattress covers (“encasings”), should be restricted to patients with already proven specific sensitization against house dust mite allergen. Children born by caesarean section have a slightly increased risk of asthma – this should be taken into account when advising on mode of delivery outside of emergency situations. Recent work also supports the recommendations on air pollutants: Active and passive exposure to tobacco smoke increase the risk of allergies, especially asthma, and should therefore be avoided. Exposure to nitrogen oxides, ozone, and small particles (PM 2.5) is associated with an increased risk, especially for asthma. Therefore, exposure to emissions of nitrogen oxides, ozone, and small particles (PM 2.5) should be kept low. The authors of this guideline are unanimously in favor of enacting appropriate regulations to minimize these air pollutants. There is no evidence that vaccinations increase the risk of allergies, but conversely there is evidence that vaccinations can reduce the risk of allergies. All children, including children at risk, should be vaccinated according to the

current recommendations of the national public health institutes, also for allergy prevention. **Conclusion:** The consensus of recommendations in this guideline is based on an extensive evidence base. The update of the guideline enables evidence-based and up-to-date recommendations for the prevention of allergic diseases including asthma and atopic dermatitis.

## Materials and methods

The procedure for creating the guideline is described in detail in the guideline report (Supplemental material).

## Objectives

The primary targets of this guideline are the most important atopic diseases: atopic eczema, food allergy, allergic rhinoconjunctivitis, and (allergic) asthma. The guideline mainly refers to primary prevention measures and is based on the following definitions, modified for the field of allergies:

Primary prevention includes, on the one hand, the elimination or reduction of (partial) causes that are important for the development of the disease, including changes in causal or predisposing environmental and workplace-related factors, and, on the other hand, the increasing tolerance of individuals. Primary prevention is mainly relevant for risk groups (genetic predisposition) but is also aimed at the general population and includes aspects of allergy-specific health promotion.

The target groups of secondary prevention are people with early signs of disease (e.g., bronchial or nasal hyperreactivity with proven sensitization) and sensitized but still asymptomatic people. The objectives of secondary prevention are to avoid disease manifestation and change in symptoms. The measures of secondary prevention include the avoidance of clinically relevant allergens and toxic-irritative substances, advice and, in the case of people with early signs of disease, pharmaco-prophylaxis and allergen-specific immunotherapy (desensitization) if appropriate.

Following this definition, the measures in the recommendation algorithm are subdivided, where applicable, into genetically predisposed and non-predisposed people. Studies on patients with manifest disease, including those aimed at preventing a second disease, were not taken into account.

The target population are people, particularly children, with and without genetic predisposition for atopic diseases. Children with a genetic predisposition (“children with an increased risk of atopic diseases”) are defined as having at least one parent or sibling suffering from one of the atopic diseases mentioned (bronchial asthma, allergic rhinitis, atopic dermatitis, food allergy). Thus, in addition to the general population, young families, couples who wish to have children, or pregnant women as well as people with a relevant family history can be considered as target groups.

### Target group

The guideline is aimed at medical and non-medical specialists who care for the people defined as the target population as part of their work.

User target group/addressees: Users and multipliers of the guideline contents are all medical and non-medical associations and groups of people involved in preventive measures and in particular in allergy prevention. In addition to representatives of the relevant groups of specialists, professionals, and affected persons, doctors from all specialist groups, in particular pediatricians, dermatologists, ENT doctors, and pulmonologists and allergologists, as well as self-help organizations and those otherwise affected, are considered addressees.

### Search for evidence

The search for evidence was carried out for the period 06/2013–11/2020 in the electronic databases Cochrane and MEDLINE, as well as in the reference lists of current reviews. Additional studies were identified by the experts involved. The literature found was checked for relevance in two filtering processes, initially according to title and abstract, and the remaining papers in full text. The studies included afterwards were classified according to the level of evidence, and the study quality was indicated according to the of the risk of bias (low/high). The revised recommendations were formally coordinated and consented to with the participation of representatives from the relevant specialist societies and (self-help) organizations (nominal group process).

Of 5,681 search hits, 286 studies were included and evaluated. The procedure for evidence search and evaluation is described in detail in the guideline report.

### Drafting of the guideline

Based on the found and evaluated studies, a proposal for the revised recommendations for prevention was circulated in preparatory meetings in different working groups. Suggestions for amendments and revision were discussed and, if necessary, incorporated. In addition, background texts on the individual topics were prepared in the working groups, which were then merged and harmonized by the guideline coordinators.

### Consensus

All persons who had participated in the development and approval of the 2014 version of the guideline were invited to the consensus group. In addition, representatives from other specialist societies were appointed upon proposal. The recommendations were approved by the consensus group. A maximum of two representatives with one common voting right were allowed per organization. The nominal group process technique was used as the formal consent process. A total of three online-based meetings took place. The process was strictly structured (see below).

The web-based consensus meetings took place in November 2020, December 2020, and March 2021 and were chaired by PD Dr. H. Sitter (University of Marburg and AWMF).

The process of the nominal group technique was as follows: 1) Presentation of the statements to be consented. 2) Each participant prepares comments and discussion requests on the given statements. 3) The chair requests the comments from each participant in turn, and similar comments are summarized. 4) For each point, a vote is taken as to who would like to discuss this point. 5) The topics are ranked according to these votes. (6) In a joint group, the individual members, one after the other, give their opinions on the individual discussion points. 7) After several rounds, the participants finally agree on a certain formulation by voting or ranking. 8) Steps 1–6 are repeated for each statement under discussion.

Based on the evidence, the recommendations that have been consented to are referred to as proofs or indications. This terminology is based on the methods formulated by IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)). In “General Methods 6.0” it says, among other things:

„Medical interventions are compared with other interventions, sham interventions (e.g. placebo), or no intervention in

respect of their effects on defined patient-relevant outcomes, and their (added) benefit and harm are described in summary. For this purpose, on the basis of the analysis of the scientific data available, for each predefined patient-relevant outcome separately a conclusion on the evidence base of the (added) benefit and harm is drawn in 4 levels with regard to the respective certainty of the conclusion: The data provide either “proof” (highest certainty of conclusions), an “indication” (medium certainty of conclusions), a “hint” (weakest certainty of conclusions) in respect of the benefit or harm of an intervention, or none of these 3 situations applies. The latter is the case if no data are available or the data available do not allow any of the other 3 conclusions to be drawn.“

The recommendations were individually adopted by the consensus group with a class of recommendation (A, B, C, or D), which is added to the respective recommendation in brackets. The classes of recommendation can be assigned in a formalized form based on the level of evidence (see guideline re-

port). In justified cases, however, deviating classes of recommendation could also be adopted as part of the consent process. On topics for which no prevention recommendations could be derived, only statements were formulated.

All recommendations could be adopted by strong consensus (> 95% agreement of the participants), by consensus (> 75 – 95% agreement), or with a majority agreement (> 50 – 75% agreement); the levels of consensus are indicated with the recommendations.

## Results

The consented recommendations for the primary prevention of bronchial asthma, allergic rhinitis, food allergy, and atopic eczema apply to people at risk and those not at risk, unless explicitly stated otherwise, and are as follows:

### 1. Nutrition.

#### 1.1. Maternal nutrition during pregnancy and lactation.

Level of recommendation	Statement
A	<p><b>Statement:</b> During pregnancy and lactation, a balanced, diverse diet covering all nutritional requirements is recommended. This also includes the consumption of vegetables, milk (products) (including fermented milk products such as yogurt), fruits, nuts, eggs, and fish.</p> <p><b>Recommendation:</b> Dietary restrictions (avoidance of potent food allergens) during pregnancy or lactation should not be made for the purpose of allergy prevention (A).</p>
Level of evidence	<p>Studies on the general statement: Celik 2019 (2-); Moonesinghe 2016 (2+); Ogawa 2018 (2+); Oien 2019 (2++); Stratakis 2017 (1++); Rucci 2016 (2++); Leermakers 2013 (2+); Miyake 2013 (2+); Pele 2013 (2+); Gardner 2020 (2+); Miyake 2014 (2+); Chisaguano 2014 (2+); Bunyavanich 2014 (2+), Bedard 2020 (2+), Rosa 2020 (2+)</p> <p>Recent studies on the recommendation to avoid dietary restriction are lacking; recommendation is based on previous recommendations and, with regard to food allergy, on the EAACI guideline</p>
Level of consensus	Strong consensus

#### 1.2. Breastfeeding.

Level of recommendation	Statement
A/B	<p><b>Statement:</b> Breastfeeding has many benefits for both mother and child.</p> <p><b>Recommendation:</b> Infants should be breastfed exclusively for the first 4 – 6 months, if possible. (A) Breastfeeding should also be continued when complementary foods are introduced. (A)</p> <p><b>Recommendation:</b> Additional feeding of cow’s milk-based infant formula in the first days of life should be avoided if the mother wishes to breastfeed. (B)</p>
Level of evidence	<p>Filipiak-Pittroff 2018 (1+); Quigley 2018 (2+); Den Dekker 2016 (2+), Azad 2017 (2++); Klopp 2017 (2++); Elbert 2017 (2+); Van Meel 2017 (2++), Groenwold 2014 (2++); Ajetunmobi 2015 (2-); Jelding-Dannemand 2015 (2+); Leung 2016 (2-), Nwaru 2013 (2++), Rosas-Salazar 2015 (2-)</p> <p>Evidence of EAACI guideline for avoidance of temporary feeding of cow’s milk-based infant formula: Urashima 2019</p>
Level of consensus:	Consensus

## 1.3. Breast milk substitute and cow's milk substitutes in children at risk.

Level of recommendation	Statement
A/B	<p><b>Recommendation:</b> If breastfeeding is not or not sufficiently possible, an infant formula should be given. For children at risk of allergies, it should be checked whether an infant formula with proven effectiveness, demonstrated in allergy prevention studies, is available until complementary food is introduced. (B)</p> <p><b>Recommendation:</b> Infant formula based on soy protein is not suitable for allergy prevention and should therefore not be given for this purpose. (A)</p> <p><b>Comment:</b> Soy products can be used as part of complementary foods, independently from the purpose of allergy prevention.</p> <p><b>Recommendation:</b> Since there is no proof of an allergy-preventive effect of other animal milk, such as goat milk (not even if they are the basis of infant formula), sheep or mare milk, these should also not be given for the purpose of allergy prevention. (B)</p> <p><b>Comment:</b> Cereal drinks are no milk substitute from a nutritional point of view.</p> <p><b>Recommendation:</b> Since there is no proof of an allergy-preventive effect of cereal drinks, these should also not be given for the purpose of allergy prevention. (B)</p>
Level of evidence	<p>Hypoallergen (HA) hydrolyzed formula: Von Berg 2016 (1++), DAVISSE-PATURET 2019 (2++)</p> <p>Soy formula: no current evidence found</p> <p>Milks of other animals: no current evidence found</p>
Level of consensus:	Consensus

## 1.4. Complementary food and transition to family nutrition.

Level of recommendation	Statement
A/B/C	<p><b>Statement:</b> There is some evidence that the diversity of the child's diet in the first year of life has a protective effect on the development of atopic diseases. A diverse diet also includes fish and a limited amount (up to 200 mL per day) of milk or natural yogurt and hen's egg as part of the complementary food.</p> <p><b>Recommendations:</b> Depending on the readiness of the infant, the feeding of complementary food should start from the beginning of the 5<sup>th</sup>, at the earliest, to the beginning of the 7<sup>th</sup> month of life, at the latest. (B)</p> <p>There is no proof of a preventive effect of dietary restriction by avoiding potent food allergens in the first year of life. Therefore, no restriction should be made. (A)</p> <p>For prevention of hen's egg allergy, well-cooked (e.g., baked or hard-boiled), but no "raw" eggs (not even scrambled eggs), should be introduced with the complementary food and given regularly. (B)</p> <p>For prevention of peanut allergy, introduction and regular consumption of peanuts in an age-appropriate form (e.g. peanut butter) may be considered in infants with atopic dermatitis living in families with regular peanut consumption. (C)</p> <p>A peanut allergy should first be ruled out, especially in infants with moderate to severe atopic dermatitis. (A)</p>
Level of evidence	<p>Studies for the statements on complementary foods regarding diversity, fish, milk (yogurt):</p> <p>Crane 2018 (2+); Turati 2016 (2++); Nwaru 2014 (2++); Roduit 2014 (2++); Roduit 2018 (2++); Oien 2019 (2++); Klingberg 2019 (2++); Vasileiadou 2018 (2+); Lumia 2015 (2+); Shoda (2+)</p> <p>Recent studies on recommendation to avoid dietary restriction are lacking; recommendation is based on previous recommendations and, with regard to food allergy, on the EAACI guideline</p>
Level of consensus:	Strong consensus

## 1.5. Body weight.

Level of recommendation	Statement
A	<p><b>Statement:</b> 1) An increased body mass index (BMI) of the mother before or at the beginning of pregnancy is positively associated with wheezing or asthma in the child, and 2) overweight and obese children are more frequently affected by asthma than normal-weight children.</p> <p><b>Recommendation:</b> Overweight/obesity in women before and during pregnancy as well as in children and adolescents should be avoided for asthma prevention. (A)</p>
Level of evidence	<p>Women before and at the beginning of pregnancy: Liu 2020 (1++); Ekstöm 2015 (2+); Eising 2013 (2+); Guerra 2013 (2+); Harpsøe 2013 (2+); Leermakers 2013 (2+); Harskamp-van Ginkel 2015 (2+); Wright 2013 (2+); Ziyab 2014 (2+); Pike 2013 (Pike 2+); Zugna 2015 (1++)</p> <p>Children: Loid 2015 (2++); Ziyab 2014 (2+); Popovic 2016 (2+); Casas 2016 (2++); Tsai 2018 (2+); Ekström 2017 (2+); Nahhas 2014 (2+); Forno 2014 (2-); Lang 2018 (2-)</p>
Level of consensus:	Consensus

## 2. Food supplements.

### 2.1. Supplementation of prebiotics and probiotics.

Level of recommendation	Statement
A	<p><b>Background:</b> Data from partly large-scale, randomized, double-blind intervention studies consistently show no preventive effects of prebiotics and probiotics for the endpoints allergic rhinitis and bronchial asthma. The vast majority of current intervention studies also show no preventive effect of supplementation with prebiotics and/or probiotics on atopic eczema.</p> <p><b>Recommendation:</b> Prebiotics and/or probiotics should not be given to pregnant women or infants for the purpose of allergy prevention, not even as part of infant formula. (A)</p>
Level of evidence	Boyle 2016 (1++); Abrahamsson 2013 (1+); Allen 2014 (1++); Loo 2014 (1+); Bertelsen 2014 (2++); Peldan 2017 (1++); Wickens 2013 and 2018a (1++); Wickens 2018b (1+); Ranucci 2018 (1++); Sierra 2015 (1++); Wopereis 2018 (1+); Lundelin 2017 (1+); Cabana 2017 (1-); Niinivirta 2014 (2+); Simpson 2015 (1-); Ro 2017 (1++); Hrdy 2018 (2+); Rutten 2015 (1+); Kim 2015 (1+); Murphy 2019 (1+)
Level of consensus:	Consensus

### 2.2. Supplementation of vitamin D.

Level of recommendation	Statement
A	<p><b>Background:</b> Current studies show no protective effect of vitamin D supplementation during pregnancy, breastfeeding or in children with regard to allergy prevention in children.</p> <p><b>Recommendation:</b> Pregnant women and healthy infants or older children should not take vitamin D supplements for the purpose of allergy prevention. (A)</p> <p><b>Statement:</b> The recommendation established in Germany to supplement infants with vitamin D (400 – 500 IU/day) up to the child's second early summer remains unchanged.</p>
Level of evidence	<p>Supplementation during pregnancy:</p> <p>Wolsk 2017a und b (1+); Zosky 2014 (2-); Maslova 2013 (2-); Litonjua 2016/2020 (1+); Chaves 2016 (2+); Brustard 2019 (2+)</p> <p>Supplementation in infancy and early childhood: Nwaro 2017 (2+), Forno 2020 (1+)</p>
Level of consensus:	Strong consensus

### 2.3. Supplementation of other vitamins.

Level of recommendation	Statement
A	<p><b>Background:</b> There is insufficient proof that vitamin supplementation (such as A, C, E, K, or folic acid) during pregnancy is associated with prevention or an increased risk of atopic diseases in the child. There are no (reliable) study data on possible effects of vitamin supplementation in infancy.</p> <p><b>Recommendation:</b> Pregnant women should not avoid taking folic acid for the purpose of allergy prevention. (A) Pregnant women and healthy infants or older children should not take vitamin supplements for allergy prevention. (A)</p> <p><b>Statement:</b> Periconceptional folic acid supplementation according to the recommendations should be performed.</p>
Level of evidence	<p>Supplementation during pregnancy: Maslova 2014 (2++); Roy 2018 (2+); Trivedi 2018; den Dekker 2018 (2+); Crider 2013 (unrated)</p> <p>Supplementation in infancy: Aage 2015 (1++); Kiraly 2013a (1+); Kiraly 2013b (1+) [all without relevance for Germany]</p>
Level of consensus:	Strong consensus

## 2.4. Supplementation of long-chain omega-3 fatty acids (EPA, DHA).

Level of recommendation	Statement
	<p><b>Background:</b> Due to the heterogeneity of the study data, no final recommendation can be given for supplementation of <math>\Omega</math>-3 LCPUFAs for allergy prevention in pregnant women, breastfeeding women and infants.</p> <p><b>Statement:</b> Some studies show that low serum levels of <math>\Omega</math>-3 LCPUFAs in pregnant women, breastfeeding women, and infants were associated with a higher risk of allergic diseases in the child, especially of asthma and wheezing, and that this risk may be reduced by supplementing <math>\Omega</math>-3 LCPUFAs.</p>
Level of evidence	Bisgaard 2016 (1++); Warstedt 2016 (1++); Hansen 2017 (1+); Best 2016 (1+); Escamilla-Nunez 2014 (1+); Berman 2016 (1-); Gunaratne 2019 (1++); Lapillonne 2014 (2+); Maslova 2019 (2++); Sordillo 2019 (2++); Yu 2015 (2++); Standl 2014 (2++); Magnusson 2018 (2+); Bisgaard 2016 (1++); Warstedt 2016 (1++); D'Vaz 2012 (1+); Furuholm 2011 (1+)
Level of consensus:	Strong consensus

## 3. Allergen exposure/allergen-specific immunotherapy.

## 3.1. Pets.

Level of recommendation	Statement
A/B	<p><b>Background:</b> Several epidemiologic studies have shown that keeping dogs in the first years or the first 3 years of life has a primary protective effect against the development of allergies and asthma. There is still conflicting data with regard to keeping cats or other typical pets.</p> <p><b>Recommendations:</b> For families without a recognizably increased risk of allergies, keeping of cats or dogs should not be limited for reasons of primary allergy prevention. (A)</p> <p>Families with an increased risk of allergies or with children with pre-existing atopic eczema should not start keeping a cat. (B)</p> <p>Families with an increased risk of allergies should not be advised against keeping dogs. (B)</p> <p><b>Statement:</b> With regard to pets other than cats and dogs, no recommendations can be made on the primary prevention of allergies and asthma. There is no evidence for giving away existing pets for reasons of allergy prevention.</p>
Level of evidence	<p><b>Dogs:</b> Marrs 2019 (1-); Collin 2015 (2+); Fall 2015 (2+); Hesselmar 2018 (2-); Al-Tamprouri 2019 (2++)</p> <p><b>Cats:</b> Al-Tamprouri 2019 (2++); Milanzi 2019 (2++)</p>
Level of consensus:	Strong consensus

## 3.2. Mites.

Level of recommendation	Statement
A/B	<p><b>Background:</b> Previous studies did not show that reducing the allergen content in the home environment was a reliably effective method for primary allergy prevention. Studies on the correlation between the early exposure to house dust mites, animal dander, and endotoxins and the later development of asthma and/or allergic sensitizations show partially contradicting results.</p> <p><b>Recommendation:</b> Interventions to reduce exposure to house dust mite allergens in the home, e.g., by using mite allergen-proof mattress covers (encasings) should not be used with the aim of <u>primary</u> prevention. (B)</p> <p>In patients with an existing mite allergy, mite allergen reduction measures should be used, as there is proof of effectiveness. (Tertiary prevention). (A)</p>
Level of evidence	Callesen 2014 (2+); O'Connor 2018 (2++); Lynch 2014 (2+); Karvonen 2014 (2+); Karvonen 2019 (2+); Thorne 2015 (4); Loo 2018 (level of evidence not indicated)
Level of consensus:	Consensus

## 3.3. Allergen-specific immunotherapy.

Level of recommendation	Statement
B	<p><b>Background:</b> Some studies have examined the development of allergic sensitization to further/new allergens during the course of AIT, mostly in children with allergic rhinitis/ allergic rhinoconjunctivitis or asthma.</p> <p>Two studies were placebo-controlled and were carried out in infants with atopy or in IgE-sensitized, non-allergic children. These studies provided some indication that primary preventive AIT with house dust mite extract can prevent sensitization to other allergens in the first 2 years of life. A modifying effect on allergic symptoms could not be demonstrated.</p> <p><b>Statement:</b> AIT for prevention of allergic sensitization and allergic symptoms in infants with increased atopy risk (primary prevention) cannot be recommended at the moment.</p> <p>To avoid allergic sensitization to further allergens and allergic symptoms in already sensitized, non-allergic children (secondary prevention), an AIT cannot be recommended at the moment.</p> <p><b>Recommendation:</b> In patients with pre-existing allergic rhinitis/rhinoconjunctivitis, AIT to prevent a not yet manifest asthma should be recommended. (Tertiary prevention). (B)</p>
Level of evidence	Crimi 2004 (1–); Marogna 2008 (1–); Szepfalusi 2014 (1+), Zolkipli 2015 (1++); Kristiansen 2018 (1+); Halken 2017 (1+); Jacobsen 2007 (1–); Song 2014 (1+); Valovirta 2017 (1+); Grembiale 2000 (1+)
Level of consensus:	Strong consensus

## 4. Biodiversity and other factors.

## 4.1. Biodiversity.

Level of recommendation	Statement
A/B	<p><b>Statement:</b> There are clear indications that growing up on a farm protects against the development of asthma and allergic diseases.</p> <p>This is mediated by early unspecific immune stimulation, among others through the microbial composition of the house dust.</p> <p><b>Statement:</b> A recommendation regarding the prevention of atopic diseases through child daycare cannot be given due to the heterogeneous study data.</p> <p><b>Statement:</b> There is no proof that vaccinations increase the risk of allergies, but there are indications that vaccinations can lower the risk of allergies.</p> <p><b>Recommendation:</b> All children, including children at risk, should be vaccinated according to the current recommendations. (A)</p> <p><b>Recommendation:</b> When giving advice on the mode of delivery, it should be taken into account that children who were born through an elective caesarean section have a slightly increased risk of asthma. (B)</p>
Level of evidence	Kirjavainen 2019 (2++); Nicklaus 2019 (2++); Louis 2014 (2++); Brick (2+); Cheng 2014 (2+); Linehan 2014 (2+); Thestesen 2018 (1+); Baxter 2018 (1+); Rusconi 2017 (2+); Kahr 2015 (2+); Wu 2016 (2+); Sevelstedt 2016 (2++); Chu 2017 (2+); Lee 2014 (2+); Brandao 2016 (2+)
Level of consensus:	Strong consensus

