



EAACI position paper on diet diversity in pregnancy, infancy and childhood: Novel concepts and implications for studies in allergy and asthma

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Abstract

To fully understand the role of diet diversity on allergy outcomes and to set standards for conducting research in this field, the European Academy of Allergy and Clinical Immunology Task Force on Diet and Immunomodulation has systematically explored the association between diet diversity and allergy outcomes. In addition, a detailed narrative review of information on diet quality and diet patterns as they pertain to allergic outcomes is presented. Overall, we 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. In order to harmonize methods for future data collection and reporting, the task force members propose relevant definitions and important factors for consideration, when measuring diet diversity in the context of allergy. Consensus was achieved on practice points through the Delphi method. It is hoped that the definitions and considerations described herein will also enable better comparison of future studies and improve mechanistic studies and pathway analysis to understand how diet diversity modulates allergic outcomes.

KEYWORDS

asthma, atopic dermatitis, Diet diversity, food allergy, prevention, rhinitis

1 | INTRODUCTION

To increase our understanding of the complex relationship between nutrients and other essential components of food, there has been a growing interest in taking a whole diet approach when studying disease outcomes. In particular, research focusing on diet diversity has received significant attention due to its potential role in the prevention of allergic diseases. Diet diversity is defined as the number of different foods or food groups consumed over a given reference period.¹ Diet variety, a term often used in the literature, is considered synonymous with diet diversity.¹ A list of nutritional definitions relevant to this paper are summarized in Box 1.

As nutrients and foods are not eaten in isolation, and an intake of one food or nutrient may inadvertently lead to reduced intake of another, dietary diversity is a challenging area of research.

The task force appreciates that intake of single food or nutrients may also play an important role in the development of allergic diseases. One such example is the study by Bisgaard et al,¹⁰ showing that supplementation with omega-3 fatty acids in the third trimester of pregnancy reduced the risk of persistent wheeze or asthma. The control group was, however, taking olive oil, a key component and indicator of the Mediterranean diet, which could be attributable to reduced allergy outcomes even in the control group.^{11,12}

The mechanistic basis for how diet diversity potentially affects allergy outcomes need further clarification,¹³⁻¹⁵ but may ultimately be mediated through a multitude of immune tolerance mechanism including T and B regulatory cells, immune-regulatory cytokines and suppressed IgE antibodies as demonstrated in other allergen

tolerance models.¹⁶ Possible mechanisms by which diet diversity could affect allergy outcomes are summarized below:

1. It is postulated that a more diverse diet may indirectly affect tolerance development via an effect on the microbiome. This is supported by studies showing that increased diet diversity leads to increased microbial diversity in the elderly¹⁷ and in infants during the introduction of solid food.¹⁸ Increased microbial diversity¹⁹ or abundance of certain bacteria²⁰ has been associated with reduced allergy outcomes. However, there is a paucity of information linking diet diversity, microbial diversity and allergy outcomes.
2. Diet diversity does not provide a finite indication of diet quality, but it may be associated with increased nutrient intake whereas a more diverse diet may indirectly affect allergy outcomes by providing nutrients associated with prevention of allergic diseases such as omega-3 fatty acids and nondigestible fibres.^{21,22}
3. A more diverse diet may also lead to exposure of different food antigens that impact development of immune tolerance, though this may be "low dose" exposure,²³ supporting recent randomized controlled trials regarding early allergen introduction.²⁴⁻²⁷

The focus of this paper is to systematically review and critically address the current knowledge of the association between *diet diversity and allergy outcomes*. To fully understand the role of diet diversity on allergy outcomes and to set standards for conducting research in this field, this review will explore the concept of diet diversity and describe this in the context of other dietary measures, such as diet quality and diet patterns. This is followed by a systematic search

Box 1 Definitions: Dietary diversity, dietary variety, dietary quality, dietary patterns

Diet: Food intake

Nutritional adequacy: The comparison between the nutrient requirement and nutritional intake of an individual or population.²

Dietary diversity: The number of different foods or food groups consumed over a given reference period. It is not a proxy for nutrient adequacy.¹

Dietary variety: A term often used in the literature, is which considered synonymous to dietary diversity.¹

Dietary quality: No official definition in the literature. Definitions vary widely, and many different measurement tools are used. Diet quality may reflect nutrient adequacy but it is not always the case.¹

Dietary patterns: This term reflect an individual's food choice and differ across nationality, culture, socio-economic class and religion. Dietary patterns represent an overall view of food intake and may be a better indicator of disease risk than studying specific foods and nutrients.³