## 4.2. Antibiotics and non-steroidal anti-inflammatory drugs.

Level of recommendation	Statement
	<p><b>Statement:</b> When using <i>antibiotics in infancy</i>, it should be taken into account that the use of antibiotics in the first 2 years of life is associated with a moderate increase in the risk of allergic asthma and a slight increase in the risk of hay fever and eczema in later life.</p> <p><i>Antibiotic use in pregnancy</i> is associated with a moderate increase in the child's risk of developing asthma and AD later in life.</p> <p>The use of paracetamol and other NSAIDs in toddlers or mothers during pregnancy cannot be clearly associated with an increased risk of asthma and rhinitis. No data on atopic dermatitis are available.</p>
Level of evidence	Antibiotics: Ahmadizar 2018 (1–); Batool 2016 (2–); Goksör 2013 (2+); Hoskin-Parr 2016 (2+); Ong 2014 (2–); Pitter 2016 (2+); Wang 2013 (2++); Yamato-Hanada 2017 (2+); Kashanian 2017 (2-); Stensballe 2013 (2+); Örtqvist 2013 (2++); Stokholm 2014 (2+); Wohl 2015 (2–); Metzler 2019 (2+); Wu 2016 (2++); Metsälä 2015 (2++)
	Studies on analgesics: Amberbier 2014 (2+); Batool 2016 (2–); Cheelo 2015 (2–); Penarando 2015 (2+); Wang 2013 (2++); Hoeke 2016 (2+); Liu 2016 (2+); Sordillo 2015 (2++); Chu 2016 (2–); Magnus 2016 (2++); Piler 2016 (2+)
Level of consensus:	Strong consensus



## 4.3. Skin barrier.

Level of recommendation	Statement
	<p><b>Statement:</b> It has not been consistently shown that primary prevention in infants with an atopic family history can be achieved by daily moisturizing of healthy skin.</p> <p><b>Comment:</b> At the present time, based on the available evidence, no recommendation can be made for daily moisturizing of healthy baby skin with the aim of primary prevention of eczema and allergies – even in families with an increased allergy risk.</p> <p><b>Recommendation:</b> In infants and children with visibly dry skin moisturizing creams <u>should</u> be used regularly. (Expert opinion)</p>
Level of evidence	Horimukai 2014 (1++); Simpson 2014 (1+); Chalmers 2020 (1–); Skjerven 2020 (1+); McClanahan 2019 (2+); Dissanayake 2019 (2+)
Level of consensus:	Consensus

## 5. Pollutants.

## 5.1. Tobacco smoke.

Level of recommendation	Statement
A	<p><b>Background:</b> Active and passive exposure to tobacco smoke increase the risk to develop allergies. In particular, the risk of asthma is increased in preschool age and early school age. This already applies during pregnancy. The risk to develop allergies and especially asthma by passive exposure to tobacco smoke during pregnancy is especially high in children with a positive family history for allergies.</p> <p><b>Recommendation:</b> Active and passive exposure to tobacco smoke should be avoided. This already applies during pregnancy. (A)</p>
Level of evidence	Hollams 2014 (2+)
Level of consensus:	Strong consensus

## 5.2. Mold exposure and humidity.

Level of recommendation	Statement
B	<p><b>Recommendation:</b> An indoor climate that favors the growth of molds (high humidity, poor ventilation) should be avoided. (B)</p>
Level of evidence	Milanzi 2019 (2+); Thacher 2017 (2++); Karvonen 2015 (2+); Wen 2015 (2+)
Level of consensus:	Consensus

## 5.3. Indoor air pollutants.

Level of recommendation	Statement
B	<p><b>Recommendation:</b> Exposure to indoor air pollutants should be kept low. (B)</p>
Level of evidence	Madureira 2016(2–); Callesen 2014 (2+); O’Connor 2018 (2++)
Level of consensus:	Strong consensus

## 5.4. Motor vehicle emissions.

Level of recommendation	Statement
A	<p><b>Background:</b> Exposure to nitrogen oxides, ozone, and particulate matter with a particle size of &lt; 2.5 µm (PM 2.5) is associated with an increased risk, especially for asthma.</p> <p><b>Recommendation:</b> Exposure to vehicle emissions should be kept low. (A)</p>
Level of evidence	Deng 2016 (2+); Brunst 2015 (2++); Gruzieva 2013 (2+); Hasunuma 2016 (2+); Hsu 2015 (2–); Molter 2015 (2++); Nishimura 2013 (2–); Rancière 2017 (2++); Ranzi 2014 (2+); Tétreault 2016 (2+); Kathunia 2016 (not rateable)
Level of consensus:	Strong consensus

## 5.5. Chlorinated pool water.

Level of recommendation	Statement
	<b>Statement:</b> Regular visits to swimming pools to prevent allergies, rhinitis, and eczema should not be discouraged.
Level of evidence	Andersson 2015 (2+); Font-Ribera 2014 (2+)
Level of consensus:	Strong consensus

## 6. Psychosocial factors.

Level of recommendation	Statement
	<b>Background:</b> There are hints that stressful psychosocial factors in the mother during pregnancy and after birth (depression, difficult life events, etc.) can increase the risk of later atopic disease in children up to the age of 14. A high level of social support and high maternal sensitivity, on the other hand, seem to reduce the risk of childhood atopic dermatitis. <b>Statement:</b> No practical recommendations for action for targeted allergy prevention can currently be given based on available data.
Level of evidence	Andersson 2016 (1++); Alton 2016 (1+); Kozyrskyj 2017 (2++); Wang 2016 (2++); Letourneau 2017 (2++); El-Heis 2017 (2+); Brew 2017 (2+); Guxens 2014 (2++); Hartwig 2014 (2+); Lee 2016 (2+); Larsen 2014 (2+)
Level of consensus:	Consensus

## Discussion

### Nutrition

During pregnancy and lactation, a balanced and diverse diet covering all nutritional requirements is recommended. Although the topic of “dietary diversity during pregnancy” has been discussed to lower the risk of allergic diseases in childhood in the past [1], recent studies failed to show any or only a limited protective effect of a diverse diet during pregnancy and breastfeeding: While indications of a beneficial effect of a greater variety of fermented foods on atopic dermatitis were seen in a case-control study [2], a birth cohort study showed no relationship between a balanced diet and the manifestation of allergic diseases in children between 3 and 10 years [3]. In another cohort study, the highest consumption of cabbage and other vegetables rich in folate in the first trimester, compared to the lowest consumption, was associated with a significantly lower risk of wheezing in children aged 2 years. However, this association could no longer be seen for the second and third trimester [4]. Earlier indications of a protective effect of a Mediterranean diet during pregnancy on the development of allergic diseases in childhood (Update 2014) were not supported by the results of a population-based birth cohort [5].

Previous indications (update 2014) of a preventive effect of fish consumption during pregnancy and breastfeeding on allergic re-

spiratory diseases in children could neither be confirmed in recent birth cohorts [6, 7, 8, 9, 10] nor in a pooled analysis of various cohorts with a total of 60,774 mother-child pairs [11]. Furthermore, no protective effect of fish consumption on atopic dermatitis or other allergic diseases can be derived from the current data [7, 8, 9, 10].

Two prospective cohort studies confirm earlier indications of an association between higher total omega-6 PUFA (polyunsaturated fatty acids) levels in the mother’s blood during pregnancy and a higher incidence of atopic dermatitis in children [7, 12], especially in children with a relevant family history [12]. Linoleic acid, an omega-6 fatty acid, is found in many vegetable and seed oils. The positive association observed by Rucci et al. [7] is largely attributed by the authors to high maternal linoleic acid levels. In contrast, there are inconsistent results regarding the association between total omega-6 PUFA levels in the mother’s blood during pregnancy and asthma in the child: While an inverse association with asthma onset at 6 years of age was observed in a prospective cohort study of 4,976 mother-child pairs by Rucci et al. [7], higher maternal levels were positively associated with childhood asthma in 4- to 6-year-olds in another prospective study including 1,019 mother-child pairs. The association was shown to be more evident when the mother herself suffered from asthma [13].

Observational studies in recent years indicated possible protective effects of milk

and milk products, including fermented milk products such as yogurt, in particular for atopic dermatitis [2, 14] but also for allergic respiratory diseases [14, 15]. A study that analyzed, among other things, fatty acids derived from ruminants in the mother's plasma during pregnancy suggests an inverse relationship between the risk of developing atopic dermatitis in the first 14 months of life and the maternal plasma level of vaccenic acid, which is typical for ruminants [16].

The body of evidence is insufficient for specific recommendations for targeted consumption of individual foods, but still supports a balanced, varied, and nutritious diet during pregnancy and breastfeeding, which among other things includes vegetables, milk, and dairy products, including fermented milk products (such as yogurt), fruits, nuts, eggs, and fish.

Dietary restriction has not been recommended anymore for a long time. There are no current studies on this topic. The EAACI guideline on the prevention of food allergies recommends no avoidance of potential food allergens during pregnancy and breastfeeding in order to prevent food allergies in infants and children [17].

### *Breastfeeding*

Breastfeeding has many benefits for both mother and child, even if the infant is only partially breastfed. Mothers should be provided with comprehensive information and support to enable them to breastfeed their child.

Even if breast milk should be ideal for reducing the risk of allergic diseases due to the numerous immunologically active substances and favorable effects on the child's microbiome, existing data on this issue are inconsistent [18]. This is, among other things, due to the following reasons: breastfeeding cannot be studied in randomized trials for ethical reasons; existing studies are difficult to compare due to their different designs and their different definitions of breastfeeding; the studies used different endpoint parameters. For example, many studies do not really distinguish between "exclusive breastfeeding" and "predominant breastfeeding". According to the WHO definition, "exclusive breastfeeding" is the exclusive use of breast milk, while "predominant breastfeeding" means that breast milk is the predominant source of food, but the infant may also receive liquids, food supplements, and medication.<sup>1</sup> In addition, mothers who exclusively breastfeed differ in many parameters that are important for the development of allergies from mothers who feed infant formula:

age, smoking during and after pregnancy, socio-economic status, level of education, pet keeping, introduction of complementary food [19, 20]. A further complicating factor is that the composition of breast milk is complex and can vary greatly from one individual to another with regard to many substances that may be relevant to allergy prevention [18].

Most current studies show no indication of protective effects [21, 22, 23, 24, 25, 26] – neither with exclusive nor with any form of breastfeeding. The endpoints were allergic respiratory disease, especially asthma, and in some studies also atopic dermatitis. However, the effect of reverse causation should be kept in mind: children at high risk of atopic dermatitis may be breastfed for a longer time. In one study, the development of eczema was slightly inversely associated with breastfeeding, especially with breastfeeding for more than 6 months or with exclusive breastfeeding for 4 months [27]. The follow-up results of the GINI intervention cohort also suggest a protective effect of breastfeeding – but only in infants with an increased allergy risk [28]. After adjustment for possible confounding factors, there was a significantly reduced cumulative incidence of eczema in children and adolescents who had received exclusively breast milk for the first 4 months of their lives compared to those who had received cow's milk-based infant formulas.

Some studies also suggest a protective effect on the development of asthma or wheezing with exclusive breastfeeding in the first 3 months [27, 29], 6 months [30] as well as with longer breastfeeding [31, 32, 33, 34].

Despite the contradicting data, the recommendation in Germany to exclusively breastfeed in the first 4 – 6 months is supported. Breastfeeding should be continued when complementary foods are introduced.

Temporary feeding of infant formulas in the first days of life is still widespread in many industrialized countries and also in Germany [35]. In accordance with the EAACI guideline on the prevention of food allergies, the recommendation to avoid temporary feeding of cow's milk-based formula in the first days of life has been adopted [17]. The recommendation is based on a study that has shown that the administration of an amino acid formula compared to a cow's milk-based infant formula was associated with a significant reduction of the risk of sensitization and allergy to cow's milk in early childhood [36]. Earlier data suggest that the administration of an extensively hydrolyzed therapeutic formula was also associated with a comparable risk reduction [37].

<sup>1</sup>[http://apps.who.int/iris/bitstream/handle/10665/43895/9789241596664\\_eng.pdf;jsessionid=6418566B6D27863F9FE4BD72A65FC26?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/43895/9789241596664_eng.pdf;jsessionid=6418566B6D27863F9FE4BD72A65FC26?sequence=1)

Therefore, if a temporary supplementation with formula is medically indicated in the first days of life, this should be done with an extensively hydrolyzed therapeutic formula or amino acid formula. Whether partially hydrolyzed formulas are also effective for allergy prevention cannot be deduced from the currently available data.

### *Breast milk substitutes and cow's milk substitutes in children at risk*

The current follow-up of the randomized controlled intervention study GINI confirms a sustained risk-reducing effect of specific hydrolyzed formula for atopic dermatitis even after 15 years [38]. In contrast, in a French birth cohort including 11,720 children, the use of partially hydrolyzed infant formula was not associated with a lower risk of atopic diseases (eczema, respiratory symptoms, or food allergy); but was actually associated with an increased risk of wheezing at 1 year of age in infants at increased risk of atopic disease [39]. However, the risk analysis included only the type of feeding during the first two months of life. A calculated increased risk of eczema at 1 year of age disappeared after excluding infants in whom allergy symptoms were reported at 2 months of age. It also must be taken into account that observational studies cannot provide the same reliable basis for recommendations results from randomized controlled trials provide [40].

With regard to the recommendation in favor of hydrolyzed infant formula, the following should be considered:

- a. The evidence on a preventive use has to be considered in a product-specific way; an overall assessment is hardly possible due to various factors (*these include, for example: the choice of protein hydrolysate per se (protein source, hydrolysis processes, peptide sizes), the evident heterogeneity in the study designs including duration of the study/intervention, study population, group sizes, endpoints, but also the influence of the industry, etc.*). As a result, there are controversial national and international discussions regarding the effectiveness of partially or extensively hydrolyzed infant formulas for the purpose of allergy prevention in general or with regard to a (*focused*) prevention of atopic dermatitis, cow's milk allergy, asthma, and/or hay fever in young children and older children [41, 42, 43, 44].
- b. The hydrolyzed infant formulas studied in previous studies are no longer available on the German market or are no

longer available in their original composition.

- c. The current requirements by EFSA as laid down for manufacturers in the Commission Delegated Regulation (EU) 2021/572 of January 20, 2021 amending Delegated Regulation (EU) 2016/127 also are to apply to infant formula and follow-on formula based on protein hydrolysates from February 22, 2022. These include the requirement for proof of effectiveness derived from clinical studies that demonstrate "if and to what extent a particular formula reduces the risk of developing short and long-term clinical manifestations of allergy in at-risk-infants who are not breast-fed."... "In addition if, after the assessment by the Authority, it is demonstrated that a specific infant formula manufactured from protein hydrolysates reduces the risk of developing allergy to milk proteins, further consideration will be given to how to adequately inform parents and caregivers about that property of the product." (Commission Delegated Regulation (EU) 2016/127 on infant formula and follow-on formula and the nutrition of infants and young children).
- d. In a recent opinion, EFSA has assessed an infant formula manufactured from the hydrolyzed whey protein currently authorized by Delegated Regulation (EU) 2016/127 with regard to reducing the risk of atopic dermatitis in infants with an increased risk and concluded that no such risk-reducing effect can be derived from the presented data [45].

In view of the aspects mentioned, infants who are not or only partially breast-fed should be given an infant formula. For children with an increased risk of atopic disease, it should be checked whether an infant formula with proven effectiveness, demonstrated in allergy prevention studies, is available until complementary food is introduced.

There is no proof of an allergy-preventive effect of animal milk such as goat's, sheep's, or mare's milk, including infant formula made from goat's milk. Also, the use of soy-based infant formula cannot be recommended for the purpose of allergy prevention [46]. Moreover, there are health concerns related to soy-based infant formula (high content of phytochemicals with a weak estrogenic effect and phytates with possible disadvantages for nutrient absorption) [47, 48], which, however, are controversially discussed [49]. The use of soy-based infant formula is recommended by the German Society of Pediatrics DGKJ (Deutsche Gesell-

schaft für Kinder und Jugendheilkunde) only for special indications (galactosemia or ethical or cultural reasons) [50]. The DGKJ recommendation does not include a statement on the use of calcium-fortified soy products (soy drink, yoghurt, etc.) or on cereal-based and other plant-based drinks as part of the complementary food. Drinks based on cereals and other plants, even with calcium fortification, are to be viewed critically due to their low fat and protein quantity and quality, and should therefore not be used as a substitute for cow's milk [52].

### *Introduction of complementary foods*

In Germany it is recommended to start feeding complementary food from the beginning of the 5<sup>th</sup>, at the earliest, to the beginning of the 7<sup>th</sup> month of life, at the latest, depending on the readiness of the baby.

While the 2014 update mainly indicated that the introduction of fish has a protective effect against the development of allergic diseases, recent publications focus more on the diversity of the diet: The current data confirm earlier indications (update 2014) of a positive effect of fish consumption [6, 53, 54, 55], especially on allergic asthma/wheezing. In addition, three cohort studies were able to show that a wide variety of complementary foods was associated with a lower incidence of atopic dermatitis and/or allergic respiratory diseases [56, 57, 58]. Thereby, the development of atopic eczema was significantly less frequent in children who had received complementary food at the age of 4 or 5 months compared to those who were exclusively breastfed – even when children with and without allergy risk were considered separately [56]. Nwaru et al. [57] did not observe any association between food diversity and atopic diseases at the age of 3 and 4 months. From the age of 6 months, on the other hand, a lower variety of complementary foods was associated with an increased risk of atopic diseases. An earlier introduction of fish (< 29 weeks) was also associated with a lower risk of developing asthma compared to a later introduction (≥ 43 weeks) with a lower risk of developing asthma [53]. In a recent EAACI position paper [1], the authors “recommend that infants of any risk category for allergic disease should have a diverse diet, given no evidence of harm and some potential association of benefit in the prevention of particular allergic outcomes.”

Earlier indications from the 2014 update on a protective effect of a Mediterranean diet, as well as of omega-3 fatty acids and

milk can possibly be explained by more recent and future study results on butyrate and the microbiome [59, 60]. Butyrate is a short-chain fatty acid that is produced by specific intestinal bacteria and modulates the activity of immune cells. Roduit et al. [61] were able to show in a cohort study that the consumption of vegetables, fish, and yogurt in the first year of life was associated with an increased concentration of butyrate in the stool and inversely associated with allergic respiratory diseases between the ages of 3 and 6 years. However, two other cohort studies did not observe an association between the consumption of vegetables and fruits and the development of asthma [53, 55]. In contrast, the consumption of dairy products was inversely associated with the risk of atopic asthma in one of the two cohorts [55].

A protective effect of yogurt in the first year of life on the development of atopic dermatitis was suggested in an observational study [62] and in an evaluation of the consumption of yogurt by infants during the complementary feeding period, which was determined in a randomized-controlled administration of probiotics to women from pregnancy through to the breastfeeding period [63, 64]. In the studies by Crane et al. [63] and Du Toit et al. [64], the inverse association between the administration of yogurt and the risk of atopic dermatitis was significantly more pronounced when yogurt was introduced in the first 6 months of life and given regularly.

There is no proof of a preventive effect of dietary restriction by avoiding potent food allergens in the first year of life. Therefore, no restriction should be made.

With reference to the EAACI guideline on the prevention of food allergies, which is based on a systematic review of the literature [43], the recommendation to introduce hen's eggs in a sufficiently heated form (e.g., hard-boiled) is adopted [17]. Both underlying studies used hard-boiled egg, but it is assumed that baked hen's egg has a similar effect. This includes, among other things, well-baked egg-containing baked goods (such as hard biscuits, specialty breads and rolls as well as muffins and cakes). Once successfully introduced, hen's eggs should be given regularly in a sufficiently heated form. Since the introduction of unheated or insufficiently heated eggs was not associated with any benefit but with risks of severe allergic reactions, the administration of raw (not fully heated) hen's eggs is not recommended for the prevention of egg allergy. This also includes scrambled eggs, soft-boiled eggs as well as marshmallow treats and macarons.

The recommendation made for countries with a high prevalence of peanut allergy to specifically introduce peanut products is not adopted since Germany cannot be classified as such a country. Only in families with regular peanut consumption and presence of atopic dermatitis in the infant, a targeted introduction of peanut products in an age-appropriate form (because of the risk of aspiration, not whole peanuts or pieces), may be considered and followed by regular administration, as these infants are at increased risk of developing peanut allergy. As there are only data on the preventive introduction of peanuts in infants with mild or no sensitization to peanut in skin prick testing [64], peanut allergy should be excluded in infants with moderate to severe atopic dermatitis before peanuts are introduced.

### Overweight and obesity

The recommendation that overweight (body mass index (BMI) percentile > 90 – 97) and obesity (BMI percentile > 97) should also be avoided for reasons of allergy prevention is further supported by recent studies. Prospective cohort studies show that overweight and obesity or a BMI  $\geq 30$  kg/m<sup>2</sup> before or at the beginning of pregnancy are positively associated with wheezing [65, 66, 67, 68, 69, 70] and/or asthma [69, 71, 72, 73] in the child. This is confirmed by a pooled analysis of 14 cohort studies including 85,509 children [74] as well as a current meta-analysis [75] that included 22 observational studies with 145,574 mother-child pairs.

Mediators or influencing factors under discussion for these associations include genetic factors and inflammatory processes as well as the subsequently increased child's BMI [69, 70, 76]. Rapid weight gain in the first 2 years of life, for example, is associated with an increased risk of wheezing or asthma later in childhood [73, 77, 78, 79]. Cohort [80, 81, 82] and case-control studies [83, 84] confirm results of cross-sectional studies [85, 86, 87, 88, 89, 90] that observed a relationship between overweight/obesity and the occurrence of wheezing or asthma in children.

While two cross-sectional studies [85, 90] and one cohort study [81] showed a positive association between BMI and asthma only for girls, a meta-analysis [91], however, showed that overweight boys had a higher risk of asthma.

Some cross-sectional studies also show positive associations of the BMI with eczema [89, 92] and allergic rhinitis [92, 93] in childhood and adolescence. However, prospective birth cohorts do not provide evidence

for associations of a high BMI in women before/at the beginning of pregnancy and an increased incidence of other atopic manifestations such as rhinitis and atopic eczema [71, 72].

Promoting normal weight development during childhood and adolescence is of great importance not only with regard to allergy prevention, but also for the health of the child in general. Maternal overweight and obesity at the beginning of pregnancy are, among other things, associated with birth complications, gestational diabetes, and later overweight of the child [94]. For all these reasons, women of childbearing age should avoid overweight or get as close as possible to normal weight before pregnancy.

### Prebiotics and probiotics

Data from partly large, randomized, double-blind intervention studies consistently show no preventive effects of prebiotics and probiotics for the endpoints allergic rhinitis and bronchial asthma. The vast majority of current intervention studies also show no preventive effect of an administration of supplements with prebiotics and/or probiotics on atopic eczema. Allergy-preventive effects for atopic eczema have been described in a few intervention studies and in cohort studies. However, in some of these studies, allergy-preventive effects were not stable over time. The allergy-preventive effects described in single intervention studies were also not reproducible in the few studies that used the same preparation and study design. In an intervention study describing an allergy-preventive effect for atopic eczema, a significantly higher rate of allergic rhinitis was found as an adverse effect. Published studies using prebiotics and/or probiotics are also characterized by a high degree of heterogeneity regarding the intervention (preparation, dose, duration and time of administration), the studied population, and the time at which individual endpoints were recorded.

Since 2014, a total of three intervention studies with prebiotics have been identified, all of which used postnatal supplementation. Using a multicenter design, Boyle et al. [95] investigated the use of a partially hydrolyzed whey infant formula enriched with prebiotics (GOS & FOS & pAOS) in a large study group. Compared to cow's milk formula, the intervention showed no effect on the prevalence of atopic eczema between the ages of 12 and 18 months. Also Ranucci et al. [96] found in an intervention study with 400 infants randomized to prebiotic (GOS/PDX) or standard infant formula after 36

and 48 weeks no effect on the frequency of eczema. In agreement with these data, in a study in Spain including 365 infants, Sierra et al. [97] also found no effect of an infant formula with added prebiotics (GOS) on eczema prevention. The intervention began in the 2<sup>nd</sup> month of life, and the children were followed up to 12 months of age. The endpoint in this study was a combined endpoint of atopic eczema & wheezing & food allergy. This endpoint was (insignificantly) more often observed in the intervention group (OR 1.56; 95% CI 0.89 – 2.73). In another paper [98] it was shown that the partially hydrolyzed infant formula with added prebiotics (GOS & FOS & pAOS) used in the intervention study by Boyle [95] modulated the intestinal microbiome in such a way that it was more similar to the microbiome of breastfed infants.

Since 2014, a total of four intervention studies with probiotics have been identified, all of which used supplementation in the pregnant woman and/or mother. Three of the four papers reported clinical endpoints. In a Norwegian follow-up study [100] of the ProPACT study by Dotterud et al. [99], at the age of 6 years there were no significant differences between children of the former placebo (n = 82) and probiotic group (n = 81) with regard to the prevalence of asthma, allergic rhinitis, and atopic dermatitis after administration of *Lactobacillus rhamnosus* GG, *Bifidobacterium animalis*, *L. acidophilus* from the 36<sup>th</sup> week of gestation up to the 3<sup>rd</sup> month after birth (to the then breastfeeding mother). An unadjusted logistic regression showed a protective effect for atopic dermatitis (OR 0.48, 95%CI 0.25 – 0.92). The number of mothers who needed to be supplemented to prevent atopic dermatitis in one child (number needed to treat) was n = 6. However, this analysis was carried out without adjusting for possible confounders. Another paper by Rø et al. [101] included a subgroup of the ProPACT study (n = 72 (placebo) and n = 68 (actively treated)) to investigate whether probiotic supplementation had an effect on T cells and whether the protective effect on the prevalence of atopic dermatitis observed by Dotterud et al. [99] can possibly be explained by this. The primary aim of this sub-analysis was to investigate in vitro effects on the T-cell population. It was shown that perinatal maternal supplementation with the probiotic combination used (*Lactobacillus rhamnosus* GG, *Bifidobacterium animalis*, *L. acidophilus*) led to a reduction in the Th22 cell population compared to placebo. This effect was also observed in children who did not develop atopic dermatitis during the 2-year follow-up period. In the group who developed atopic dermatitis, the proportion of the Th22 cell population was increased.

The authors conclude that immunological effects of probiotics may be partially mediated through the reduction of Th22 cells.

A cohort study from Norway showed a very weak inverse association between the consumption of probiotic milk and milk products (with lactic acid and bifidobacteria) during pregnancy and the risk of eczema in children aged 6 months (OR 0.94; 95% CI 0.89 – 0.99); however, at the age of 18 months this association was no longer observable (OR 1.0; 95% CI 0.95 – 1.05) [102].

Numerous other intervention studies that have examined the use of probiotic supplementation in the mother during pregnancy and in the child after birth, or studies that have used supplementation only in the child as an intervention, also show, in most cases, no protective effect on atopic eczema [103, 104, 105, 106, 107].

In a large randomised placebo-controlled study from Finland with 1,223 pregnant women, supplementation of a mixture of pre- and probiotics (LGG, *L. rhamnosus*, *Bifidobacterium breve* Bb99, *Propionibacterium freudenreichii* ssp. *shermanii* JS, and GOS) significantly reduced atopic eczema in children at 2 years of age [108]. In this study, supplementation was started in pregnant women with a probiotic preparation or placebo 2 to 4 weeks before delivery and was continued in the infants with the same probiotics plus GOS or placebo for the first 6 months. At the age of 5 years, no difference was found in the frequencies of eczema. In a post-hoc defined group of children who had been delivered by caesarean section, less IgE-associated allergic disease were observed [109]. In a follow-up of this population at the age of 10 years, in which almost 80% of the original study population participated, it was found that children from the probiotic group had allergic rhinoconjunctivitis significantly more often between the ages of 5 and 10 than the placebo group (36.5% vs 29.0%, OR: 1.43; 95% CI: 1.06 – 1.94; p = 0.03). This difference was seen, however, only in vaginally delivered children (38.6% vs 25.8%, OR: 1.80; 95% CI: 1.29 – 2.51; p < 0.01), but not in children after cesarean delivery [110]. In a paper by Hrdý et al. [111], immunological effects after probiotic supplementation (*Escherichia coli* O83: K24: H31) in newborns were described and discussed as a possible explanation for the observed preventive effects on allergic diseases (rhinoconjunctivitis, asthma, atopic eczema).

In an intervention study by Wickens et al. [112] from New Zealand, *Lactobacillus rhamnosus* HN001 supplementation was compared to supplementation with *Bifidobacterium animalis* subsp *lactis* HN019 in pregnant women starting from the 35<sup>th</sup> week

of gestation and for another 6 months during breastfeeding as well as in the first 2 years of the child's life. In this study, a specific effect of HN001 was observed at the age of 6 years on the cumulative prevalence of atopic eczema (HR = 0.56, 95% CI 0.39 – 0.80) and allergic sensitization as shown in the skin prick test (HR = 0.69, 95% CI 0.48 – 0.99) [112]. However, the point prevalence at this point in time showed no significant difference for atopic eczema (RR = 0.66, 95% CI 0.44 – 1.00) and allergic sensitization (RR = 0.72, 95% CI 0.53 – 1.00). For the second probiotic examined in this study, *Bifidobacterium animalis subsp lactis* HN019, no significant effects could be shown [112]. Wickens et al. [113] observed a protective effect of HN001 on the cumulative eczema prevalence even at the age of 11 years. However, when supplementation was restricted to mothers (from the 14<sup>th</sup> to the 16<sup>th</sup> week of gestation and 6 months postpartum), there was no preventive effect on eczema, wheezing, or atopic sensitization in children aged 12 months [114].

The first intervention study that showed a significant protective effect of probiotics against atopic eczema was published in Finland in 2001 [115]. For this study, a population with an increased allergy risk had been recruited, i.e., women who either themselves or their partners had an atopic disease. The women were supplemented with *Lactobacillus* GG or placebo during pregnancy and the children received *Lactobacillus* GG or placebo during the first 6 months of their lives. After 2 years, there was a significantly reduced prevalence of atopic eczema in the probiotic group (RR 0.51 [95% CI 0.32 – 0.84]). This effect could not be confirmed in a study identical in design that investigated an identical probiotic in a German high-risk population (RR 0.96 [95% CI 0.38 – 2.33]) [116]. In the meantime, a third intervention study with a comparable design has been published, in which the initial data from Finland could not be reproduced either (RR 0.95 [95% CI 0.59 – 1.53]) [107]. However, in this study, only the infants were supplemented with probiotics and not the mothers during pregnancy.

The discussion about the effectiveness of prebiotics and probiotics is increasingly accompanied by a controversy about the safety and tolerability of individual preparations. It has to be considered among other things, that the studied populations, such as newborns, are a particularly vulnerable group in which the administration of probiotics could lead to infections and sepsis. In addition, attention is drawn to the risk of plasmid-borne antibiotic resistance [117, 118]. In view of the limited effectiveness of the preparations examined, aspects of safety must therefore

also be included in the evaluation of prebiotics and probiotics with regard to allergy prevention.

### Vitamin D supplementation

The preventive administration of vitamin D in population groups such as breastfeeding women, toddlers, and older children did not indicate a positive effect on the development of allergic diseases in children.

Also interventional studies including women during pregnancy do not indicate a preventive effect of vitamin D supplementation on the prevalence of atopic eczema, allergic rhinitis, or food allergies in their children [310].

The problem with all these studies is the heterogeneity of the populations examined, the number of subjects studied, the period of investigation and the geographical location (impact of UV exposure). Another major issue that complicates the interpretation of the data is the different baseline vitamin D status (measured as serum 25-OH-D values) of the study populations. Two observations are striking: (1) 25-OH-D values below 25 – 30 or below 50 nmol/L at baseline were partly associated with an increased risk of allergic diseases and (2) serum 25-OH-D values > 75 nmol/L (30 ng/mL) were associated with a lower risk. To definitely clarify the question of primary prevention, further studies are required that take into account both vitamin D supplementation during pregnancy and in the postnatal phase without discontinuation. Recommendations cannot be made at the moment. There is contradictory evidence regarding the association between vitamin D supplement intake during pregnancy and the development of allergic diseases in childhood. For example, a combined analysis of two placebo-controlled intervention trials suggests that administration of 4,000 and 2,400 IU of vitamin D per day in pregnancy was only associated with a lower risk of asthma/wheezing in children aged 3 years if the pregnant women had vitamin D levels  $\geq$  30 ng/mL (75 nmol/L) at baseline [119].

In an intervention study by Chawes et al. [120], 623 pregnant women received a placebo-controlled supplementation of 2,400 IU vitamin D/day starting at 24 weeks of gestation until 1 week postpartum, in addition to the standard supplementation of 400 IU/day. During the first 3 years, wheezing was observed in 16% of the children of those mothers who had received the additional vitamin D supplementation, while 20% of the children whose mothers had received a placebo developed wheezing. This difference was, however, not significant. Another randomized, placebo-controlled study from



the USA examined 876 pregnant women who received 4,000 IU vitamin D/day after the 10<sup>th</sup> – 18<sup>th</sup> weeks of gestation until delivery in addition to the standard dose of 400 IU. Out of the children born to mothers who had received the additional supplementation, 24.3% developed asthma until the age of 3 years, compared to 30.4% in the control group. This difference was also not significant [121]. There were no adverse effects observed in either study.

Follow-ups to the interventions by Chawes et al. [121] and Litonjua et al. [120] also failed to show an effect of high-dose vitamin D supplementation during pregnancy on the endpoints asthma and wheezing in children aged 6 years [122, 123].

An analysis of long-term observations of a birth cohort showed that maternal vitamin D serum concentrations < 50 nmol/L between the 16<sup>th</sup> and 20<sup>th</sup> week of gestation were associated with an increased risk of wheezing and asthma (the latter only in boys) at the age of 6 years. The authors conclude that vitamin D supply during pregnancy is important for fetal lung development [124]. In other birth cohorts, it was observed that vitamin D intakes during pregnancy far below the D-A-CH reference values were associated with an increased risk of childhood asthma and allergic rhinitis [124, 125]. Another cohort study that assessed dietary and supplemental vitamin D intake in the 25<sup>th</sup> week of gestation showed no clear association between vitamin D intake and asthma or allergic rhinitis at 18 months or 7 years of age [126].

The overall evidence for effects of vitamin D supplementation in children is also contradictory. For example, a case-control study, conducted as part of a Finnish birth cohort study, showed that children who had a higher vitamin D intake from (fortified) foods and supplements during their first 4 years of life had an increased risk of bronchial asthma by the age of 5 years [127]. However, the differences in vitamin D intakes between cases and controls were very small, so the results should be viewed with caution. In addition, children from the control group had a higher gestational age, had been breastfed longer, and less frequently had parents who were affected by allergies.

A recent placebo-controlled study in children with asthma was able to show that the supplementation of 4,000 IU vitamin D per day did not affect the time to the next exacerbation [128].

### *Supplementation of other vitamins*

With the exception of studies on vitamin D supplementation, there are only a

few studies examining the impact of vitamin supplementation (vitamins A, E, C, and folic acid) during pregnancy or in infancy on the risk of developing an atopic disease. The available study data do not provide sufficient proof that supplementation of these vitamins is associated with the development of atopic diseases: Two older systematic reviews with meta-analyses [129, 130] came to contradictory conclusions about possible associations between intakes of vitamin C, vitamin A, beta-carotene, and vitamin E or corresponding serum concentrations and the occurrence of asthma or wheezing. A more recent cross-sectional study [131] observed that higher intakes of vitamin C and E (from food and supplements) were associated with a lower prevalence of asthma in children aged 3 – 6 years. In contrast, a prospective cohort study [132] found that the intake of vitamins A and E from supplements (but not from food) during pregnancy was associated with an increased risk of wheezing in the child at the age of 18 months. Also a higher vitamin K intake from food and supplements during pregnancy was positively associated with the prevalence of asthma at the age of 7 years. However, those data do not allow reliable conclusions.

Given the recommendation to supplement folic acid before and during pregnancy to reduce the risk of neural tube defects, several prospective cohort studies [133, 134, 135] investigated whether there is an association between folic acid supplementation or intake of folate equivalents or the folate status of the expectant mother and wheezing, asthma, or atopic dermatitis in the child. The available study results indicate that folate equivalent intake or folate status during pregnancy are not associated with the development of asthma, wheezing, or dermatitis in children up to the age of 3 years. This conclusion was also drawn in an earlier systematic review [136]. Two later studies [137, 138] indicated that folic acid supplementation, depending on the onset (3<sup>rd</sup> trimester vs. 1<sup>st</sup> trimester or earlier) and duration of intake, might increase the risk of developing childhood asthma. However, these data have to be interpreted with caution and were not confirmed by two recent intervention studies [139, 140]. It has also been indicated that the impact of folic acid supplementation on the child's lung function could be modified by a gene polymorphism of the methylenetetrahydrofolate reductase (MTHFR C677T polymorphism) in the pregnant woman [133].

There are no studies relevant for Germany that have examined the impact of vitamin supplements in infants or children on the risk to develop an atopic disease in later life.

Intervention studies [141, 142] conducted with infants in Guinea-Bissau (West Africa) indicate that supplementation of high doses (25,000 or 50,000 IU, equivalent to 7.5 or 15 mg) of vitamin A in the first few days after birth may be associated with an increased risk of atopic diseases between the ages of 3 and 9 years, particularly in girls. In another intervention study, vitamin A supplementation of 100,000 IU (= 30 mg) after the 6<sup>th</sup> month of life had no effect on the child's risk of atopic diseases [143]. Since healthy infants in Germany usually do not receive vitamin A supplements (in such high doses) and the other conditions in Germany also differ from those in Guinea-Bissau, the relevance of these studies for the derivation of a guideline recommendation for Europe is questionable. Irrespective of this, further studies are necessary in order to be able to better assess the risk of vitamin A supplementation in infancy for the development of atopic diseases in children.

In summary, based on the available study data, no reliable conclusion can be made about a relationship between the intake of vitamins A, C, E, and K (from food and/or supplements) during pregnancy and the risk of asthma in the child. These vitamins should not be supplemented with the aim of allergy prevention. According to the available studies, periconceptional supplementation of folic acid is not associated with an increased risk of atopic diseases in the child, as long as it is carried out according to the recommendations (4 weeks before pregnancy and in the 1<sup>st</sup> trimester).

### *Supplementation of omega-3 fatty acids (EPA, DHA)*

Due to the substantial heterogeneity of studies published to date, no conclusive recommendation can be given for supplementation of long-chain, polyunsaturated  $\Omega$ -3 fatty acids ( $\Omega$ -3 LCPUFAs) in pregnant women, breastfeeding women, and infants to prevent allergies. Overall, the studies differ significantly in terms of intervention (dosage, content of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA), treatment period), the study population examined, and study duration. While some intervention studies, especially those using low-dose supplementation (usually <1 g  $\Omega$ -3 LCPUFAs), show no effects, other intervention studies that used higher doses (usually  $\geq$  2.4 g  $\Omega$ -3 LCPUFAs) show a protective effect of supplementation of  $\Omega$ -3 LCPUFAs during pregnancy or pregnancy/lactation on the development of allergic diseases in the child, especially

with regard to asthma and wheezing. A recent EAACI position paper on a possible impact of the intake of fatty acids on the risk of allergic diseases indicates that an improved  $\Omega$ -3 LCPUFA supply seems to be decisive for the allergy-preventive effect of supplementation; however, not only the dose but also the bioavailability and the incorporation of the  $\Omega$ -3 LCPUFAs into the cells, which can vary greatly in the case of supplementation, have to be taken into account [144]. In addition to the heterogeneity of the studies, this makes a conclusive assessment and pooled analyzes more difficult. These aspects were also discussed in two recently published systematic reviews and meta-analyses, which found no significant risk reduction of allergic diseases (atopic eczema, asthma, allergic rhinitis) in childhood with supplementation of  $\Omega$ -3 LCPUFAs during pregnancy [1, 145, 146] but showed a positive trend in terms of a protective effect on the development of asthma/wheezing [1, 145]. Overall, only few studies assessed the  $\Omega$ -3 LCPUFAs supply of the mother or the child before the start or during the course of the intervention. However, these studies consistently show that low  $\Omega$ -3 LCPUFA levels are associated with an increased risk of allergic diseases in the child. This risk could be reduced if the  $\Omega$ -3 LCPUFA levels were improved by supplementation. This points to a possible individualized or target group-oriented recommendation for supplementation with  $\Omega$ -3 LCPUFAs in the case of poor supply of DHA and EPA during pregnancy, lactation, or infancy. In order to formulate conclusive and specific recommendations, however, further studies are necessary, which, for example, include explicitly women with a poor supply, or which assess the  $\Omega$ -3 LCPUFA status in both mother and child at baseline and during the course of the intervention.

A number of recent observational studies, some with long-term follow-up, also provide evidence for an association between a better supply of  $\Omega$ -3 LCPUFAs in mothers and their children and a less frequent occurrence of allergic diseases: In a cross-sectional study, Maslova et al. [147], for example, observed an inverse relationship between  $\Omega$ -3 and  $\Omega$ -6 LCPUFAs in maternal blood during pregnancy and asthma in middle childhood, and between  $\Omega$ -3 and  $\Omega$ -6 LCPUFAs in umbilical cord blood and wheezing in early childhood. A cohort study from Germany showed no significant association between  $\Omega$ -3 and  $\Omega$ -6 LCPUFA concentrations or  $\Omega$ -6/ $\Omega$ -3 LCPUFA ratios in umbilical cord blood and the frequency of eczema, asthma, hay fever, allergic rhinitis, or sensitization to inhalant allergens in children. However, it was observed that children

who had developed eczema by the age of 2 years had significantly lower  $\Omega$ -3 LCPUFA concentrations and higher  $\Omega$ -6/ $\Omega$ -3 ratios. In addition, significantly lower  $\Omega$ -3 LCPUFA concentrations were measured in 6-year-old children with asthma [148]. Also, in a Swedish cohort, higher plasma concentrations of  $\Omega$ -3 LCPUFAs in children aged 8 years were inversely associated with the prevalence of asthma and allergic rhinitis at 8 years of age and with a reduced risk of developing asthma between 8 and 16 years of age [149].

Since 2014, data from six intervention studies with pregnant and breastfeeding women and one intervention study with infants have been published that investigated the impact of supplementation with  $\Omega$ -3 LCPUFAs during pregnancy or during pregnancy/breastfeeding on the risk of atopic diseases: In a large Danish study, pregnant women were randomized to a fish oil (2.4 g  $\Omega$ -3 LCPUFAs/day; 55% EPA, 37% DHA) or placebo group (olive oil) and supplemented accordingly from the 24<sup>th</sup> week of gestation until 1 week after delivery. Children in the fish oil group showed a significantly lower risk of persistent wheezing or asthma at the age of 3 – 5 years compared to the control group (n = 695). A sub-analysis showed that the preventive effect of supplementation was most evident in children born to mothers whose pre-intervention EPA and DHA blood levels were in the lowest tertile. There were no significant group differences with regard to the occurrence of eczema or allergic rhinitis at the age of 5 years [150]. Another intervention study from Denmark examined the impact of supplementation during pregnancy on allergic respiratory diseases up to young adulthood. In this study, pregnant women in the 3<sup>rd</sup> trimester were also supplemented with either fish oil (2.7 g  $\Omega$ -3 LCPUFAs/day; 32% EPA, 23% DHA) or olive oil (n = 396) compared to a capsule without oil (control), and the children were followed up to the age of 24 years. There was a significantly reduced probability of being prescribed asthma medication and receiving a discharge diagnosis of asthma in the fish oil group compared to the olive oil group. With regard to the prescription of medication for allergic rhinitis, there was a lower risk in the fish oil group, but without statistical significance [151].

A Swedish intervention study from 2011 examined supplementation during pregnancy and breastfeeding: 145 pregnant women with an increased allergy risk took daily capsules with 2.7 g  $\Omega$ -3 LCPUFAs (1.6 g EPA, 1.1 g DHA) or soybean oil as a placebo from the 25<sup>th</sup> week of gestation until the 3<sup>rd</sup> month of breastfeeding. A protective effect of maternal supplementation on the cumulative

incidence of IgE-mediated allergic diseases (eczema, food allergy, asthma, or rhinoconjunctivitis) was observed within the first 2 years of life. In addition, it was found that, regardless of the group, higher DHA and EPA plasma levels in the mother and child were less frequently associated with allergic diseases within the first 2 years of life; this effect was dose dependent [152]. A more recent sub-analysis of this study examined whether the observed preventive effect can also be explained by increased concentrations of  $\Omega$ -3 LCPUFA in breast milk due to supplementation during pregnancy and lactation. It was shown that the supplementation led to significantly higher concentrations of  $\Omega$ -3 LCPUFAs in breast milk and to a preventive effect on the occurrence of IgE-mediated diseases in the child [153].

In contrast, three other intervention studies showed no allergy-preventive effects of supplementation with  $\Omega$ -3 LCPUFA during pregnancy. However, in comparison to the studies described above, in some cases lower amounts were supplemented and serum concentrations were not measured before or during the intervention: For example, in a large Australian intervention study no differences were found in children at risk of atopic disease (n = 668) with regard to the development of IgE-mediated allergic diseases (atopic eczema, IgE-mediated wheezing, allergic rhinitis, or rhinoconjunctivitis) at the age of 6 years, following maternal supplementation of 900 mg fish oil (800 mg DHA, 100 mg EPA) or placebo (vegetable oil) daily from the 21<sup>st</sup> week of gestation until birth [154]. A randomized study from Mexico also found no protective effect of supplementation with 400 mg algae-based DHA compared to placebo (cereal and soybean oil) in pregnancy on the occurrence of wheezing up to the 18<sup>th</sup> month of life (n = 869) [155]. In another study from the USA with a comparatively small number of cases (n = 84), which primarily examined the effect of supplementation with  $\Omega$ -3 LCPUFAs (fish oil) on the prevention of depression during pregnancy, both an EPA-rich (1,060 mg EPA and 274 mg DHA/day) and a DHA-rich (900 mg DHA and 180 mg EPA/day) prenatal supplementation were associated with an increased risk of developing atopic eczema at the age of 36 months [156].

In line with the data available for pregnancy and lactation, an Australian study from 2012 had already shown that a daily dose of 650 mg fish oil (280 mg DHA, 110 mg EPA) compared to placebo (olive oil) administered to infants at an increased risk of allergies in the first 6 months of life resulted in significantly higher  $\Omega$ -3 LCPUFA concentrations at the age of 6 months. Although

postnatal supplementation was associated with a potentially positive effect on infant immune function at 6 months of age [157], there was no difference in the prevalence of eczema or other atopic diseases between the intervention and control groups. However, regardless of the group, high levels of  $\Omega$ -3 LCPUFAs in the child's blood were associated with a lower risk of eczema and wheezing [157, 158].

Since 2014, two further studies have been identified that examined whether feeding infants with  $\Omega$ -3-LCPUFA-fortified infant formula (but without measuring the LCPUFA serum level in the child) may reduce the risk of atopic diseases in later childhood: In an Australian intervention study, 657 preterm infants were fed an infant formula highly fortified with DHA (DHA: 1% of the fatty acids) compared to an infant formula with standard DHA content (DHA: 0.3% of the fatty acids), while at the same time breastfeeding mothers received 0.5 g fish oil (900 mg DHA and 195 mg EPA) (or soybean oil as a placebo) to increase the DHA concentration in the breast milk. At the age of 7 years, there was no difference between the groups with regard to the development of asthma/wheezing, hay fever, and eczema [159]. A French prospective observational study including 325 newborns who were either fed an infant formula fortified with DHA and arachidonic acid (ARA) (17 mg DHA/100 kcal and 34 mg ARA/100 kcal) or an infant formula without these fatty acids also showed no significant differences regarding the occurrence of eczema in the 1<sup>st</sup> year of life [160].

No side effects were reported in the intervention studies described here on supplementation of  $\Omega$ -3 LCPUFAs for allergy prevention. According to EFSA, there are no safety concerns regarding the daily intake of  $\Omega$ -3 LCPUFAs via supplements for adults up to a combined dose of 5 g EPA and DHA or up to a dose of 1.8 g EPA alone or up to a dose of 1 g DHA alone for healthy adults [161]. Regardless of the purpose of allergy prevention, German professional societies recommend DHA supplementation during pregnancy and breastfeeding in order to achieve the recommended average daily intake of at least 200 mg DHA if no oily sea fish is consumed [94, 162]. According to the EFSA, the appropriate daily intake for infants up to the age of 6 months is 100 mg DHA [163]. According to the Delegated Regulation (EU) 2016/127, a mandatory addition of DHA of at least 20 mg/100 kcal and at most 50 mg/100 kcal is stipulated for infant formula and follow-on formula.

## Pets

Various epidemiological studies showed that having a dog in the household during the first years or the first 3 years of a child's life has a primary protective effect with regard to the development of food allergies [164], airborne allergies, and bronchial asthma at school age (6 – 13 years) [165, 166, 167, 168, 169]. A Swedish birth cohort study [169] found no protective association of dogs in the household during the 1<sup>st</sup> year of life and allergic rhinitis at the age of 13 years. With regard to keeping cats or other typical pets, there are still conflicting data. In the Swedish BAS cohort, keeping cats in the 1<sup>st</sup> year of life turned out to be protective with regard to the development of allergic rhinitis at 13 years of age, but these data are based on parent questionnaire and not on a physician's diagnosis [169]. In a large Dutch study, no association was found between pet exposure in childhood and bronchial asthma at 17 years of age [170]. It remains to be seen whether keeping a dog should be explicitly recommended for families as a primary allergy prevention. Controlled studies are lacking. However, the evidence of protection through early contact with dogs has become very clear in the last 6 years. An influence on the child's microbiome can be assumed.

## House dust mites, endotoxins in house dust

Earlier studies could not demonstrate reliable effectiveness of the reduction of the domestic allergen content as a measure of primary allergy prevention. Studies on the correlation of early exposure to house dust mites, animal dander, and endotoxins and the later development of asthma and/or allergic sensitization show partially contradictory results [171, 172]. In the U.S. birth cohort study URECA, exposure to house dust mite allergens in the 1<sup>st</sup> year of life was not associated with an increased risk of recurrent wheezing at 3 years of age [173]. The microbial content of the house dust was also examined in a sub-sample [173]. A combined analysis of this nested case-control study showed the lowest rates of allergic sensitization and wheezing at age 3 years in the group of children exposed to high levels of both indoor allergens and bacterial endotoxins during the 1<sup>st</sup> year of life, indicating a synergistic effect. In a Finnish birth cohort study, a sub-analysis assessed the associations between quantity and diversity of microbial markers in house dust samples collected at 2 months of age and later respiratory symptoms and allergies in

children [174, 175]. The microbial diversity correlated negatively with the asthma risk at 6 years [174] and at 10.5 years [175]. Other studies found differences in the qualitative and quantitative composition as well as the microbial diversity of house dust from homes in which children grow up with and without asthma symptoms [176, 177, 178]; in particular, the indoor microbiota in poorer urban residential areas (lower richness, lower Shannon index, specific germ clusters) appear to be associated with a risk for the development of respiratory symptoms. Further research is necessary to clarify whether the child's microbiome is altered as a result and to better characterize protective factors and risk factors.

### Allergen-specific immunotherapy (AIT)

Allergen-specific immunotherapy (AIT) is a form of therapy that has been well documented in terms of its effectiveness in allergic rhinitis and/or allergic bronchial asthma. The indication is to be made according to the AWMF guideline.

The disease-modifying effect of AIT comprises:

- Prevention of new IgE sensitizations [179, 180]
- Prevention of bronchial asthma by AIT in allergic rhinitis and allergic rhinokonjunctivitis [179, 180]

Some studies have investigated the prevention of new IgE sensitizations by AIT, mostly in children with allergic rhinitis/ allergic rhinokonjunctivitis or asthma [181, 182, 183, 184, 185, 186, 187, 188, 189]. Two studies were placebo-controlled and were carried out in atopic infants [190, 191, 192] or in IgE-sensitized, non-allergic children [193]. It has been indicated that primary preventive AIT with house dust mite extract can prevent new sensitizations in the first 2 years of life. A modifying effect on allergic symptoms has not been reported [179].

The prevention of bronchial asthma by AIT in allergic rhinitis/allergic rhinokonjunctivitis was considered to be secondary/tertiary prevention at best and is not discussed in detail in the present guideline. A small double-blind, placebo-controlled study [194] in patients with perennial rhinitis due to house dust mite allergy showed not only improvement in bronchial hyperreactivity but also a significantly lower rate of asthma after 2 years of AIT compared to the control group (0 vs. 9%). The significantly larger PAT study [188] also showed a clear effect in terms of a reduced risk of developing asthma after 3

and 10 years of follow-up in children with seasonal allergic rhinitis. Data from a 3-year double-blind, placebo-controlled SLIT study on the treatment of children with allergic rhinitis due to grass pollen failed to meet the primary endpoint (time to first diagnosis of asthma) but showed reduced asthma symptoms and asthma medication use compared to the placebo group after 3 and 5 years.

### Farms

On the subject of farms, an updated statement was adopted. This takes the evidence into account that it has repeatedly been shown that exposure to a farm in the first years of life is associated with a reduced prevalence of asthma and also allergic diseases.

It has been suggested that the reasons for this are (1) a more efficient stimulation of the innate immune system in children exposed to farms compared to those who are not s. (2) a microbial composition of the house dust on farms (with only small amounts of *Streptococcaceae*) being protective against the development of asthma. Children not exposed to farms are also protected when the microbial composition of house dust is similar to that of the farm environment [195]. Mechanistically, a reduced pro-inflammatory cytokine response can also be seen.

Exposure to farm milk and to barns shows a protective effect against childhood asthma. The better function and higher number of regulatory T cells [196], which are functionally active up to the age of 4.5 years [197] are regarded as the cause here. On the other hand, increased amounts of omega-3 polyunsaturated fatty acids [198] and increased exposure to non-microbial N-glycolyneuraminic acid (Neu5Gc) have been discussed as playing a role in the protective farm effect [199].

Not only in Europe but also in South Africa, exposure to animals has been shown to be strongly protective against allergic diseases in rural areas, while in the cities the consumption of fermented milk in particular is protective [200].

### Caesarean section

Already in the last version of the guideline it was stated that the evidence of the studies available at that time showed an increased risk, for asthma, in children who were born through an elective caesarean section. In the meantime, further studies have been published that reinforce the

recommendation made at that time with a higher level of evidence and also a higher level of recommendation. It has also been shown that children, especially after elective caesarean sections, have an increased risk of asthma in infancy and at school age.

A meta-analysis of 9 European cohort studies showed a significantly increased risk of developing asthma in patients aged 5 – 9 years (adjusted OR 1.49; 95% CI 1.13 – 1.97). Other international studies with different designs came to the same conclusions [201, 202]. In particular, a large population-based study with more than 136,098 children from the USA [203] also confirmed this result (adjusted OR 1.11; 95% CI 1.06 – 1.15).

A German prospective birth cohort study could not show any significant results at the age of 15 years (OR: 0.87 (95% CI 0.57 – 1.33). The same applies to a Brazilian cross-sectional study [204]. In both studies, however, no distinction was made between elective and secondary or emergency caesarean section.

Most studies assume that the protective effects of natural birth are due to a change in the infant microbiome. Particularly in elective caesarean section there is no transmission of the maternal microbiome to the child.

The current literature does not suggest that a reduction of other allergic diseases is possible by avoiding a caesarean section. Studies on atopic dermatitis and on rhinitis allergica in particular did not show any correlation with the mode of birth [205].

## Vaccinations

Data from various cohort studies show neither increases nor reductions of allergic sensitizations, atopic eczema, or bronchial asthma after vaccinations in infancy [206, 207].

A better vaccination coverage rate (higher number of vaccine doses received) is associated with a lower probability of allergic sensitizations [208], allergic rhinoconjunctivitis [209], and/or bronchial asthma [208]. Lower prevalences [208] and lower severities [206] were observed in atopic dermatitis.

A delayed primary immunization also showed inconsistent results in several cohort studies with regard to the development of allergic diseases [210, 211].

Changing the pertussis vaccine from a cell-based to an acellular vaccine was not associated with an increased risk of food allergies or allergic diseases [213, 214, 215].

In a randomized trial, BCG vaccination within 7 days after birth was associated with

a lower risk of atopic eczema in children with an atopic disposition [216]. On the other hand, there was no effect on recurrent wheezing in the first year of life [217], on allergic sensitization, and on suspected food allergy up to the 13<sup>th</sup> month of life [218] or on the number of hospitalizations [219].

Various retrospective cohort studies showed no effect of previous routine BCG vaccinations on the development of sensitizations, hay fever, asthma, or eczema in childhood [220, 221].

In utero exposure to influenza vaccination is not associated with bronchial asthma in children [222].

## Day care centers

There is conflicting data on the association between care at day care centers and the prevalence of childhood asthma at different ages so that a recommendation cannot be derived. In this context, the studies did not take into account essential trigger factors for the later course of asthma, namely infections and allergic sensitizations.

While kindergarten care in infancy may temporarily lead to an increased prevalence of obstructive respiratory symptoms, presumably due to a higher number of viral infections [223], retrospective data show a protective effect on bronchial asthma in school children [223], but also increases of prevalences [224]. Therefore, no recommendation can be derived from the small number of studies with retrospective data collection so far, even if the number of cases is high. Further studies are necessary addressing the presumably relevant influencing factors – very early admission to care before the 6<sup>th</sup>/12<sup>th</sup> months of life (possibly increasing prevalence), duration of weekly care [224], and development of an allergy to environmental allergens.

Overall, the effects are not pronounced. For children who started day care after the 12<sup>th</sup>/18<sup>th</sup> months of life, the effects were very small or not detectable in the studies mentioned above.

The data from a study showing an increased prevalence of atopic dermatitis [223] in day-care children are based solely on retrospective statements from parents on that diagnosis during a visit to the doctor.

With regard to the prevalence of food allergies, no differences were found between children in child care and those who are not [223].

## Drugs

Numerous controlled studies show low associations (mean increases in the RR in the range of 1.2 – 2.5) between drug intake (antibiotics, NSAIDs) and atopic diseases [225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240]. A distinction has to be made between prenatal intake by the mother and postnatal exposure of the child. The data on the increase in the relative risk of atopic diseases are more extensive for the use of antibiotics [225, 226, 227, 228, 229, 230, 231, 232, 233] than for the use of NSAID [234, 235, 236, 237, 238, 239, 240].

In summary, the data show that children whose mothers took antibiotics during pregnancy have an increased mean risk of developing asthma (11 studies, RR 1.3 – 3.2) [225, 226, 227, 228, 229, 230, 231, 232, 233, 235]. Studies (mainly birth cohorts) on the exposure of children in their 1<sup>st</sup> or 2<sup>nd</sup> years of life show a slightly increased risk of allergic asthma in the case of postpartum exposure to antibiotics, and a less increased risk of allergic rhinitis or of eczema later in life. A study from Germany showed an age-dependent effect with regard to atopic dermatitis only (birth cohort Pasture, up to the age of 6 years RR AD 2.65) [231].

Contradictory data are available intake of paracetamol in the first years of life (birth cohorts and case-control studies) [232, 233, 234, 235, 236] or during pregnancy [237, 238, 239, 240] so that no clear connection can be established between the intake of paracetamol and atopic diseases.

Due to potential confounding factors, the available studies on medication intake and atopic diseases should generally be interpreted with caution.

## Skin barrier

A disturbed skin barrier often precedes the development of atopic dermatitis and sensitizations to allergens including protein allergens. 6 years ago, two independent, smaller studies (n = 118 and n = 135) described that a consequent application of emollients significantly reduced the incidence of eczema (i.e., between 30 and 50%) in infants from atopic risk families [241, 242]. The main criticism of the studies, which attracted a lot of attention, was the relatively small number of participants. The results could not be reproduced in a larger Japanese study including 800 children [243]. Two negative follow-up studies with even higher case numbers are currently available: In the BEEP (Barrier Enhancement for Eczema Prevention) study from the UK,

1,394 newborns at high risk of eczema (i.e., at least one first-degree relative with medically diagnosed eczema, allergic rhinitis, or asthma) were recruited, randomized 1:1, and either treated daily with an emollient plus standard skin care regimen (“emollient group”) or with standard skin care regimen only (“control group”) during their first year of life [244]. The primary objective of the study was to assess the frequency of eczema at 2 years of age (defined according to the UK Working Party criteria of AD). By the age of 2 years, eczema had manifested in 139 (23%) of 598 infants in the emollient group and 150 (25%) of 612 infants in the control group. The mean number of skin infections per child was 0.23/year in the emollient group versus 0.15 in the control group [244].

In a similar Norwegian study, 2,397 infants were randomized into four groups at birth [245]: (1) controls without advice on specific skin care and with recommendations to follow national infant feeding guidelines (no intervention); (2) skin intervention group (emollients including regular use of bath additives and face cream); (3) food intervention group: early supplemental feeding of peanut, cow’s milk, wheat, and egg; or (4) combined skin and food interventions. The primary outcome to be compared was the onset of atopic dermatitis at 12 months of age. Clinical examinations were performed at 3, 6, and 12 months of age by blinded investigators. Atopic dermatitis was observed in 8% in the no-intervention group, in 11% in the skin intervention group, in 9% in the food intervention group, and in 5% in the combined intervention group, with no significant differences. Thus, neither the use of emollients nor early introduction of complementary foods reduced the development of atopic dermatitis.

There is still a lack of controlled studies investigating the daily use of emollients in infants and toddlers with visibly dry skin who already have eczema or who have genodermatosis with skin barrier disorders associated with IgE-mediated sensitization (especially ichthyosis vulgaris, Netherton syndrome) – also with the aim of preventing further eczema and allergies.

## Pollutants

There is very heterogeneous and weak data on molds and moisture as indoor pollutants. The existing studies are cross-sectional analyzes that were carried out on the basis of information provided by parents. The study by Milanzi et al. [170] (n = 1,871) shows no association between mold/moisture at different time points in childhood and the development of asthma. In contrast, another

paper (n = 4,089) shows that exposure to mold and moisture directly correlates with the risk of developing asthma. No impact on rhinitis was found [246]. A small Finnish study (n = 214) observed an increased risk of developing rhinitis and asthma in children [247]. Zhang et al. [248] (n = 36,541) evaluated parent questionnaires and found an increased risk of rhinitis when moisture and molds were present.

The connection between exposure to tobacco smoke and the development of bronchial asthma has been clearly documented. The evaluated studies show a stringent association between active and passive exposure to tobacco smoke and the development of allergies and, especially, asthma. This mainly affects children from high-risk families [249, 250, 251].

Active smoking appears to have little, if any, impact on the development of other allergic diseases such as atopic eczema, or food allergies. There are no high-quality studies on this topic.

For other *indoor pollutants*, the following papers were found: In a cohort study including 560 children, O'Connor et al. [172] found no association of nitrogen dioxide, ergosterol, and endotoxin in the room air during the first 3 years of life and asthma at the age of 7 years in children from high-risk families.

On the basis of Danish cohorts, Callesen et al. [171] investigated phthalates, nicotine, and CO<sub>2</sub> in the indoor air in a sample of atopic children (74 of them asthmatics, 83 with rhinoconjunctivitis, and 90 with atopic dermatitis). An interesting finding was the increased nicotine content in house dust in asthmatic children. With regard to phthalates, no relevant association was seen, except for a higher proportion of DEHP in the homes of children whose parents reported "current wheeze".

In a small case control study, Madureira et al. [252] showed an association between the presence of air conditioning, water damage, and visible mold in the previous year in 38 asthmatic children. A large number of analyzed indoor pollutants, such as volatile organic compounds (VOC), PM<sub>2.5/10</sub>, bacteria, and fungi, did not show any such association apart from D-limonene; however, the range of fluctuation in the measurements was small.

Two more extensive cross-sectional studies from Portugal [253] and China [254] used surrogates to show a moderate influence of air pollutants on asthma. The Portuguese study showed an association of indoor CO<sub>2</sub> concentrations (day care centers) with asthma (OR 1.1) and wheezing in the previous 12 months; the Chinese study demonstrated

risks of a similar magnitude for atopic respiratory diseases when, e.g., pungent odor and tobacco smell were present.

Studies proving or excluding an association between exposure to *plasticizers* (such as phthalates) and the development of allergic diseases could not be identified.

There are (two) conflicting studies on whether regular exposure to *chlorinated pool water* during swimming pool visits could increase the risk of asthma. Both studies do not show a connection between regular swimming pool visits and an increased risk of rhinitis and eczema.

A cross-sectional study shows an increased risk of asthma, especially in children with atopic sensitization, but no increased risk of rhinitis and eczema due to regular swimming [255].

In another study, there was no significant association between early, late, or current swimming/swimming pool visits and asthma, dermatitis, wheezing, allergic rhinitis, and eczema in children up to the age of 12 years [256].

### Motor vehicle emissions

With regard to the influence of indoor and outdoor air pollutants, including exposure to tobacco smoke, the previous recommendations are further supported by the results of current studies. With regard to the exposure to motor vehicle pollutants, data from the different studies show heterogeneous results. In some studies, exposure to nitrogen oxides and particulate matter with a particle size < 2.5 µm during pregnancy was associated with the development of rhinitis and hay fever [257, 258, 259] or asthma [260]. Additionally, data from cohort studies show that increased exposure to traffic-related pollutants was associated with an increased incidence of wheezing [261] or asthma [262, 263]. One study showed that living near a busy road was associated with an increased risk of developing asthma [264, 265, 266, 267]. On the other hand, there are also various studies that do not show an association between exposure to vehicle pollutants and allergic or respiratory diseases [268, 269, 270, 271]. A long-term study from South Korea [272, 273] shows that increased ozone levels also increase the relative risk of acute asthma attacks.

### Psychosocial factors

Depression and other types of psychological stress and illnesses in the mother during pregnancy and after birth have been



shown in epidemiological meta-analyses [274, 275, 276] to be factors that contribute to the development of an atopic disease. There has been only little research on the influence of the father's psychological stress. Relationships could be shown for:

- Prenatal maternal stress in the form of negative life events, anxiety/depression, experiencing severe loss and violence, experiencing stress, socioeconomic stress, and work-related stress. These factors showed a positive interaction with allergy-related parameters such as asthma, atopic dermatitis, allergic rhinitis, and IgE [274, 275] in 21 of 25 studies and in 25 of 30 studies, respectively; however, there were strong quality differences in the study design and in the choice of outcome measures between the studies. The results are consistent with an older meta-analysis including 22 studies [276] and indicate that anxiety and depression in the last trimester in particular are associated with negative effects [275].
- Prenatal maternal stress is related to symptoms of atopic dermatitis in the 2-year-old child [277], wheezing in the 1- to 4-year-old child [278, 279], and atopic dermatitis in the 7-year-old child [280].
- Prenatal stressful life events of the mother are related to asthma, allergic rhinitis, and eczema in the 14-year-old child but not in the 6-year-old child if the stress was experienced between the 18<sup>th</sup> and 34<sup>th</sup> week of pregnancy [281], as well as in 6-year-old girls [282].
- Prenatal maternal anxiety and depression are related to the development of atopic dermatitis in the 1-year-old child [283], to wheezing episodes in the 1- to 4-year-old child [284], to allergic rhinoconjunctivitis within the first 5 years of life [285], to atopic dermatitis in the 5-year-old child [284], to asthma in the 7-year-old child [286], and to sensitization to inhaled allergens in the 10-year-old child [287].
- Postpartum maternal depression is related to atopic dermatitis in the 12-month-old child [288], in the 3-year-old child [289], to respiratory symptoms in preschool children, with girls being affected 3 times more often than boys [290], and to asthma in the 6- to 8-year-old child [291].
- Maternal lack of sensitivity, anxiety, and apathy is related to atopic dermatitis in the 18-month-old child [286].
- Maternal depression is associated with bronchial asthma and atopic dermatitis in the child [292].

- Use of psychological therapy offers by the mother is related to asthma in the 12-year-old child [293].
- Paternal depression symptoms at any point in life are related to an increased risk of asthma in the 7-year-old child [294].

Epidemiological studies also show a connection between emotional abuse in early childhood as well as traumatic experiences at any point in life and the development of allergy symptoms later in life [295]. In addition, an interaction between depressive symptoms and other risk factors for allergy, such as obesity, with the severity of allergy symptoms has been shown [296]. Furthermore, a connection between a lack of maternal sensitivity and the development of atopic dermatitis could be shown [286]. At the same time, a protective effect of high maternal sensitivity with regard to the development of atopic dermatitis in children up to the age of 18 months was observed, as was an equally positive effect of social support [286].

Complementary to this, numerous epidemiological and prospective studies have shown that the development of allergic diseases might subsequently increase the probability of developing psychological stress and associated diseases [297, 298, 299, 300, 301, 302] (phobias, depression, ADHD), which can possibly be reduced by good disease control but which, on the other hand, can also impair disease control [303]. In the case of comorbidity of allergy and mental illness, a higher disease severity and lower quality of life and the development of further complications can be expected, which can be prevented by simultaneous diagnosis and treatment of mental comorbidity in allergy [304, 305, 306].

In animal experiments, stress transmitter-reducing and anti-depressive therapies show good effectiveness in reducing stress, anxiety, and depression in allergy patients [307]. Clinical evidence currently exists for educational programs and anti-depressive drug therapy as well as psychotherapy [28, 51, 308, 309].

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## Conflict of interest

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## References

- [1] Venter C, Greenhawt M, Meyer RW, Agostoni C, Reese I, du Toit G, Feeney M, Maslin K, Nwaru BI, Roduit C, Untersmayr E, Vlieg-Boerstra B, Pali-Schöll I, Roberts GC, Smith P, Akdis CA, Agache I, Ben-Adallah M, Bischoff S, Frei R, et al. EAACI position paper on diet diversity in pregnancy, infancy and childhood: Novel concepts and implications for studies in allergy and asthma. *Allergy*. 2020; 75: 497-523. [CrossRef PubMed](#)
- [2] Celik V, Beken B, Yazicioglu M, Ozdemir PG, Sut N. Do traditional fermented foods protect against infantile atopic dermatitis. *Pediatr Allergy Immunol*. 2019; 30: 540-546. [CrossRef PubMed](#)
- [3] Moonesinghe H, Patil VK, Dean T, Arshad SH, Glasbey G, Grundy J, Venter C. Association between healthy eating in pregnancy and allergic status of the offspring in childhood. *Ann Allergy Asthma Immunol*. 2016; 116: 163-165. [CrossRef PubMed](#)
- [4] Ogawa K, Morisaki N, Kobayashi M, Jwa SC, Tani Y, Sago H, Horikawa R, Fujiwara T. Maternal vegetable intake in early pregnancy and wheeze in offspring at the age of 2 years. *Eur J Clin Nutr*. 2018; 72: 761-771. [CrossRef PubMed](#)
- [5] Bédard A, Northstone K, Henderson AJ, Shaheen SO. Mediterranean diet during pregnancy and childhood respiratory and atopic outcomes: birth cohort study. *Eur Respir J*. 2020; 55: 1901215. [CrossRef PubMed](#)
- [6] Øien T, Schjelvaag A, Storrø O, Johnsen R, Simpson MR. Fish Consumption at One Year of Age Reduces the Risk of Eczema, Asthma and Wheeze at Six Years of Age. *Nutrients*. 2019; 11: 1969. [CrossRef PubMed](#)
- [7] Rucci E, den Dekker HT, de Jongste JC, Steenweg-de-Graaff J, Gaillard R, Pasmans SG, Hofman A, Tiemeier H, Jaddoe VW, Duijts L. Maternal fatty acid levels during pregnancy, childhood lung function and atopic diseases. The Generation R Study. *Clin Exp Allergy*. 2016; 46: 461-471. [CrossRef PubMed](#)
- [8] Leermakers ET, Sonnenschein-van der Voort AM, Heppe DH, de Jongste JC, Moll HA, Franco OH, Hofman A, Jaddoe VW, Duijts L. Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: the Generation R Study. *Eur J Clin Nutr*. 2013; 67: 353-359. [CrossRef PubMed](#)
- [9] Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal fat intake during pregnancy and wheeze and eczema in Japanese infants: the Kyushu Okinawa Maternal and Child Health Study. *Ann Epidemiol*. 2013; 23: 674-680. [CrossRef PubMed](#)
- [10] Pelé F, Bajoux E, Gendron H, Monfort C, Rouget F, Multigner L, Viel JF, Cordier S. Maternal fish and shellfish consumption and wheeze, eczema and food allergy at age two: a prospective cohort study in Brittany, France. *Environ Health*. 2013; 12: 102. [CrossRef PubMed](#)
- [11] Stratakis N, Roumeliotaki T, Oken E, Ballester F, Barros H, Basterrechea M, Cordier S, de Groot R, den Dekker HT, Duijts L, Eggesbø M, Fantini MP, Forastiere F, Gehring U, Gielen M, Gori D, Govarts E, Inskip HM, Iszatt N, Jansen M, et al. Fish and seafood consumption during pregnancy and the risk of asthma and allergic rhinitis in childhood: a pooled analysis of 18 European and US birth cohorts. *Int J Epidemiol*. 2017; 46: 1465-1477. [CrossRef PubMed](#)
- [12] Gardner KG, Gebretsadik T, Hartman TJ, Rosa MJ, Tyllavsky FA, Adgent MA, Moore PE, Kocak M, Bush NR, Davis RL, Lewinn KZ, Wright RJ, Carroll KN. Prenatal omega-3 and omega-6 polyunsaturated fatty acids and childhood atopic dermatitis. *J Allergy Clin Immunol Pract*. 2020; 8: 937-944. [CrossRef PubMed](#)
- [13] Rosa MJ, Hartman TJ, Adgent M, Gardner K, Gebretsadik T, Moore PE, Davis RL, LeWinn KZ, Bush NR, Tyllavsky F, Wright RJ, Carroll KN. Prenatal polyunsaturated fatty acids and child asthma: Effect modification by maternal asthma and child sex. *J Allergy Clin Immunol*. 2020; 145: 800-807.e4. [CrossRef PubMed](#)
- [14] Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal consumption of dairy products, calcium, and vitamin D during pregnancy and infantile allergic disorders. *Ann Allergy Asthma Immunol*. 2014; 113: 82-87. [CrossRef PubMed](#)
- [15] Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA Jr, Gillman MW, Gold DR, Litonjua AA. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. *J Allergy Clin Immunol*. 2014; 133: 1373-1382. [CrossRef PubMed](#)
- [16] Chisaguano AM, Montes R, Castellote AI, Morales E, Júlvez J, Vioque J, Sunyer J, López-Sabater MC. Elaidic, vaccenic, and rumenic acid status during pregnancy: association with maternal plasmatic LC-PUFAs and atopic manifestations in infants. *Pediatr Res*. 2014; 76: 470-476. [CrossRef PubMed](#)
- [17] Halken S, Muraro A, de Silva D, Khaleva E, Angier E, Arasi S, Arshad H, Bahnson HT, Beyer K, Boyle R, du Toit G, Ebisawa M, Eigenmann P, Grimshaw K, Hoest A, Jones C, Lack G, Nadeau K, O'Mahony L, Szajewska H, et al; European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). *Pediatr Allergy Immunol*. 2021; 32: 843-858. [CrossRef PubMed](#)
- [18] Munblit D, Peroni DG, Boix-Amorós A, Hsu PS, Van't Land B, Gay MCL, Kalotilina A, Skevaki C, Boyle RJ, Collado MC, Garssen J, Geddes DT, Nanan R, Slupsky C, Wegienka G, Kozyrskij AL, Warner JO. Human milk and allergic diseases: An unsolved puzzle. *Nutrients*. 2017; 9: 894. [CrossRef PubMed](#)
- [19] Schoetzau A, Filipiak-Pittroff B, Franke K, Koletzko S, Von Berg A, Gruebl A, Bauer CP, Berdel D, Reinhardt D, Wichmann HE; German Infant Nutritional Intervention Study Group. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol*. 2002; 13: 234-242. [CrossRef PubMed](#)
- [20] Berg A, Krämer U, Link E, Bollrath C, Heinrich J, Brockow I, Koletzko S, Grübl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, Reinhardt D, Berdel D; GINIplus study group. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course – the GINIplus study up to the age of 6 years. *Clin Exp Allergy*. 2010; 40: 627-636. [CrossRef PubMed](#)
- [21] van Meel ER, de Jong M, Elbert NJ, den Dekker HT, Reiss IK, de Jongste JC, Jaddoe VVW, Duijts L. Duration and exclusiveness of breastfeeding and school-age lung function and asthma. *Ann Allergy Asthma Immunol*. 2017; 119: 21-26.e2. [CrossRef PubMed](#)
- [22] Groenwold RH, Tilling K, Moons KG, Hoes AW, van der Ent CK, Kramer MS, Martin RM, Sterne JA. Breast-feeding and health consequences in early childhood: is there an impact of time-dependent confounding? *Ann Nutr Metab*. 2014; 65: 139-148. [CrossRef PubMed](#)
- [23] Ajetunmobi OM, Whyte B, Chalmers J, Tappin DM, Wolfson L, Fleming M, MacDonald A, Wood R, Stock-

- ton DL; Glasgow Centre for Population Health Breastfeeding Project Steering Group. Breastfeeding is associated with reduced childhood hospitalization: evidence from a Scottish Birth Cohort (1997-2009). *J Pediatr*. 2015; 166: 620-625.e4. [CrossRef PubMed](#)
- [24] Jelding-Dannemand, E, Malby Schoos AM, Bisgaard H. Breast-feeding does not protect against allergic sensitization in early childhood and allergy-associated disease at age 7 years. *J Allergy Clin Immunol*. 2015; 136: 1302-1308.e1-13. [CrossRef PubMed](#)
- [25] Leung JY, Kwok MK, Leung GM, Schooling CM. Breastfeeding and childhood hospitalizations for asthma and other wheezing disorders. *Ann Epidemiol*. 2016; 26: 21-27.e1-3. [PubMed](#)
- [26] Filippiak-Pittroff B, Koletzko S, Krämer U, Standl M, Bauer CP, Berdel D, von Berg A. Full breastfeeding and allergies from infancy until adolescence in the GINIplus cohort. *Pediatr Allergy Immunol*. 2018; 29: 96-101. [CrossRef PubMed](#)
- [27] Elbert NJ, van Meel ER, den Dekker HT, de Jong NW, Nijsten TEC, Jaddoe VVW, de Jongste JC, Pasmans SGMA, Duijts L. Duration and exclusiveness of breastfeeding and risk of childhood atopic diseases. *Allergy*. 2017; 72: 1936-1943. [CrossRef PubMed](#)
- [28] Knibb R, Halsey M, James P, du Toit G, Young J. Psychological services for food allergy: The unmet need for patients and families in the United Kingdom. *Clin Exp Allergy*. 2019; 49: 1390-1394. [CrossRef PubMed](#)
- [29] Klopp A, Vehling L, Becker AB, Subbarao P, Mandhane PJ, Turvey SE, Lefebvre DL, Sears MR, Azad MB, Daley D, Silverman F, Hayglass K, Kobar M, Turvey S, Kollmann T, Brook J, Ramsey C, Macri J, Sandford A, Pare P, et al; CHILD Study Investigators. Modes of infant feeding and the risk of childhood asthma: A prospective birth cohort study. *J Pediatr*. 2017; 190: 192-199.e2. [CrossRef PubMed](#)
- [30] Nwaru BI, Craig LC, Allan K, Prabhu N, Turner SW, McNeill G, Erkkola M, Seaton A, Devereux G. Breast-feeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years. *Clin Exp Allergy*. 2013; 43: 1263-1273. [CrossRef PubMed](#)
- [31] Azad MB, Vehling L, Lu Z, Dai D, Subbarao P, Becker AB, Mandhane PJ, Turvey SE, Lefebvre DL, Sears MR; CHILD Study Investigators. Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. *Eur Respir J*. 2017; 49: 1602019. [CrossRef PubMed](#)
- [32] den Dekker HT, Sonnenschein-van der Voort AM, Jaddoe VV, Reiss IK, de Jongste JC, Duijts L. Breastfeeding and asthma outcomes at the age of 6 years: The Generation R Study. *Pediatr Allergy Immunol*. 2016; 27: 486-492. [CrossRef PubMed](#)
- [33] Quigley MA, Carson C, Kelly Y. Breastfeeding and childhood wheeze: Age-specific analyses and longitudinal wheezing phenotypes as complementary approaches to the analysis of cohort data. *Am J Epidemiol*. 2018; 187: 1651-1661. [CrossRef PubMed](#)
- [34] Rosas-Salazar C, Forno E, Brehm JM, Han YY, Acosta-Pérez E, Cloutier MM, Wakefield DB, Alvarez M, Colón-Semidey A, Canino G, Celedón JC. Breastfeeding duration and asthma in Puerto Rican children. *Pediatr Pulmonol*. 2015; 50: 527-534. [CrossRef PubMed](#)
- [35] Riihonen A, Hadley D, Uusitalo U, Miller N, Koletzko S, Yang J, Andrén Aronsson C, Hummel S, Norris JM, Virtanen SM; TEDDY Study Group. Milk feeding and first complementary foods during the first year of life in the TEDDY study. *Matern Child Nutr*. 2018; 14: e12611. [CrossRef PubMed](#)
- [36] Urashima M, Mezawa H, Okuyama M, Urashima T, Hirano D, Gocho N, Tachimoto H. Primary prevention of cow's milk sensitization and food allergy by avoiding supplementation with cow's milk formula at birth: A randomized clinical trial. *JAMA Pediatr*. 2019; 173: 1137-1145. [CrossRef PubMed](#)
- [37] Saarinen KM, Juntunen-Backman K, Järvenpää AL, Kuitunen P, Lope L, Renlund M, Siivola M, Savilahti E. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A prospective study of 6209 infants. *J Allergy Clin Immunol*. 1999; 104: 457-461. [CrossRef PubMed](#)
- [38] von Berg A, Filippiak-Pittroff B, Schulz H, Hoffmann U, Link E, Sußmann M, Schnappinger M, Brüske I, Standl M, Krämer U, Hoffmann B, Heinrich J, Bauer CP, Koletzko S, Berdel D; GINIplus study group. Allergic manifestation 15 years after early intervention with hydrolyzed formulas – the GINI Study. *Allergy*. 2016; 71: 210-219. [CrossRef PubMed](#)
- [39] Davisse-Paturet C, Raheison C, Adel-Patient K, Divaret-Chauveau A, Bois C, Dufourg MN, Lioret S, Charles MA, de Lauzon-Guillain B. Use of partially hydrolysed formula in infancy and incidence of eczema, respiratory symptoms or food allergies in toddlers from the ELFE cohort. *Pediatr Allergy Immunol*. 2019; 30: 614-623. [CrossRef PubMed](#)
- [40] Heinrich J. Comment on the recent article by Davisse-Paturet et al. *Pediatr Allergy Immunol*. 2020; 31: 106-107. [CrossRef PubMed](#)
- [41] Boyle RJ, Ierodiakonou D, Khan T, Chivinge J, Robinson Z, Geoghegan N, Jarrold K, Afxentiou T, Reeves T, Cunha S, Trivella M, Garcia-Larsen V, Leonardi-Bee J. Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. *BMJ*. 2016; 352: i974. [CrossRef PubMed](#)
- [42] Szajewska H, Horvath A. A partially hydrolyzed 100% whey formula and the risk of eczema and any allergy: an updated meta-analysis. *World Allergy Organ J*. 2017; 10: 27. [CrossRef PubMed](#)
- [43] de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, Arshad H, Beyer K, Boyle R, du Toit G, Eigenmann P, Grimshaw K, Hoest A, Jones C, Khaleva E, Lack G, Szajewska H, Venter C, Verhasselt V, Roberts G; European Academy of Allergy, Clinical Immunology Food Allergy, Anaphylaxis Guidelines Group. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. *Pediatr Allergy Immunol*. 2020; 31: 813-826. [CrossRef PubMed](#)
- [44] Osborn DA, Sinn JK, Jones LJ. Infant formulas containing hydrolysed protein for prevention of allergic disease. *Cochrane Database Syst Rev*. 2018; 10: CD003664. [CrossRef PubMed](#)
- [45] EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Castenmiller J, Hirsch-Ernst KI, Kearney J, Knutsen HK, Maciuk A, Mangelsdorf I, McArdle HJ, Naska A, Pelaez C, Pentieva K, Siani A, Thies F, Tsbouri S, Turck D, Vinceti M, Marchelli R, van Loveren H, Dumas C, Titz A, de Henauw S. Efficacy of an infant formula manufactured from a specific protein hydrolysate derived from whey protein isolate and concentrate produced by Société des Produits Nestlé S.A. in reducing the risk of developing atopic dermatitis. *EFSA J*. 2021; 19: e06603. [CrossRef PubMed](#)
- [46] Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev*. 2006; CD003741. [CrossRef PubMed](#)
- [47] Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis J, Rieu D, Rigo J, Shamir R, Szajewska H, Turck D; ESPGHAN Committee on Nutrition. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2006; 42: 352-361. [CrossRef PubMed](#)
- [48] Westmark CJ. Soy infant formula may be associated with autistic behaviors. *Autism Open Access*. 2013; 3: 20727. [CrossRef PubMed](#)
- [49] Vandenplas Y, Castellon PG, Rivas R, Gutiérrez CJ, Garcia LD, Jimenez JE, Anzo A, Hegar B, Alarcon P. Safety of soya-based infant formulas in children. *Br J Nutr*. 2014; 111: 1340-1360. [CrossRef PubMed](#)
- [50] Bührer C, Genzel-Boroviczény O, Jochum F, Kauth T, Kersting M, Koletzko B, Mihatsch W, Przyrembel H, Reinehr T, Zimmer P; Ernährungskommission der Deutschen Gesellschaft für Kinder- und Jugendmedizin. Ernährung gesunder Säuglinge. *Monatsschr Kinderheilkd*. 2014; 162: 527-538. [CrossRef](#)
- [51] Rangachari P, May KR, Stepleman LM, Tingen MS, Looney S, Liang Y, Rockich-Winston N, Rethemeyer RK. Measurement of key constructs in a holistic framework for assessing self-management effective-

- ness of pediatric asthma. *Int J Environ Res Public Health*. 2019; 16: 3060. [CrossRef PubMed](#)
- [52] Morency ME, Birken CS, Lebovic G, Chen Y, L'Abbé M, Lee GJ, Maguire JL; TARGet Kids! Collaboration. Association between noncow milk beverage consumption and childhood height. *Am J Clin Nutr*. 2017; 106: 597-602. [CrossRef PubMed](#)
- [53] Klingberg S, Brekke HK, Ludvigsson J. Introduction of fish and other foods during infancy and risk of asthma in the All Babies In Southeast Sweden cohort study. *Eur J Pediatr*. 2019; 178: 395-402. [CrossRef PubMed](#)
- [54] Vasileiadou S, Wennergren G, Strömberg Celind F, Åberg N, Pettersson R, Alm B, Goksör E. Eating fish and farm life reduce allergic rhinitis at the age of twelve. *Pediatr Allergy Immunol*. 2018; 29: 283-289. [CrossRef PubMed](#)
- [55] Lumia M, Takkinen HM, Luukkainen P, Kaila M, Lehtinen-Jacks S, Nwaru BI, Tuokkola J, Niemelä O, Haapala AM, Ilonen J, Simell O, Knip M, Veijola R, Virtanen SM. Food consumption and risk of childhood asthma. *Pediatr Allergy Immunol*. 2015; 26: 789-796. [CrossRef PubMed](#)
- [56] Turati F, Bertuccio P, Galeone C, Pelucchi C, Naldi L, Bach JF, La Vecchia C, Chatenoud L; HYGIENE Study Group. Early weaning is beneficial to prevent atopic dermatitis occurrence in young children. *Allergy*. 2016; 71: 878-888. [CrossRef PubMed](#)
- [57] Nwaru BI, Takkinen HM, Kaila M, Erkkola M, Ahonen S, Pekkanen J, Simell O, Veijola R, Ilonen J, Hyöty H, Knip M, Virtanen SM. Food diversity in infancy and the risk of childhood asthma and allergies. *J Allergy Clin Immunol*. 2014; 133: 1084-1091. [CrossRef PubMed](#)
- [58] Roduit C, Frei R, Depner M, Schaub B, Loss G, Genuneit J, Pfefferle P, Hyvärinen A, Karvonen AM, Riedler J, Dalphin JC, Pekkanen J, von Mutius E, Braun-Fahrlander C, Lauener R; PASTURE study group. Increased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol*. 2014; 133: 1056-1064. [CrossRef PubMed](#)
- [59] Cait A, Cardenas E, Dimitriou PA, Amenyogbe N, Dai D, Cait J, Sbihi H, Stiemsma L, Subbarao P, Mandhane PJ, Becker AB, Moraes TJ, Sears MR, Lefebvre DL, Azad MB, Kollmann T, Turvey SE, Mohn WW. Reduced genetic potential for butyrate fermentation in the gut microbiome of infants who develop allergic sensitization. *J Allergy Clin Immunol*. 2019; 144: 1638-1647.e3. [CrossRef PubMed](#)
- [60] Aitoro R, Paparo L, Amoroso A, Di Costanzo M, Cosenza L, Granata V, Di Scala C, Nocerino R, Trinchese G, Montella M, Ercolini D, Berni Canani R. Gut microbiota as a target for preventive and therapeutic intervention against food allergy. *Nutrients*. 2017; 9: 672. [CrossRef PubMed](#)
- [61] Roduit C, Frei R, Ferstl R, Loeliger S, Westermann P, Rhyner C, Schiavi E, Barcik W, Rodriguez-Perez N, Wawrzyniak M, Chassard C, Lacroix C, Schmausser-Hechfellner E, Depner M, von Mutius E, Braun-Fahrlander C, Karvonen AM, Kirjavainen PV, Pekkanen J, Dalphin JC, et al; PASTURE/EFRAIM study group. High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy*. 2019; 74: 799-809. [CrossRef PubMed](#)
- [62] Shoda T, Futamura M, Yang L, Narita M, Saito H, Ohya Y. Yogurt consumption in infancy is inversely associated with atopic dermatitis and food sensitization at 5 years of age: A hospital-based birth cohort study. *J Dermatol Sci*. 2017; 86: 90-96. [CrossRef PubMed](#)
- [63] Crane J, Barthow C, Mitchell EA, Stanley TV, Purdie G, Rowden J, Kang J, Hood F, Barnes P, Fitzharris P, Maude R, Stone P, Murphy R, Wickens K. Is yoghurt an acceptable alternative to raw milk for reducing eczema and allergy in infancy? *Clin Exp Allergy*. 2018; 48: 604-606. [CrossRef PubMed](#)
- [64] Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, Turcanu V, Sever ML, Gomez Lorenzo M, Plaut M, Lack G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015; 372: 803-813. [CrossRef PubMed](#)
- [65] Eising JB, Uiterwaal CS, van der Ent CK. Maternal body mass index, neonatal lung function and respiratory symptoms in childhood. *Eur Respir J*. 2015; 46: 1342-1349. [CrossRef PubMed](#)
- [66] Guerra S, Sartini C, Mendez M, Morales E, Guxens M, Basterrechea M, Arranz L, Sunyer J. Maternal pre-pregnancy obesity is an independent risk factor for frequent wheezing in infants by age 14 months. *Paediatr Perinat Epidemiol*. 2013; 27: 100-108. [CrossRef PubMed](#)
- [67] Leermakers ET, Sonnenschein-van der Voort AM, Gaillard R, Hofman A, de Jongste JC, Jaddoe VW, Duijts L. Maternal weight, gestational weight gain and preschool wheezing: the Generation R Study. *Eur Respir J*. 2013; 42: 1234-1243. [CrossRef PubMed](#)
- [68] Pike KC, Inskip HM, Robinson SM, Cooper C, Godfrey KM, Roberts G, Lucas JS; Southampton Women's Survey Study Group. The relationship between maternal adiposity and infant weight gain, and childhood wheeze and atopy. *Thorax*. 2013; 68: 372-379. [CrossRef PubMed](#)
- [69] Harskamp-van Ginkel MW, London SJ, Magnus MC, Gademann MG, Vrijkotte TG. A Study on Mediation by Offspring BMI in the Association between Maternal Obesity and Child Respiratory Outcomes in the Amsterdam Born and Their Development Study Cohort. *PLoS One*. 2015; 10: e0140641. [CrossRef PubMed](#)
- [70] Wright RJ, Fisher K, Chiu YH, Wright RO, Fein R, Cohen S, Coull BA. Disrupted prenatal maternal cortisol, maternal obesity, and childhood wheeze. Insights into prenatal programming. *Am J Respir Crit Care Med*. 2013; 187: 1186-1193. [CrossRef PubMed](#)
- [71] Ekström S, Magnusson J, Kull I, Lind T, Almqvist C, Melén E, Bergström A. Maternal body mass index in early pregnancy and offspring asthma, rhinitis and eczema up to 16 years of age. *Clin Exp Allergy*. 2015; 45: 283-291. [CrossRef PubMed](#)
- [72] Harpsøe MC, Basit S, Bager P, Wohlfahrt J, Benn CS, Nøhr EA, Linneberg A, Jess T. Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: a study within the Danish National Birth Cohort. *J Allergy Clin Immunol*. 2013; 131: 1033-1040. [CrossRef PubMed](#)
- [73] Ziyab AH, Karmaus W, Kurukulaaratchy RJ, Zhang H, Arshad SH. Developmental trajectories of Body Mass Index from infancy to 18 years of age: prenatal determinants and health consequences. *J Epidemiol Community Health*. 2014; 68: 934-941. [CrossRef PubMed](#)
- [74] Zugna D, Galassi C, Annesi-Maesano I, Baiz N, Barros H, Basterrechea M, Correia S, Duijts L, Esplugues A, Fantini MP, Forastiere F, Gascon M, Gori D, Inskip H, Larsen PS, Mommers M, Nybo Andersen AM, Penders J, Petersen MS, Pike K, et al. Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. *Int J Epidemiol*. 2015; 44: 199-208. [CrossRef PubMed](#)
- [75] Liu S, Zhou B, Wang Y, Wang K, Zhang Z, Niu W. Pre-pregnancy maternal weight and gestational weight gain increase the risk for childhood asthma and wheeze: An updated meta-analysis. *Front Pediatr*. 2020; 8: 134. [CrossRef PubMed](#)
- [76] Wilson RM, Marshall NE, Jeske DR, Purnell JQ, Thornburg K, Messaoudi I. Maternal obesity alters immune cell frequencies and responses in umbilical cord blood samples. *Pediatr Allergy Immunol*. 2015; 26: 344-351. [CrossRef PubMed](#)
- [77] Popovic M, Pizzi C, Rusconi F, Galassi C, Gagliardi L, De Marco L, Migliore E, Merletti F, Richiardi L. Infant weight trajectories and early childhood wheezing: the NINFEA birth cohort study. *Thorax*. 2016; 71: 1091-1096. [CrossRef PubMed](#)
- [78] Casas M, den Dekker HT, Kruihof CJ, Reiss IK, Vrijheid M, de Jongste JC, Jaddoe VW, Duijts L. Early childhood growth patterns and school-age respiratory resistance, fractional exhaled nitric oxide and asthma. *Pediatr Allergy Immunol*. 2016; 27: 854-860. [CrossRef PubMed](#)

- [79] Tsai HJ, Wang G, Hong X, Yao TC, Ji Y, Radovick S, Ji H, Cheng TL, Wang X. Early life weight gain and development of childhood asthma in a prospective birth cohort. *Ann Am Thorac Soc*. 2018; 15: 1197-1204. [CrossRef PubMed](#)
- [80] Loid P, Goksör E, Alm B, Pettersson R, Möllborg P, Erdes L, Åberg N, Wennergren G. A persistently high body mass index increases the risk of atopic asthma at school age. *Acta Paediatr*. 2015; 104: 707-712. [CrossRef PubMed](#)
- [81] Ekström S, Magnusson J, Kull I, Andersson N, Bottai M, Besharat Pour M, Melén E, Bergström A. Body mass index development and asthma throughout childhood. *Am J Epidemiol*. 2017; 186: 255-263. [CrossRef PubMed](#)
- [82] Lang JE, Bunnell HT, Hossain MJ, Wysocki T, Lima JJ, Finkel TH, Bacharier L, Dempsey A, Sarzynski L, Test M, Forrest CB. Being overweight or obese and the development of asthma. *Pediatrics*. 2018; 142: e20182119. [CrossRef PubMed](#)
- [83] Nahhas M, Bhopal R, Anandan C, Elton R, Sheikh A. Investigating the association between obesity and asthma in 6- to 8-year-old Saudi children: a matched case-control study. *NPJ Prim Care Respir Med*. 2014; 24: 14004. [CrossRef PubMed](#)
- [84] Forno E, Acosta-Pérez E, Brehm JM, Han YY, Alvarez M, Colón-Semidey A, Canino G, Celedón JC. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. *J Allergy Clin Immunol*. 2014; 133: 1308-14. [CrossRef PubMed](#)
- [85] Wang D, Qian Z, Wang J, Yang M, Lee YL, Liu F, Liu MM, Zhao Y, Liu YQ, Huang MM, Liu Y, Sun J, Liu YZ, Wu CC, Dong GH. Gender-specific differences in associations of overweight and obesity with asthma and asthma-related symptoms in 30 056 children: result from 25 districts of Northeastern China. *J Asthma*. 2014; 51: 508-514. [CrossRef PubMed](#)
- [86] Weinmayr G, Forastiere F, Büchele G, Jaensch A, Strachan DP, Nagel G; ISAAC Phase Two Study Group. Overweight/obesity and respiratory and allergic disease in children: international study of asthma and allergies in childhood (ISAAC) phase two. *PLoS One*. 2014; 9: e113996. Erratum in: *PLoS One*. 2015; 10: e0126678. [CrossRef PubMed](#)
- [87] Egan KB, Ettinger AS, DeWan AT, Holford TR, Holmen TL, Bracken MB. Longitudinal associations between asthma and general and abdominal weight status among Norwegian adolescents and young adults: the HUNT Study. *Pediatr Obes*. 2015; 10: 345-352. [CrossRef PubMed](#)
- [88] Yiallourous PK, Lamnisos D, Kolokotroni O, Moustaki M, Middleton N. Associations of body fat percent and body mass index with childhood asthma by age and gender. *Obesity (Silver Spring)*. 2013; 21: E474-E482. [CrossRef PubMed](#)
- [89] Mitchell EA, Beasley R, Björkstén B, Crane J, Garcia-Marcos L, Keil U; ISAAC Phase Three Study Group. The association between BMI, vigorous physical activity and television viewing and the risk of symptoms of asthma, rhinoconjunctivitis and eczema in children and adolescents: ISAAC Phase Three. *Clin Exp Allergy*. 2013; 43: 73-84. [CrossRef PubMed](#)
- [90] Willeboordse M, van den Bersselaar DL, van de Kant KD, Muris JW, van Schayck OC, Dompeling E. Sex differences in the relationship between asthma and overweight in Dutch children: a survey study. *PLoS One*. 2013; 8: e77574. [CrossRef PubMed](#)
- [91] Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev*. 2013; 14: 222-231. [Cross-Ref PubMed](#)
- [92] Lin MH, Hsieh CJ, Caffrey JL, Lin YS, Wang JJ, Ho WC, Chen PC, Wu TN, Lin RS. Fetal growth, obesity, and atopic disorders in adolescence: a retrospective birth cohort study. *Paediatr Perinat Epidemiol*. 2015; 29: 472-479. [CrossRef PubMed](#)
- [93] Kreißl S, Radon K, Dressel H, Genuneit J, Kellberger J, Nowak D, von Mutius E, Weiland SK, Weinmayr G, Windstetter D, Vogelberg C. Body mass index change and atopic diseases are not always associated in children and adolescents. *Ann Allergy Asthma Immunol*. 2014; 113: 440-444. [CrossRef PubMed](#)
- [94] Koletzko B, Cremer M, Flothkötter M, Graf C, Hauner H, Hellmers C, Kersting M, Krawinkel M, Przyrembel H, Röbl-Mathieu M, Schifflner U, Vetter K, Weißborn A, Wöckel A. Diet and lifestyle before and during pregnancy – Practical recommendations of the Germany-wide healthy start – Young Family Network. *Geburtshilfe Frauenheilkd*. 2018; 78: 1262-1282. [CrossRef PubMed](#)
- [95] Boyle RJ, Tang ML, Chiang WC, Chua MC, Ismail I, Nauta A, Hourihane JOB, Smith P, Gold M, Ziegler J, Peake J, Quinn P, Rao R, Brown N, Rijnerse A, Garsen J, Warner JO, Axelrad C, Jeffries S, Donald Y, et al; PATCH study investigators. Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: a randomized controlled trial. *Allergy*. 2016; 71: 701-710. [CrossRef PubMed](#)
- [96] Ranucci G, Buccigrossi V, Borgia E, Piacentini D, Visentin F, Cantarutti L, Baiardi P, Felisi M, Spagnuolo MI, Zanconato S, Baraldi E, Giaquinto C, Guarino A. Galacto-oligosaccharide/polidextrose enriched formula protects against respiratory infections in infants at high risk of atopy: A randomized clinical trial. *Nutrients*. 2018; 10: 286. [CrossRef PubMed](#)
- [97] Sierra C, Bernal MJ, Blasco J, Martínez R, Dalmau J, Ortuño I, Espin B, Vasallo MI, Gil D, Vidal ML, Infante D, Leis R, Maldonado J, Moreno JM, Román E. Prebiotic effect during the first year of life in healthy infants fed formula containing GOS as the only prebiotic: a multicentre, randomised, double-blind and placebo-controlled trial. *Eur J Nutr*. 2015; 54: 89-99. [CrossRef PubMed](#)
- [98] Wopereis H, Sim K, Shaw A, Warner JO, Knol J, Kroll JS. Intestinal microbiota in infants at high risk for allergy: Effects of prebiotics and role in eczema development. *J Allergy Clin Immunol*. 2018; 141: 1334-1342. [CrossRef PubMed](#)
- [99] Dotterud CK, Storrø O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol*. 2010; 163: 616-623. [CrossRef PubMed](#)
- [100] Simpson MR, Brede G, Johansen J, Johnsen R, Storrø O, Sætrom P, Øien T. Human breast milk miRNA, maternal probiotic supplementation and atopic dermatitis in offspring. *PLoS One*. 2015; 10: e0143496. [CrossRef PubMed](#)
- [101] Rø ADB, Simpson MR, Rø TB, Storrø O, Johnsen R, Videm V, Øien T. Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation. *Clin Exp Allergy*. 2017; 47: 1014-1021. [CrossRef PubMed](#)
- [102] Bertelsen RJ, Brantsæter AL, Magnus MC, Haugen M, Myhre R, Jacobsson B, Longnecker MP, Meltzer HM, London SJ. Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. *J Allergy Clin Immunol*. 2014; 133: 165-171. [CrossRef PubMed](#)
- [103] Abrahamsson TR, Jakobsson T, Björkstén B, Oldaeus G, Jenmalm MC. No effect of probiotics on respiratory allergies: a seven-year follow-up of a randomized controlled trial in infancy. *Pediatr Allergy Immunol*. 2013; 24: 556-561. [CrossRef PubMed](#)
- [104] Allen SJ, Jordan S, Storey M, Thornton CA, Gravenor MB, Garaiova I, Plummer SF, Wang D, Morgan G. Probiotics in the prevention of eczema: a randomised controlled trial. *Arch Dis Child*. 2014; 99: 1014-1019. [CrossRef PubMed](#)
- [105] Loo EX, Llanora GV, Lu Q, Aw MM, Lee BW, Shek LP. Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk Asian infants: a 5-year follow-up. *Int Arch Allergy Immunol*. 2014; 163: 25-28. [CrossRef PubMed](#)
- [106] Lundelin K, Poussa T, Salminen S, Isolauri E. Long-term safety and efficacy of perinatal probiotic intervention: Evidence from a follow-up study of four randomized, double-blind, placebo-controlled trials. *Pediatr Allergy Immunol*. 2017; 28: 170-175. [Cross-Ref PubMed](#)

- [107] Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A, Leong R, Boushey HA, Hilton JF. Early probiotic supplementation for eczema and asthma prevention: A randomized controlled trial. *Pediatrics*. 2017; 140: e20163000. [CrossRef PubMed](#)
- [108] Kukkonen K, Savilahti E, Haahela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2007; 119: 192-198. [CrossRef PubMed](#)
- [109] Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Haahela T, Savilahti E. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol*. 2009; 123: 335-341. [CrossRef PubMed](#)
- [110] Peldan P, Kukkonen AK, Savilahti E, Kuitunen M. Perinatal probiotics decreased eczema up to 10 years of age, but at 5-10 years, allergic rhino-conjunctivitis was increased. *Clin Exp Allergy*. 2017; 47: 975-979. [CrossRef PubMed](#)
- [111] Hrdý J, Vlasáková K, Černý V, Súkeníková L, Novotná O, Petrásková P, Boráková K, Lodiňová-Žádníková R, Kolářová L, Prokešová L. Decreased allergy incidence in children supplemented with *E. coli* O83:K24:H31 and its possible modes of action. *Eur J Immunol*. 2018; 48: 2015-2030. [CrossRef PubMed](#)
- [112] Wickens K, Stanley TV, Mitchell EA, Barthow C, Fitzharris P, Purdie G, Siebers R, Black PN, Crane J. Early supplementation with *Lactobacillus rhamnosus* HN001 reduces eczema prevalence to 6 years: does it also reduce atopic sensitization? *Clin Exp Allergy*. 2013; 43: 1048-1057. [CrossRef PubMed](#)
- [113] Wickens K, Barthow C, Mitchell EA, Kang J, van Zyl N, Purdie G, Stanley T, Fitzharris P, Murphy R, Crane J. Effects of *Lactobacillus rhamnosus* HN001 in early life on the cumulative prevalence of allergic disease to 11 years. *Pediatr Allergy Immunol*. 2018; 29: 808-814. [CrossRef PubMed](#)
- [114] Wickens K, Barthow C, Mitchell EA, Stanley TV, Purdie G, Rowden J, Kang J, Hood F, van den Elsen L, Forbes-Blom E, Franklin I, Barnes P, Fitzharris P, Maude RM, Stone P, Abels P, Murphy R, Crane J. Maternal supplementation alone with *Lactobacillus rhamnosus* HN001 during pregnancy and breastfeeding does not reduce infant eczema. *Pediatr Allergy Immunol*. 2018; 29: 296-302. [CrossRef PubMed](#)
- [115] Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet*. 2001; 357: 1076-1079. [CrossRef PubMed](#)
- [116] Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of *Lactobacillus GG* supplementation. *Pediatrics*. 2008; 121: e850-e856. [CrossRef PubMed](#)
- [117] Kothari D, Patel S, Kim SK. Probiotic supplements might not be universally-effective and safe: A review. *Biomed Pharmacother*. 2019; 111: 537-547. [CrossRef PubMed](#)
- [118] Daliri EB, Tango CN, Lee BH, Oh DH. Human microbiome restoration and safety. *Int J Med Microbiol*. 2018; 308: 487-497. [CrossRef PubMed](#)
- [119] Wolsk HM, Chawes BL, Litonjua AA, Hollis BW, Waage J, Stokholm J, Bønnelykke K, Bisgaard H, Weiss ST. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: A combined analysis of two randomized controlled trials. *PLoS One*. 2017; 12: e0186657. [CrossRef PubMed](#)
- [120] Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, Sandel M, Iverson RE Jr, Lee-Paritz A, Strunk RC, Bacharier LB, Macones GA, Zeiger RS, Schatz M, Hollis BW, Hornsby E, Hawrylowicz C, Wu AC, Weiss ST. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: The VDAART randomized clinical trial. *JAMA*. 2016; 315: 362-370. [CrossRef PubMed](#)
- [121] Chawes BL, Bønnelykke K, Stokholm J, Vissing NH, Bjarnadóttir E, Schoos AM, Wolsk HM, Pedersen TM, Vinding RK, Thorsteinsdóttir S, Arianto L, Hallas HW, Heickendorff L, Brix S, Rasmussen MA, Bisgaard H. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: A randomized clinical trial. *JAMA*. 2016; 315: 353-361. [CrossRef PubMed](#)
- [122] Litonjua AA, Carey VJ, Laranjo N, Stubbs BJ, Mirzakhani H, O'Connor GT, Sandel M, Beigelman A, Bacharier LB, Zeiger RS, Schatz M, Hollis BW, Weiss ST. Six-year follow-up of a trial of antenatal vitamin D for asthma reduction. *N Engl J Med*. 2020; 382: 525-533. [CrossRef PubMed](#)
- [123] Brustad N, Eliassen AU, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. High-dose vitamin D supplementation during pregnancy and asthma in offspring at the age of 6 years. *JAMA*. 2019; 321: 1003-1005. [CrossRef PubMed](#)
- [124] Zosky GR, Hart PH, Whitehouse AJ, Kusel MM, Ang W, Foong RE, Chen L, Holt PG, Sly PD, Hall GL. Vitamin D deficiency at 16 to 20 weeks' gestation is associated with impaired lung function and asthma at 6 years of age. *Ann Am Thorac Soc*. 2014; 11: 571-577. [CrossRef PubMed](#)
- [125] Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, Nevalainen J, Veijola R, Pekkanen J, Ilonen J, Simell O, Knip M, Virtanen SM. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy*. 2009; 39: 875-882. [CrossRef PubMed](#)
- [126] Maslova E, Hansen S, Jensen CB, Thorne-Lyman AL, Strøm M, Olsen SF. Vitamin D intake in mid-pregnancy and child allergic disease – a prospective study in 44,825 Danish mother-child pairs. *BMC Pregnancy Childbirth*. 2013; 13: 199. [CrossRef PubMed](#)
- [127] Nwaru BI, Hadkhale K, Hämäläinen N, Takkinen HM, Ahonen S, Ilonen J, Toppari J, Niemelä O, Haapala AM, Veijola R, Knip M, Virtanen SM. Vitamin D intake during the first 4 years and onset of asthma by age 5: A nested case-control study. *Pediatr Allergy Immunol*. 2017; 28: 641-648. [CrossRef PubMed](#)
- [128] Forno E, Bacharier LB, Phipatanakul W, Guilbert TW, Cabana MD, Ross K, Covar R, Gern JE, Rosser FJ, Blatter J, Durrani S, Han YY, Wisniewski SR, Celedón JC. Effect of vitamin D3 supplementation on severe asthma exacerbations in children with asthma and low vitamin D levels: The VDKA Randomized Clinical Trial. *JAMA*. 2020; 324: 752-760. [CrossRef PubMed](#)
- [129] Allen S, Britton JR, Leonard-Bee JA. Association between antioxidant vitamins and asthma outcome measures: systematic review and meta-analysis. *Thorax*. 2009; 64: 610-619. [CrossRef PubMed](#)
- [130] Gao J, Gao X, Li W, Zhu Y, Thompson PJ. Observational studies on the effect of dietary antioxidants on asthma: a meta-analysis. *Respirology*. 2008; 13: 528-536. [CrossRef PubMed](#)
- [131] Nakamura K, Wada K, Sahashi Y, Tamai Y, Tsuji M, Watanabe K, Ohtsuchi S, Ando K, Nagata C. Associations of intake of antioxidant vitamins and fatty acids with asthma in pre-school children. *Public Health Nutr*. 2013; 16: 2040-2045. [CrossRef PubMed](#)
- [132] Maslova E, Hansen S, Strøm M, Halldorsson TI, Olsen SF. Maternal intake of vitamins A, E and K in pregnancy and child allergic disease: a longitudinal study from the Danish National Birth Cohort. *Br J Nutr*. 2014; 111: 1096-1108. [CrossRef PubMed](#)
- [133] den Dekker HT, Jaddoe VVW, Reiss IK, de Jongste JC, Duijts L. Maternal folic acid use during pregnancy, methylenetetrahydrofolate reductase gene polymorphism, and child's lung function and asthma. *Clin Exp Allergy*. 2018; 48: 175-185. [CrossRef PubMed](#)
- [134] Roy A, Kocak M, Hartman TJ, Vereen S, Adgent M, Piyathilake C, Tylavsky FA, Carroll KN. Association of prenatal folate status with early childhood wheeze and atopic dermatitis. *Pediatr Allergy Immunol*. 2018; 29: 144-150. [CrossRef PubMed](#)
- [135] Trivedi MK, Sharma S, Rifas-Shiman SL, Camargo CA Jr, Weiss ST, Oken E, Gillman MW, Gold DR, DeMeo DL, Litonjua AA. Folic acid in pregnancy and child-

- hood asthma: A US Cohort. *Clin Pediatr (Phila)*. 2018; 57: 421-427. [CrossRef PubMed](#)
- [136] Crider KS, Cordero AM, Qi YP, Mulinare J, Dowling NF, Berry RJ. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013; 98: 1272-1281. [CrossRef PubMed](#)
- [137] Alfonso VH, Bandoli G, von Ehrenstein O, Ritz B. Early folic acid supplement initiation and risk of adverse early childhood respiratory health: A population-based study. *Matern Child Health J*. 2018; 22: 111-119. [CrossRef PubMed](#)
- [138] Veeranki SP, Gebretsadik T, Mitchel EF, Tylavsky FA, Hartert TV, Cooper WO, Dupont WD, Dorris SL, Hartman TJ, Carroll KN. Maternal folic acid supplementation during pregnancy and early childhood asthma. *Epidemiology*. 2015; 26: 934-941. [CrossRef PubMed](#)
- [139] Fortes C, Mastroeni S, Mannooranparampil TJ, Di Lallo D. Pre-natal folic acid and iron supplementation and atopic dermatitis in the first 6 years of life. *Arch Dermatol Res*. 2019; 311: 361-367. [CrossRef PubMed](#)
- [140] Liu J, Li Z, Ye R, Liu J, Ren A. Periconceptional folic acid supplementation and risk of parent-reported asthma in children at 4-6 years of age. *ERJ Open Res*. 2020; 6: 00250-2019. [CrossRef PubMed](#)
- [141] Kiraly N, Benn CS, Biering-Sørensen S, Rodrigues A, Jensen KJ, Ravn H, Allen KJ, Aaby P. Vitamin A supplementation and BCG vaccination at birth may affect atopy in childhood: long-term follow-up of a randomized controlled trial. *Allergy*. 2013; 68: 1168-1176. [CrossRef PubMed](#)
- [142] Aage S, Kiraly N, Da Costa K, Byberg S, Bjerregaard-Andersen M, Fisker AB, Aaby P, Benn CS. Neonatal vitamin A supplementation associated with increased atopy in girls. *Allergy*. 2015; 70: 985-994. [CrossRef PubMed](#)
- [143] Kiraly N, Balde A, Lisse IM, Eriksen HB, Aaby P, Benn CS. Vitamin A supplementation and risk of atopy: long-term follow-up of a randomized trial of vitamin A supplementation at six and nine months of age. *BMC Pediatr*. 2013; 13: 190. [CrossRef PubMed](#)
- [144] Venter C, Meyer RW, Nwaru BI, Roduit C, Untersmayr E, Adel-Patient K, Agache I, Agostoni C, Akdis CA, Bischoff SC, du Toit G, Feeney M, Frei R, Garn H, Greenhawt M, Hoffmann-Sommergruber K, Lunjani N, Maslin K, Mills C, Muraro A, et al. EAACI position paper: Influence of dietary fatty acids on asthma, food allergy, and atopic dermatitis. *Allergy*. 2019; 74: 1429-1444. [CrossRef PubMed](#)
- [145] Venter C, Agostoni C, Arshad SH, Ben-Abdallah M, Du Toit G, Fleischer DM, Greenhawt M, Glueck DH, Groetch M, Lunjani N, Maslin K, Maiorella A, Meyer R, Antonella M, Netting MJ, Ibeabughichi Nwaru B, Palmer DJ, Palumbo MP, Roberts G, Roduit C, et al. Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology. *Pediatr Allergy Immunol*. 2020; 31: 889-912. [CrossRef PubMed](#)
- [146] Vahdaninia M, Mackenzie H, Dean T, Helps S. ω-3 LCPUFA supplementation during pregnancy and risk of allergic outcomes or sensitization in offspring: A systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. 2019; 122: 302-313.e2. [CrossRef PubMed](#)
- [147] Maslova E, Rifas-Shiman SL, Oken E, Platts-Mills TAE, Gold DR. Fatty acids in pregnancy and risk of allergic sensitization and respiratory outcomes in childhood. *Ann Allergy Asthma Immunol*. 2019; 122: 120-122.e3. [CrossRef PubMed](#)
- [148] Standl M, Demmelmair H, Koletzko B, Heinrich J. Cord blood LC-PUFA composition and allergic diseases during the first 10 yr. Results from the LISAPlus study. *Pediatr Allergy Immunol*. 2014; 25: 344-350. [CrossRef PubMed](#)
- [149] Magnusson J, Ekström S, Kull I, Håkansson N, Nilsson S, Wickman M, Melén E, Risérus U, Bergström A. Polyunsaturated fatty acids in plasma at 8 years and subsequent allergic disease. *J Allergy Clin Immunol*. 2018; 142: 510-516.e6. [CrossRef PubMed](#)
- [150] Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos AM, Wolsk HM, Pedersen TM, Vinding RK, Thorsteinsdóttir S, Følsgaard NV, Fink NR, Thorsen J, Pedersen AG, Waage J, Rasmussen MA, Stark KD, Olsen SF, Bønnelykke K. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016; 375: 2530-2539. [CrossRef PubMed](#)
- [151] Hansen S, Strøm M, Maslova E, Dahl R, Hoffmann HJ, Rytter D, Bech BH, Henriksen TB, Granström C, Halldorsson TI, Chavarro JE, Linneberg A, Olsen SF. Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring. *J Allergy Clin Immunol*. 2017; 139: 104-111.e4. [CrossRef PubMed](#)
- [152] Furuhejm C, Warstedt K, Fagerås M, Fälth-Magnusson K, Larsson J, Fredriksson M, Duchén K. Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. *Pediatr Allergy Immunol*. 2011; 22: 505-514. [CrossRef PubMed](#)
- [153] Warstedt K, Furuhejm C, Fälth-Magnusson K, Fagerås M, Duchén K. High levels of omega-3 fatty acids in milk from omega-3 fatty acid-supplemented mothers are related to less immunoglobulin E-associated disease in infancy. *Acta Paediatr*. 2016; 105: 1337-1347. [CrossRef PubMed](#)
- [154] Best KP, Sullivan T, Palmer D, Gold M, Kennedy DJ, Martin J, Makrides M. Prenatal fish oil supplementation and allergy: 6-year follow-up of a randomized controlled trial. *Pediatrics*. 2016; 137: e20154443. [CrossRef PubMed](#)
- [155] Escamilla-Núñez MC, Barraza-Villarreal A, Hernández-Cadena L, Navarro-Olivos E, Sly PD, Romieu I. Omega-3 fatty acid supplementation during pregnancy and respiratory symptoms in children. *Chest*. 2014; 146: 373-382. [CrossRef PubMed](#)
- [156] Berman D, Clinton C, Limb R, Somers EC, Romero V, Mozurkewich E. Prenatal omega-3 supplementation and eczema risk among offspring at age 36 months. *Insights Allergy Asthma Bronchitis*. 2016; 2: 1. [CrossRef PubMed](#)
- [157] D'Vaz N, Meldrum SJ, Dunstan JA, Martino D, McCarthy S, Metcalfe J, Tulic MK, Mori TA, Prescott SL. Postnatal fish oil supplementation in high-risk infants to prevent allergy: randomized controlled trial. *Pediatrics*. 2012; 130: 674-682. [CrossRef PubMed](#)
- [158] D'Vaz N, Meldrum SJ, Dunstan JA, Lee-Pullen TF, Metcalfe J, Holt BJ, Serralha M, Tulic MK, Mori TA, Prescott SL. Fish oil supplementation in early infancy modulates developing infant immune responses. *Clin Exp Allergy*. 2012; 42: 1206-1216. [CrossRef PubMed](#)
- [159] Gunaratne AW, Makrides M, Collins CT, Gibson RA, McPhee AJ, Sullivan TR, Gould JF, Green TJ, Doyle LW, Davis PG, French NP, Colditz PB, Simmer K, Morris SA, Best KP. Docosahexaenoic acid supplementation of preterm infants and parent-reported symptoms of allergic disease at 7 years corrected age: follow-up of a randomized controlled trial. *Am J Clin Nutr*. 2019; 109: 1600-1610. [CrossRef PubMed](#)
- [160] Lapillonne A, Pastor N, Zhuang W, Scalabrini DM. Infants fed formula with added long chain polyunsaturated fatty acids have reduced incidence of respiratory illnesses and diarrhea during the first year of life. *BMC Pediatr*. 2014; 14: 168. [CrossRef PubMed](#)
- [161] EFSA European Food Safety Authority (efsa). Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion related to the tolerable upper intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). *EFSA J*. 2012; 10: 2815. [CrossRef](#)
- [162] Koletzko B. Human Milk Lipids. *Ann Nutr Metab*. 2016; 69 (Suppl 2): 28-40. [CrossRef PubMed](#)
- [163] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. *EFSA J*. 2013; 11: 3408. [CrossRef](#)

- [164] Marrs T, Sim K. Demystifying Dysbiosis: Can the Gut Microbiome Promote Oral Tolerance Over IgE-mediated Food Allergy? *Curr Pediatr Rev.* 2018; 14: 156-163. [CrossRef PubMed](#)
- [165] Collin SM, Granell R, Westgarth C, Murray J, Paul ES, Sterne JA, Henderson AJ. Associations of pet ownership with wheezing and lung function in childhood: Findings from a UK Birth Cohort. *PLoS One.* 2015; 10: e0127756. [CrossRef PubMed](#)
- [166] Collin SM, Granell R, Westgarth C, Murray J, Paul E, Sterne JA, John Henderson A. Pet ownership is associated with increased risk of non-atopic asthma and reduced risk of atopy in childhood: findings from a UK birth cohort. *Clin Exp Allergy.* 2015; 45: 200-210. [CrossRef PubMed](#)
- [167] Fall T, Lundholm C, Örtqvist AK, Fall K, Fang F, Hedhammar Å, Kämpe O, Ingelsson E, Almqvist C. Early exposure to dogs and farm animals and the risk of childhood asthma. *JAMA Pediatr.* 2015; 169: e153219. [CrossRef PubMed](#)
- [168] Hesselmar B, Hicke-Roberts A, Lundell AC, Adlerberth I, Rudin A, Saalman R, Wennnergren G, Wold AE. Pet-keeping in early life reduces the risk of allergy in a dose-dependent fashion. *PLoS One.* 2018; 13: e0208472. [CrossRef PubMed](#)
- [169] Al-Tamprouri C, Malin B, Bill H, Lennart B, Anna S. Cat and dog ownership during/after the first year of life and risk for sensitization and reported allergy symptoms at age 13. *Immun Inflamm Dis.* 2019; 7: 250-257. [CrossRef PubMed](#)
- [170] Milanzi EB, Koppelman GH, Smit HA, Wijga AH, Vonk JM, Brunekreef B, Gehring U. Role of timing of exposure to pets and dampness or mould on asthma and sensitization in adolescence. *Clin Exp Allergy.* 2019; 49: 1352-1361. [CrossRef PubMed](#)
- [171] Callesen M, Bekö G, Weschler CJ, Sigsgaard T, Jensen TK, Clausen G, Toftum J, Norberg LA, Høst A. Associations between selected allergens, phthalates, nicotine, polycyclic aromatic hydrocarbons, and bedroom ventilation and clinically confirmed asthma, rhinoconjunctivitis, and atopic dermatitis in preschool children. *Indoor Air.* 2014; 24: 136-147. [CrossRef PubMed](#)
- [172] O'Connor GT, Lynch SV, Bloomberg GR, Kattan M, Wood RA, Gergen PJ, Jaffee KF, Calatroni A, Bacharier LB, Beigelman A, Sandel MT, Johnson CC, Faruqi A, Santee C, Fujimura KE, Fadrosch D, Boushey H, Visness CM, Gern JE. Early-life home environment and risk of asthma among inner-city children. *J Allergy Clin Immunol.* 2018; 141: 1468-1475. [CrossRef PubMed](#)
- [173] Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, O'Connor GT, Sandel MT, Calatroni A, Matsui E, Johnson CC, Lynn H, Visness CM, Jaffee KF, Gergen PJ, Gold DR, Wright RJ, Fujimura K, Rauch M, Busse WW, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol.* 2014; 134: 593-601.e12. [CrossRef PubMed](#)
- [174] Karvonen AM, Hyvärinen A, Rintala H, Korppi M, Täubel M, Doeke G, Gehring U, Renz H, Pfeifferle PI, Genuneit J, Keski-Nisula L, Remes S, Lampi J, von Mutius E, Pekkanen J. Quantity and diversity of environmental microbial exposure and development of asthma: a birth cohort study. *Allergy.* 2014; 69: 1092-1101. [CrossRef PubMed](#)
- [175] Karvonen AM, Kirjavainen PV, Täubel M, Jayaprakash B, Adams RI, Sordillo JE, Gold DR, Hyvärinen A, Remes S, von Mutius E, Pekkanen J. Indoor bacterial microbiota and development of asthma by 10.5 years of age. *J Allergy Clin Immunol.* 2019; 144: 1402-1410. [CrossRef PubMed](#)
- [176] Thorne PS, Kulhánková K, Yin M, Cohn R, Arbes SJ Jr, Zeldin DC. Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. *Am J Respir Crit Care Med.* 2005; 172: 1371-1377. [CrossRef PubMed](#)
- [177] Ciaccio CE, Barnes C, Kennedy K, Chan M, Portnoy J, Rosenwasser L. Home dust microbiota is disordered in homes of low-income asthmatic children. *J Asthma.* 2015; 52: 873-880. [CrossRef PubMed](#)
- [178] Loo EXL, Chew LJM, Zulkifli AB, Ta LDH, Kuo IC, Goh A, Teoh OH, Van Bever H, Gluckman PD, Yap F, Tan KH, Chong YS, Lee BW, Shek LP. Comparison of microbiota and allergen profile in house dust from homes of allergic and non-allergic subjects- results from the GUSTO study. *World Allergy Organ J.* 2018; 11: 37. [CrossRef PubMed](#)
- [179] Halcken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, Ryan D, Agache I, Ansotegui IJ, Arasi S, Du Toit G, Fernandez-Rivas M, Geerth van Wijk R, Jutel M, Kleine-Tebbe J, Lau S, Matricardi PM, Pajno GB, Papadopoulos NG, Penagos M, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol.* 2017; 28: 728-745. [CrossRef PubMed](#)
- [180] Cardona V, Luengo O, Labrador-Horrillo M. Immunotherapy in allergic rhinitis and lower airway outcomes. *Allergy.* 2017; 72: 35-42. [CrossRef PubMed](#)
- [181] Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy.* 1996; 51: 430-433. [CrossRef PubMed](#)
- [182] Reha CM, Ebru A. Specific immunotherapy is effective in the prevention of new sensitivities. *Allergol Immunopathol (Madr).* 2007; 35: 44-51. [CrossRef PubMed](#)
- [183] Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy.* 2001; 31: 1392-1397. [CrossRef PubMed](#)
- [184] Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, Canonica GW, Passalacqua G. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy.* 2003; 33: 206-210. [Cross-Ref PubMed](#)
- [185] Madonini E, Agostinis F, Barra R, Berra A, Donadio D, Pappacoda A, Stefani E, Tierno E. Long-term and preventive effects of sublingual allergen-specific immunotherapy: a retrospective, multicentric study. *Int J Immunopathol Pharmacol.* 2003; 16: 73-79. [Cross-Ref PubMed](#)
- [186] Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of pre-seasonal grass pollen immunotherapy in childhood. *Allergy.* 2006; 61: 198-201. [CrossRef PubMed](#)
- [187] Inal A, Altıntaş DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol.* 2007; 17: 85-91. [PubMed](#)
- [188] Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halcken S, Høst A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Möller C; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy.* 2007; 62: 943-948. [Cross-Ref PubMed](#)
- [189] Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, Ricciardi L. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy.* 2001; 31: 1295-1302. [CrossRef PubMed](#)
- [190] Zolkipli Z, Roberts G, Cornelius V, Clayton B, Pearson S, Michaelis L, Djukanovic R, Kurukulaaratchy R, Arshad SH. Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood. *J Allergy Clin Immunol.* 2015; 136: 1541-1547.e11. [CrossRef PubMed](#)
- [191] Alviani C, Roberts G, Mitchell F, Martin J, Zolkipli Z, Michaelis LJ, Vijayanand P, Kurukulaaratchy R, Arshad SH. Primary prevention of asthma in high-risk children using HDM SLIT: Assessment at age 6 years.



- J Allergy Clin Immunol. 2020; 145: 1711-1713. [Cross-Ref PubMed](#)
- [192] Alviani C, Roberts G, Moyses H, Pearson S, Larsson M, Zolkipli Z, Michaelis LJ, Kurukulaaratchy R, Arshad SH. Follow-up, 18 months off house dust mite immunotherapy, of a randomized controlled study on the primary prevention of atopy. *Allergy*. 2019; 74: 1406-1408. [CrossRef PubMed](#)
- [193] Szépfalusi Z, Bannert C, Ronceray L, Mayer E, Hassler M, Wissmann E, Dehlink E, Gruber S, Graf A, Lupinek C, Valenta R, Eiwegger T, Urbanek R. Preventive sublingual immunotherapy in preschool children: first evidence for safety and pro-tolerogenic effects. *Pediatr Allergy Immunol*. 2014; 25: 788-795. [CrossRef PubMed](#)
- [194] Grembale RD, Camporota L, Natty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med*. 2000; 162: 2048-2052. [CrossRef PubMed](#)
- [195] Kirjavainen PV, Karvonen AM, Adams RI, Täubel M, Roponen M, Tuoresmäki P, Loss G, Jayaprakash B, Depner M, Ege MJ, Renz H, Pfefferle PI, Schaub B, Lauener R, Hyvärinen A, Knight R, Heederik DJJ, von Mutius E, Pekkanen J. Author Correction: Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nat Med*. 2019; 25: 1319 [CrossRef PubMed](#)
- [196] Lluís A, Depner M, Gaugler B, Saas P, Casaca VI, Raedler D, Michel S, Tost J, Liu J, Genuneit J, Pfefferle P, Roponen M, Weber J, Braun-Fahrländer C, Riedler J, Dalphin J, Lauener R, Vuitton DA, Dalphin JC, Pekkanen J, von Mutius E, et al; Protection Against Allergy: Study in Rural Environments Study Group. Increased regulatory T-cell numbers are associated with farm milk exposure and lower atopic sensitization and asthma in childhood. *J Allergy Clin Immunol*. 2014; 133: 551-559. [CrossRef PubMed](#)
- [197] Schröder PC, Illi S, Casaca VI, Lluís A, Böck A, Roduit C, Depner M, Frei R, Genuneit J, Pfefferle PI, Roponen M, Weber J, Braun-Fahrländer C, Riedler J, Dalphin JC, Pekkanen J, Lauener R, von Mutius E, Schaub B; PASTURE study group. A switch in regulatory T cells through farm exposure during immune maturation in childhood. *Allergy*. 2017; 72: 604-615. [CrossRef PubMed](#)
- [198] Brick T, Schober Y, Böcking C, Pekkanen J, Genuneit J, Loss G, Dalphin JC, Riedler J, Lauener R, Nockher WA, Renz H, Vaarala O, Braun-Fahrländer C, von Mutius E, Ege MJ, Pfefferle PI, Karvonen A, Tiittanen P, Dalphin M-L, Schaub B, et al; PASTURE study group. ω-3 fatty acids contribute to the asthma-protective effect of unprocessed cow's milk. *J Allergy Clin Immunol*. 2016; 137: 1699-1706.e13. [CrossRef PubMed](#)
- [199] Frei R, Ferstl R, Roduit C, Ziegler M, Schiavi E, Barcik W, Rodriguez-Perez N, Wirz OF, Wawrzyniak M, Pugin B, Nehrbass D, Jutel M, Smolinska S, Konieczna P, Bieli C, Loeliger S, Waser M, Pershagen G, Riedler J, Depner M, et al; Prevention of Allergy Risk factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study group; Protection Against Allergy Study in Rural Environments (PASTURE)/Mechanisms of Early Protective Exposures on Allergy Development (EFRAME) study group. Exposure to nonmicrobial N-glycolylneuraminic acid protects farmers' children against airway inflammation and colitis. *J Allergy Clin Immunol*. 2018; 141: 382-390.e7. [CrossRef PubMed](#)
- [200] Levin ME, Botha M, Basera W, Facey-Thomas HE, Gaunt B, Gray CL, Kiragu W, Ramjith J, Watkins A, Genuneit J. Environmental factors associated with allergy in urban and rural children from the South African Food Allergy (SAFFA) cohort. *J Allergy Clin Immunol*. 2020; 145: 415-426. [CrossRef PubMed](#)
- [201] Chu S, Chen Q, Chen Y, Bao Y, Wu M, Zhang J. Cesarean section without medical indication and risk of childhood asthma, and attenuation by breastfeeding. *PLoS One*. 2017; 12: e0184920 [CrossRef PubMed](#)
- [202] Sevelsted A, Stokholm J, Bisgaard H. Risk of Asthma from Cesarean Delivery Depends on Membrane Rupture. *J Pediatr*. 2016 Apr;171:38-42.e1-4.
- [203] Wu P, Feldman AS, Rosas-Salazar C, James K, Escobar G, Gebretsadik T, Li SX, Carroll KN, Walsh E, Mitchell E, Das S, Kumar R, Yu C, Dupont WD, Hartert TV. Relative Importance and Additive Effects of Maternal and Infant Risk Factors on Childhood Asthma. *PLoS One*. 2016; 11: e0151705 [CrossRef PubMed](#)
- [204] Brandão HV, Vieira GO, de Oliveira Vieira T, Camargos PA, de Souza Teles CA, Guimarães AC, Cruz AA, Cruz CMS. Increased risk of allergic rhinitis among children delivered by cesarean section: a cross-sectional study nested in a birth cohort. *BMC Pediatr*. 2016; 16: 57 [CrossRef PubMed](#)
- [205] Richards M, Ferber J, Chen H, Swor E, Quesenberry CP, Li DK, Darrow LA. Cesarean delivery and the risk of atopic dermatitis in children. *Clin Exp Allergy*. 2020; 50: 805-814. [CrossRef PubMed](#)
- [206] Grüber C, Warner J, Hill D, Bauchau V; EPAAC Study Group. Early atopic disease and early childhood immunization – is there a link? *Allergy*. 2008; 63: 1464-1472. [CrossRef PubMed](#)
- [207] Nilsson L, Kjellman NI, Björkstén B. Allergic disease at the age of 7 years after pertussis vaccination in infancy: results from the follow-up of a randomized controlled trial of 3 vaccines. *Arch Pediatr Adolesc Med*. 2003; 157: 1184-1189. [CrossRef PubMed](#)
- [208] Grüber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, Bauer CP, Wahn V, Wahn U; MAS-90 Study Group. Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics*. 2003; 111: e282-e288. [CrossRef PubMed](#)
- [209] Schlaud M, Schmitz R, Poethko-Müller C, Kuhnert R. Vaccinations in the first year of life and risk of atopic disease - Results from the KiGGs study. *Vaccine*. 2017; 35: 5156-5162. [CrossRef PubMed](#)
- [210] McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *Am J Public Health*. 2004; 94: 985-989. [CrossRef PubMed](#)
- [211] Kiraly N, Koplin JJ, Crawford NW, Bannister S, Flanagan KL, Holt PG, Gurrin LC, Lowe AJ, Tang ML, Wake M, Ponsonby AL, Dharmage SC, Allen KJ. Timing of routine infant vaccinations and risk of food allergy and eczema at one year of age. *Allergy*. 2016; 71: 541-549. [CrossRef](#). Published online February 8, 2016 [PubMed](#)
- [212] Swartz J, Aronsson B, Lindblad F et al. Vaccination and Allergic Sensitization in Early Childhood - The ALADDIN Birth Cohort. *EclinicalMedicine*. 2018; 4-5: 92-98. [CrossRef](#)
- [213] Toelle BG, Garden FL, McIntyre PB, Wood N, Marks GB. Pertussis vaccination and allergic illness in Australian children. *Pediatr Allergy Immunol*. 2020; 31: 857-861. [CrossRef PubMed](#)
- [214] Mrozek-Budzyn D, Majewska R, Kiełtyka A, Augustyniak M. Whole-cell pertussis vaccine (DTwP) has no influence on allergic diseases and atopic sensitization in children. *Postepy Dermatol Alergol*. 2018; 35: 381-386. [CrossRef](#). Published online August 21, 2018 [PubMed](#)
- [215] Venter C, Stowe J, Andrews NJ, Miller E, Turner PJ. No association between atopic outcomes and type of pertussis vaccine given in children born on the Isle of Wight 2001-2002. *J Allergy Clin Immunol Pract*. 2016; 4: 1248-1250. [CrossRef](#). Published online June 30, 2016 [PubMed](#)
- [216] Thøstesen LM, Kjaergaard J, Pihl GT, Birk NM, Nissen TN, Aaby P, Jensen AKG, Olesen AW, Stensballe LG, Jeppesen DL, Benn CS, Kofoed PE. Neonatal BCG vaccination and atopic dermatitis before 13 months of age: A randomized clinical trial. *Allergy*. 2018; 73: 498-504. [CrossRef](#). Published online October 9, 2017 [PubMed](#)
- [217] Thøstesen LM, Stensballe LG, Pihl GT, Kjaergaard J, Birk NM, Nissen TN, Jensen AKG, Aaby P, Olesen AW, Jeppesen DL, Benn CS, Kofoed PE. Neonatal BCG vaccination has no effect on recurrent wheeze in the first year of life: A randomized clinical trial. *J Allergy*

- Clin Immunol. 2017; 140: 1616-1621.e3. [CrossRef](#). Published online March 25, 2017 [PubMed](#)
- [218] Thøstesen LM, Kjaer HF, Pihl GT, Nissen TN, Birk NM, Kjærgaard J, Jensen AKG, Aaby P, Olesen AW, Stensballe LG, Jeppesen DL, Benn CS, Kofoed PE. Neonatal BCG has no effect on allergic sensitization and suspected food allergy until 13 months. *Pediatr Allergy Immunol.* 2017; 28: 588-596. [CrossRef PubMed](#)
- [219] Stensballe LG, Sørup S, Aaby P, Benn CS, Greisen G, Jeppesen DL, Birk NM, Kjærgaard J, Nissen TN, Pihl GT, Thøstesen LM, Kofoed PE, Pryds O, Ravn H. BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial. *Arch Dis Child.* 2017; 102: 224-231. [CrossRef](#). Published online July 21, 2016 [PubMed](#)
- [220] Linehan MF, Nurmatov U, Frank TL, Niven RM, Baxter DN, Sheikh A. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. *J Allergy Clin Immunol.* 2014; 133: 688-95.e14. [CrossRef PubMed](#)
- [221] El-Zein M, Conus F, Benedetti A, Menzies D, Parent ME, Rousseau MC. Association Between Bacillus Calmette-Guérin Vaccination and Childhood Asthma in the Quebec Birth Cohort on Immunity and Health. *Am J Epidemiol.* 2017; 186: 344-355. [CrossRef PubMed](#)
- [222] Foo DYP, Sarna M, Pereira G, Moore HC, Fell DB, Regan AK. Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review. *Pediatrics.* 2020; 146: e20200375 [CrossRef](#). Published online July 27, 2020 [PubMed](#)
- [223] Tokinobu A, Yorifuji T, Yamakawa M, Tsuda T, Doi H. Association of early daycare attendance with allergic disorders in children: a longitudinal national survey in Japan. *Arch Environ Occup Health.* 2020; 75: 18-26. [CrossRef PubMed](#)
- [224] Cheng G, Smith AM, Levin L, Epstein T, Ryan PH, LeMasters GK, Khurana Hershey GK, Reponen T, Villareal M, Lockey J, Bernstein DI. Duration of day care attendance during infancy predicts asthma at the age of seven: the Cincinnati Childhood Allergy and Air Pollution Study. *Clin Exp Allergy.* 2014; 44: 1274-1281. [CrossRef PubMed](#)
- [225] Ahmadizar F, Vijverberg SJH, Arets HGM, de Boer A, Lang JE, Garssen J, Kraneveld A, Maitland-van der Zee AH. Early-life antibiotic exposure increases the risk of developing allergic symptoms later in life: A meta-analysis. *Allergy.* 2018; 73: 971-986. [CrossRef PubMed](#)
- [226] Goksör E, Alm B, Pettersson R, Möllborg P, Erdes L, Aberg N, Wennergren G. Early fish introduction and neonatal antibiotics affect the risk of asthma into school age. *Pediatr Allergy Immunol.* 2013; 24: 339-344. [CrossRef PubMed](#)
- [227] Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJ. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a dose-dependent relationship. *Pediatr Allergy Immunol.* 2013; 24: 762-771. [CrossRef PubMed](#)
- [228] Yamamoto-Hanada K, Futamura M, Yang L, Shoda T, Narita M, Kobayashi F, Saito H, Ohya Y. Preconceptional exposure to oral contraceptive pills and the risk of wheeze, asthma and rhinitis in children. *Allergol Int.* 2016; 65: 327-331. [CrossRef PubMed](#)
- [229] Mulder B, Pouwels KB, Schuiling-Veninga CC, Bos HJ, de Vries TW, Jick SS, Hak E. Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. *Clin Exp Allergy.* 2016; 46: 1214-1226. [CrossRef PubMed](#)
- [230] Örtqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W, Almqvist C. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ.* 2014; 349 (nov28 3): g6979 [CrossRef PubMed](#)
- [231] Metzler S, Frei R, Schmaußer-Hechfellner E, von Mutius E, Pekkanen J, Karvonen AM, Kirjavainen PV, Dalphin JC, Divaret-Chauveau A, Riedler J, Lauener R, Roduit C, Hyvärinen A, Sami R, Roponen M, Chauveau A, Dalphin M-L, Kaulek V, Ege M, Genuneit J, et al; PASTURE/EFRAM study group. Association between antibiotic treatment during pregnancy and infancy and the development of allergic diseases. *Pediatr Allergy Immunol.* 2019; 30: 423-433. [CrossRef PubMed](#)
- [232] Wu P, Feldman AS, Rosas-Salazar C, James K, Escobar G, Gebretsadik T, Li SX, Carroll KN, Walsh E, Mitchell E, Das S, Kumar R, Yu C, Dupont WD, Hartert TV. Relative Importance and Additive Effects of Maternal and Infant Risk Factors on Childhood Asthma. *PLoS One.* 2016; 11: e0151705 [CrossRef](#)
- [233] Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clin Exp Allergy.* 2015; 45: 137-145. [CrossRef PubMed](#)
- [234] Amberbir A, Medhin G, Hanlon C, Britton J, Davey G, Venn A. Effects of early life paracetamol use on the incidence of allergic disease and sensitization: 5 year follow-up of an Ethiopian birth cohort. *PLoS One.* 2014; 9: e93869 [CrossRef PubMed](#)
- [235] Peñaranda A, Garcia E, Barragán AM, Rondón MA, Pérez A, Rojas MX, Caraballo L, Dennis RJ. Factors associated with Allergic Rhinitis in Colombian subpopulations aged 1 to 17 and 18 to 59. *Rhinology.* 2016; 54: 56-67. [CrossRef PubMed](#)
- [236] Wang JY, Liu LF, Chen CY, Huang YW, Hsiung CA, Tsai HJ. Acetaminophen and/or antibiotic use in early life and the development of childhood allergic diseases. *Int J Epidemiol.* 2013; 42: 1087-1099. [CrossRef PubMed](#)
- [237] Hoeke H, Roeder S, Mueller A, Bertsche T, Borte M, Rolle-Kampczyk U, von Bergen M, Wissenbach DK. Biomonitoring of prenatal analgesic intake and correlation with infantile anti-aeroallergens IgE. *Allergy.* 2016; 71: 901-906. [CrossRef PubMed](#)
- [238] Liu X, Liew Z, Olsen J, Pedersen LH, Bech BH, Agerbo E, Yuan W, Li J. Association of prenatal exposure to acetaminophen and coffee with childhood asthma. *Pharmacoepidemiol Drug Saf.* 2016; 25: 188-195. [CrossRef PubMed](#)
- [239] Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA Jr, Weiss ST, Gold DR, Litonjua AA. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *J Allergy Clin Immunol.* 2015; 135: 441-448. [CrossRef PubMed](#)
- [240] Magnus MC, Karlstad Ø, Håberg SE, Nafstad P, Davey Smith G, Nystad W. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. *Int J Epidemiol.* 2016; 45: 512-522. [CrossRef PubMed](#)
- [241] Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, Shigematsu Y, Yoshida K, Niizeki H, Motomura K, Sago H, Takimoto T, Inoue E, Kamemura N, Kido H, Hisatsune J, Sugai M, Murota H, Katayama I, Sasaki T, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol.* 2014; 134: 824-830.e6. [CrossRef PubMed](#)
- [242] Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, Brown SJ, Chen Z, Chen Y, Williams HC. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol.* 2014; 134: 818-823. [CrossRef PubMed](#)
- [243] Dissanayake E, Tani Y, Nagai K, Sahara M, Mitsuishi C, Togawa Y, Suzuki Y, Nakano T, Yamada F, Ohno H, Shimojo N. Skin care and synbiotics for prevention of atopic dermatitis or food allergy in newborn infants: a 2 x 2 factorial, randomized, non-treatment controlled trial. *Int Arch Allergy Immunol.* 2019; 180: 202-211. [CrossRef](#).
- [244] Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, Ridd MJ, Lawton S, Simpson EL, Cork MJ, Sach TH, Flohr C, Mitchell EJ, Swinden R, Tarr S, Davies-Jones S, Jay N, Kelleher MM, Perkin MR, Boyle RJ, et al. BEEP study team. *Lancet.* 2020; 395: 962-972. [CrossRef PubMed](#)
- [245] Skjerven HO, Rehinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, Hedlin G, Landrø L, Marsland

- BJ, Rudi K, Sjöborg KD, Söderhäll C, Staff AC, Carlsen KH, Asaranoj A, Bains KES, Carlsen OCL, Endre KMA, Granlund PA, Hermansen JU, et al.* Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multi-centre, cluster-randomised trial. *Lancet*. 2020; 395: 951-9610. [CrossRef PubMed](#)
- [246] *Thacher JD, Gruziova O, Pershagen G, Melén E, Lorentzen JC, Kull I, Bergström A.* Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. *Allergy*. 2017; 72: 967-974. [CrossRef PubMed](#)
- [247] *Karvonen AM, Hyvärinen A, Korppi M, Haverinen-Shaughnessy U, Renz H, Pfefferle PI, Remes S, Genuneit J, Pekkanen J.* Moisture damage and asthma: a birth cohort study. *Pediatrics*. 2015; 135: e598-e606. [CrossRef PubMed](#)
- [248] *Zhang X, Norbäck D, Fan Q, Bai X, Li T, Zhang Y, Li B, Zhao Z, Huang C, Deng Q, Lu C, Qian H, Xu Y, Sun Y, Sundell J, Wang J.* Dampness and mold in homes across China: Associations with rhinitis, ocular, throat and dermal symptoms, headache and fatigue among adults. *Indoor Air*. 2019; 29: 30-42. [CrossRef PubMed](#)
- [249] *Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J; ISAAC Phase Three Study Group.* The association between tobacco and the risk of asthma, rhinoconjunctivitis and eczema in children and adolescents: analyses from Phase Three of the ISAAC programme. *Thorax*. 2012; 67: 941-949. [CrossRef PubMed](#)
- [250] *Carlsten C, Dimich-Ward H, DyBuncio A, Becker AB, Chan-Yeung M.* Cotinine versus questionnaire: early-life environmental tobacco smoke exposure and incident asthma. *BMC Pediatr*. 2012; 12: 187. [CrossRef PubMed](#)
- [251] *Keil T, Lau S, Roll S, Grüber C, Nickel R, Niggemann B, Wahn U, Willich SN, Kulig M.* Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy*. 2009; 64: 445-451. [CrossRef PubMed](#)
- [252] *Madureira J, Paciência I, Cavaleiro-Rufo J, de Oliveira Fernandes E.* Indoor pollutant exposure among children with and without asthma in Porto, Portugal, during the cold season. *Environ Sci Pollut Res Int*. 2016; 23: 20539-20552. [CrossRef PubMed](#)
- [253] *Carreiro-Martins P, Viegas J, Papoila AL, Aelenei D, Caires I, Araújo-Martins J, Gaspar-Marques J, Cano MM, Mendes AS, Virella D, Rosado-Pinto J, Leiria-Pinto P, Annesi-Maesano I, Neuparth N.* CO(2) concentration in day care centres is related to wheezing in attending children. *Eur J Pediatr*. 2014; 173: 1041-1049. [CrossRef PubMed](#)
- [254] *Qian H, Zheng X, Zhang M, Weschler L, Sundell J.* Associations between parents' perceived air quality in homes and health among children in Nanjing, China. *PLoS One*. 2016; 11: e0155742. [CrossRef PubMed](#)
- [255] *Andersson M, Hedman L, Nordberg G, Forsberg B, Eriksson K, Rönmark E.* Swimming pool attendance is related to asthma among atopic school children: a population-based study. *Environ Health*. 2015; 14: 37. [CrossRef PubMed](#)
- [256] *Font-Ribera L, Villanueva CM, Gràcia-Lavedan E, Borràs-Santos A, Kogevinas M, Zock JP.* Indoor swimming pool attendance and respiratory and dermal health in schoolchildren – HITEA Catalonia. *Respir Med*. 2014; 108: 1056-1059. [CrossRef PubMed](#)
- [257] *Deng Q, Lu C, Li Y, Sundell J, Dan Norbäck.* Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environ Res*. 2016; 150: 119-127. [CrossRef PubMed](#)
- [258] *Deng Q, Lu C, Ou C, Chen L, Yuan H.* Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children. *Chemosphere*. 2016; 152: 459-467. [CrossRef PubMed](#)
- [259] *Deng Q, Lu C, Yu Y, Li Y, Sundell J, Norbäck D.* Early life exposure to traffic-related air pollution and allergic rhinitis in preschool children. *Respir Med*. 2016; 121: 67-73. [CrossRef PubMed](#)
- [260] *Hsu HH, Chiu YH, Coull BA, Kloog I, Schwartz J, Lee A, Wright RO, Wright RJ.* Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. *Am J Respir Crit Care Med*. 2015; 192: 1052-1059. [CrossRef PubMed](#)
- [261] *Brunst KJ, Ryan PH, Brokamp C, Bernstein D, Reponen T, Lockey J, Khurana Hershey GK, Levin L, Grinshpun SA, LeMasters G.* Timing and duration of traffic-related air pollution exposure and the risk for childhood wheeze and asthma. *Am J Respir Crit Care Med*. 2015; 192: 421-427. [CrossRef PubMed](#)
- [262] *Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, Thyne S, Farber HJ, Serebrisky D, Kumar R, Brigino-Buenaventura E, Davis A, LeNoir MA, Meade K, Rodriguez-Cintron W, Avila PC, Borrell LN, Bibbins-Domingo K, Rodriguez-Santana JR, Sen S, et al.* Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am J Respir Crit Care Med*. 2013; 188: 309-318. [CrossRef PubMed](#)
- [263] *Rancière F, Bougas N, Viola M, Momas I.* Early exposure to traffic-related air pollution, respiratory symptoms at 4 years of age, and potential effect modification by parental allergy, stressful family events, and sex: A prospective follow-up study of the PARIS Birth Cohort. *Environ Health Perspect*. 2017; 125: 737-745. [CrossRef PubMed](#)
- [264] *Tétreault LF, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, Smargiassi A.* Childhood exposure to ambient air pollutants and the onset of asthma: An administrative cohort Study in Québec. *Environ Health Perspect*. 2016; 124: 1276-1282. [CrossRef PubMed](#)
- [265] *Tétreault LF, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, Smargiassi A.* Severe and moderate asthma exacerbations in asthmatic children and exposure to ambient air pollutants. *Int J Environ Res Public Health*. 2016; 13: 771. [CrossRef PubMed](#)
- [266] *Bowatte G, Erbas B, Lodge CJ, Knibbs LD, Gurrin LC, Marks GB, Thomas PS, Johns DP, Giles GG, Hui J, Dennekamp M, Perret JL, Abramson MJ, Walters EH, Matheson MC, Dharmage SC.* Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. *Eur Respir J*. 2017; 50: 1602357. [CrossRef PubMed](#)
- [267] *Bowatte G, Lodge CJ, Knibbs LD, Lowe AJ, Erbas B, Dennekamp M, Marks GB, Giles G, Morrison S, Thompson B, Thomas PS, Hui J, Perret JL, Abramson MJ, Walters H, Matheson MC, Dharmage SC.* Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. *J Allergy Clin Immunol*. 2017; 139: 122-129.e1. [CrossRef PubMed](#)
- [268] *Gruziova O, Bergström A, Hulchiy O, Kull I, Lind T, Melén E, Moskalenko V, Pershagen G, Bellander T.* Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology*. 2013; 24: 54-61. [CrossRef PubMed](#)
- [269] *Hasunuma H, Sato T, Iwata T, Kohno Y, Nitta H, Odajima H, Ohara T, Omori T, Ono M, Yamazaki S, Shima M.* Association between traffic-related air pollution and asthma in preschool children in a national Japanese nested case-control study. *BMJ Open*. 2016; 6: e010410. [CrossRef PubMed](#)
- [270] *Möller A, Lindley S.* Influence of walking route choice on primary school children's exposure to air pollution – A proof of concept study using simulation. *Sci Total Environ*. 2015; 530-531: 257-262. [CrossRef PubMed](#)
- [271] *Ranzi A, Porta D, Badaloni C, Cesaroni G, Lauriola P, Davoli M, Forastiere F.* Exposure to air pollution and respiratory symptoms during the first 7 years of life in an Italian birth cohort. *Occup Environ Med*. 2014; 71: 430-436. [CrossRef PubMed](#)
- [272] *Lee EY, Oh SS, White MJ, Eng CS, Elhawary JR, Borrell LN, Nuckton TJ, Zeiger AM, Keys KL, Mak AC, Hu D, Huntsman S, Contreras MG, Samedy LA, Goddard PC, Salazar SL, Brigino-Buenaventura EN, Davis A, Meade KE, LeNoir MA, et al.* Ambient air pollution,

- asthma drug response, and telomere length in African American youth. *J Allergy Clin Immunol.* 2019; 144: 839-845.e10. [CrossRef PubMed](#)
- [273] Lee SW, Yan DK, James CC, Lee S, Koh HY, Sheen YH, Oh JW, Han MY, Sugihara G. Short-term effects of multiple outdoor environmental factors on risk of asthma exacerbations: Age-stratified time-series analysis. *J Allergy Clin Immunol.* 2019; 144: 1542-1550.e1. [CrossRef PubMed](#)
- [274] Andersson NW, Hansen MV, Larsen AD, Hougaard KS, Kolstad HA, Schlünssen V. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. *Allergy.* 2016; 71: 15-26. [CrossRef PubMed](#)
- [275] Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: A systematic review and meta-analysis. *Clin Exp Allergy.* 2018; 48: 403-414. [CrossRef PubMed](#)
- [276] Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. *Psychosom Med.* 2008; 70: 102-116. [CrossRef PubMed](#)
- [277] Braig S, Weiss JM, Stalder T, Kirschaum C, Rothenbacher D, Genuneit J. Maternal prenatal stress and child atopic dermatitis up to age 2 years: The Ulm SPATZ health study. *Pediatr Allergy Immunol.* 2017; 28: 144-151. [CrossRef PubMed](#)
- [278] Rosa MJ, Just AC, Tamayo Y, Ortiz M, Schnaas L, Svensson K, Wright RO, Téllez Rojo MM, Wright RJ. Prenatal and postnatal stress and wheeze in Mexican children: Sex-specific differences. *Ann Allergy Asthma Immunol.* 2016; 116: 306-312.e1. [CrossRef PubMed](#)
- [279] Guxens M, Sonnenschein-van der Voort AM, Tiemeier H, Hofman A, Sunyer J, de Jongste JC, Jaddoe VW, Duijts L. Parental psychological distress during pregnancy and wheezing in preschool children: the Generation R Study. *J Allergy Clin Immunol.* 2014; 133: 59-67.e1-12. [CrossRef PubMed](#)
- [280] Larsen AD, Schlünssen V, Christensen BH, Bonde JP, Obel C, Thulstrup AM, Hannerz H, Hougaard KS. Exposure to psychosocial job strain during pregnancy and odds of asthma and atopic dermatitis among 7-year old children – a prospective cohort study. *Scand J Work Environ Health.* 2014; 40: 639-648. [CrossRef PubMed](#)
- [281] Hartwig IR, Sly PD, Schmidt LA, van Lieshout RJ, Bienenstock J, Holt PG, Arck PC. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. *J Allergy Clin Immunol.* 2014; 134: 160-169. [CrossRef PubMed](#)
- [282] Lee A, Mathilda Chiu YH, Rosa MJ, Jara C, Wright RO, Coull BA, Wright RJ. Prenatal and postnatal stress and asthma in children: Temporal- and sex-specific associations. *J Allergy Clin Immunol.* 2016; 138: 740-747.e3. [CrossRef PubMed](#)
- [283] Chang HY, Suh DI, Yang SI, Kang MJ, Lee SY, Lee E, Choi IA, Lee KS, Shin YJ, Shin YH, Kim YH, Kim KW, Ahn K, Won HS, Choi SJ, Oh SY, Kwon JY, Kim YH, Park HJ, Lee KJ, et al. Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress. *J Allergy Clin Immunol.* 2016; 138: 468-475.e5. [CrossRef PubMed](#)
- [284] Brew BK, Gong T, Williams DM, Larsson H, Almqvist C. Using fathers as a negative control exposure to test the Developmental Origins of Health and Disease Hypothesis: A case study on maternal distress and offspring asthma using Swedish register data. *Scand J Public Health.* 2017; 45 (suppl): 36-40. [Cross-Ref PubMed](#)
- [285] Zhou C, Ibanez G, Miramont V, Steinecker M, Baiz N, Banerjee S, Just J, Annesi-Maesano I, Chastang J, Charles MA, de Agostini M, Forhan A, Heude B, Ducimetère P, Kaminski M, Saurel-Cubizolles M-J, Dargent-Molina P, Fritel X, Larroque B, Lelong N, et al. Prenatal maternal depression related to allergic rhinoconjunctivitis in the first 5 years of life in children of the EDEN mother-child cohort study. *Allergy Rhinol (Providence).* 2017; 8: 132-138. [CrossRef PubMed](#)
- [286] Letourneau NL, Kozyrskyj AL, Cosic N, Ntanda HN, Anis L, Hart MJ, Campbell TS, Giesbrecht GF; APRON Team. Maternal sensitivity and social support protect against childhood atopic dermatitis. *Allergy Asthma Clin Immunol.* 2017; 13: 26. [CrossRef PubMed](#)
- [287] Elbert NJ, Duijts L, den Dekker HT, de Jong NW, Nijsten TE, Jaddoe VW, de Jongste JC, van Wijk RG, Tiemeier H, Pasmans SG. Maternal psychiatric symptoms during pregnancy and risk of childhood atopic diseases. *Clin Exp Allergy.* 2017; 47: 509-519. [Cross-Ref PubMed](#)
- [288] El-Heis S, Crozier SR, Healy E, Robinson SM, Harvey NC, Cooper C, Inskip HM, Baird J, Godfrey KM; Southampton Women's Survey Study Group. Maternal stress and psychological distress preconception: association with offspring atopic eczema at age 12 months. *Clin Exp Allergy.* 2017; 47: 760-769. [Cross-Ref PubMed](#)
- [289] Wang JJ, Wen HJ, Chiang TL, Lin SJ, Guo YL. Maternal psychologic problems increased the risk of childhood atopic dermatitis. *Pediatr Allergy Immunol.* 2016; 27: 169-176. [CrossRef PubMed](#)
- [290] Alton ME, Zeng Y, Tough SC, Mandhane PJ, Kozyrskyj AL. Postpartum depression, a direct and mediating risk factor for preschool wheeze in girls. *Pediatr Pulmonol.* 2016; 51: 349-357. [CrossRef PubMed](#)
- [291] Kozyrskyj AL, Letourneau NL, Kang LJ, Salmani M. Associations between postpartum depressive symptoms and childhood asthma diminish with child age. *Clin Exp Allergy.* 2017; 47: 324-330. [CrossRef PubMed](#)
- [292] Kim CH, Kim SH, Lee JS. Association of maternal depression and allergic diseases in Korean children. *Allergy Asthma Proc.* 2017; 38: 300-308. [CrossRef PubMed](#)
- [293] Radhakrishnan D, Shariff SZ, To T. The influence of prenatal mental health service use on the incidence of childhood asthma: a population-based cohort study. *J Asthma.* 2019; 56: 395-403. [CrossRef PubMed](#)
- [294] Magnus MC, Wright RJ, Røysamb E, Parr CL, Karlstad Ø, Page CM, Nafstad P, Håberg SE, London SJ, Nystad W. Association of maternal psychosocial stress with increased risk of asthma development in offspring. *Am J Epidemiol.* 2018; 187: 1199-1209. [CrossRef PubMed](#)
- [295] Strathearn L, Giannotti M, Mills R, Kisely S, Najman J, Abajobir A. Long-term cognitive, psychological, and health outcomes associated with child abuse and neglect. *Pediatrics.* 2020; 146: e20200438. [CrossRef PubMed](#)
- [296] Hsu CY, Lehman HK, Wood BL, Benipal J, Humayun Q, Miller BD. Comorbid obesity and depressive symptoms in childhood asthma: A harmful Synergy. *J Allergy Clin Immunol Pract.* 2020; 8: 2689-2697. [Cross-Ref PubMed](#)
- [297] DunnGalvin A, Blumchen K, Timmermans F, Regent L, Schnadt S, Podestà M, Sánchez A, Couratier P, Feeney M, Hjorth B, Patel R, Lush T, Ryan R, Vereda A, Fernández-Rivas M, Fisher HR. APPEAL-1: A multiple-country European survey assessing the psychosocial impact of peanut allergy. *Allergy.* 2020; 75: 2899-2908. [Cross-Ref PubMed](#)
- [298] Urbstonaitis R, Deshpande M, Arnoldi J. Asthma and health related quality of life in late midlife adults. *Res Social Adm Pharm.* 2019; 15: 61-69. [CrossRef PubMed](#)
- [299] Tao R, Fu Z, Xiao L. Chronic food antigen-specific IgG-mediated hypersensitivity reaction as a risk factor for adolescent depressive disorder. *Genomics Proteomics Bioinformatics.* 2019; 17: 183-189. [CrossRef PubMed](#)
- [300] Cowell WJ, Bellinger DC, Wright RO, Wright RJ. Antenatal active maternal asthma and other atopic disorders is associated with ADHD behaviors among school-aged children. *Brain Behav Immun.* 2019; 80: 871-878. [CrossRef PubMed](#)

- [301] Cheng CM, Hsu JW, Huang KL, Bai YM, Su TP, Li CT, Yang AC, Chang WH, Chen TJ, Tsai SJ, Chen MH. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. *J Affect Disord.* 2015; **178**: 60-65. [CrossRef PubMed](#)
- [302] Brzyski P, Cichożka-Jarosz E, Tarczoń I, Jedynak-Wąsowicz U, Tomasiak T, Lis G. Health-related quality of life in children and adolescents after systemic stinging reaction. *Ann Agric Environ Med.* 2019; **26**: 103-108. [CrossRef PubMed](#)
- [303] Licari A, Ciprandi R, Marseglia G, Ciprandi G. Anxiety and depression in adolescents with asthma and in their parents: a study in clinical practice. *Monaldi Arch Chest Dis.* 2019; **89**. [CrossRef PubMed](#)
- [304] Levinson J, Kohl K, Baltag V, Ross DA. Investigating the effectiveness of school health services delivered by a health provider: A systematic review of systematic reviews. *PLoS One.* 2019; **14**: e0212603. [Cross-Ref PubMed](#)
- [305] Barnes PJ, Szeffler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: Clinical implications for use of reliever medications. *J Allergy Clin Immunol.* 2019; **144**: 1180-1186. [CrossRef PubMed](#)
- [306] Azzi EA, Kritikos V, Peters MJ, Price DB, Srour P, Cvetkovski B, Bosnic-Anticevich S. Understanding reliever overuse in patients purchasing over-the-counter short-acting beta<sub>2</sub> agonists: an Australian community pharmacy-based survey. *BMJ Open.* 2019; **9**: e028995. [CrossRef PubMed](#)
- [307] Li Y, Chen L, Du Y, Huang D, Han H, Dong Z. Fluoxetine ameliorates atopic dermatitis-like skin lesions in BALB/c mice through reducing psychological stress and inflammatory response. *Front Pharmacol.* 2016; **7**: 318. [CrossRef PubMed](#)
- [308] Heratizadeh A, Werfel T, Wollenberg A, Abraham S, Plank-Habibi S, Schnopp C, Sticherling M, Apfelbacher C, Biedermann T, Breuer K, Fell I, Fölster-Holst R, Heine G, Grimm J, Hennighausen L, Kugler C, Reese I, Ring J, Schäkel K, Schmitt J, et al; Arbeitsgemeinschaft Neurodermitisschulung für Erwachsene (ARNE) Study Group. Effects of structured patient education in adults with atopic dermatitis: Multi-center randomized controlled trial. *J Allergy Clin Immunol.* 2017; **140**: 845-853.e3. [CrossRef PubMed](#)
- [309] Amaral SCO, Pimenta F, Marôco J, Sant'Anna CC. Stress reduction intervention with mothers of children/adolescents with asthma: a randomized controlled study in Brazil. *Health Care Women Int.* 2020; **41**: 266-283. [CrossRef PubMed](#)
- [310] Yepes-Nuñez JJ, Brożek JL, Fiocchi A, Pawankar R, Cuello-García C, Zhang Y, Morgano GP, Agarwal A, Gandhi S, Terracciano L, Schünemann HJ. Vitamin D supplementation in primary allergy prevention: Systematic review of randomized and non-randomized studies. *Allergy.* 2018; **73**: 37-49. [CrossRef PubMed](#)

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