Complementary food/Wearing foods: "When breastmilk is no longer enough to meet the nutritional needs of the infant, complementary foods should be added to the diet of the child. The transition from exclusive breastfeeding to family foods, referred to as complementary feeding, typically covers the period from 6 to 18-24 months of age, and is a very vulnerable period."⁴

Sensitization to food allergens: Sensitization is defined as the presence of allergen-specific IgE (sIgE) to food allergens without having clinical symptoms on exposure to those foods.⁵

IgE-mediated food allergy requires both the presence of specific IgE to the food (sensitization) and the development of signs and symptoms when exposed to the food.⁵

Food Frequency Questionnaire: A questionnaire which enquires about the frequency of consumption of a specific list foods over a period of time.⁶

Semi-quantitative/quantitative food frequency questionnaire: Asks about portion size, gathered either by using free description, as standardized portions or a choice of portion sizes in addition to frequency of consumption.

Quantitative food frequency questionnaire: Uses measures of food eaten, for example measures such as grams or mls as opposed to using measures such as portion sizes/cups/spoons.⁷

24-hour recall: Gathers information about all foods and drinks (and nutritional supplements in some cases) consumed over the previous 24 hours.⁸

Processed food: Considered to be natural foods manufactured with the addition of salt or sugar.⁹

and review of the association between diet diversity and allergy outcomes. An overview of information on diet quality and diet patterns as they pertain to allergic outcomes is also given. Finally, this European Academy of Allergy and Clinical Immunology (EAACI) Task

Force proposes factors for consideration and relevant definitions when measuring diet diversity in the context of allergy, with the aim to standardize methods for future data collection and reporting. The authors of this taskforce hope that this paper and its recommendations (Table 1) will also better enable comparison of future studies and improve mechanistic studies and pathway analysis.

2 | METHODS

The EAACI taskforce was formed in 2017 and met in person in 2017 and 2018 at the EAACI annual Congress to discuss proposed publications on the role of diet diversity and allergic outcomes. A search of the literature regarding diet quality, diet diversity and food patterns to inform future practice and research relating to allergic outcomes was performed. The full literature search and terms are listed in File S1. Studies on single nutrients or single foods were excluded from the search as the review focused on diet diversity and quality opposed to nutrient/food outcomes.

Searches 1 and 2 were conducted to give background information on the use of diet diversity and diet quality in characterizing nutrition intake and healthy/nutrition outcomes. Search 1 focused on diet diversity in pregnancy, infancy, childhood and in households compared to health/nutrition outcomes (Section 1). Search 2 focused on diet quality in pregnancy, infancy, childhood and households compared to nutrient/food outcomes (Section 2). Searches 3 and 4 included a systematic literature search regarding diet diversity, diet quality and food patterns compared to allergy outcomes. Search 3 focused on diet diversity and diet patterns during pregnancy and allergy outcomes in the infant (Section 3), whereas search 4 focused on diet diversity and food patterns during infancy and childhood and allergy outcomes (Section 4). Key opinion leaders in the field of diet diversity and diet quality were contacted to enquire about guideline papers or book chapters in this field. A modified Delphi panel was used among the task force members to provide consensus on key themes and potential recommendations.²⁸

2.1 | Section 1: Overview of the use of diet diversity to measure nutrition intake in pregnancy, infancy or childhood

Historically, studies on diet diversity investigated (1) child nutrient intake or (2) growth status, and (3) a number of other health outcomes. Studies from both developed²⁹ and developing countries^{30,31} have noted that an increase in diet diversity was associated with an increase in nutrient adequacy. Studies focusing on diet diversity have shown that an increase in diet diversity was associated with better growth indices in young children using height, weight, skin fold thickness and length for age or height for age z-scores to describe stunting, underweight and overweight,³²⁻³⁹ though this might be confounded by socio-economic status. The association between diet diversity and other health outcomes in pregnancy, infancy and childhood (eg obesity)⁴⁰⁻⁴² has also been studied and is summarized in online supplementary Tables S1a-d.

TABLE 1 Factors to consider when measuring diet diversity to improve the validity and reliability of diet diversity measured

Current state of knowledge	
Definitions	See Box 1
Factors to consider in order to measure diet diversity	
Population studied	The majority of studies on diet diversity have been carried out in children. The tool used should take into account measurements in developed vs. developing countries ^{1,126}
Food vs. food group	It is unclear if foods, food groups or both best describe diet diversity since some studies favour foods, others favour food groups or favour both ^{30,43,127,128}
Defining food groups	Food group selection and whether these food groups should be selected based on their nutritional value. This decision should be dependent on the outcome being studied, for example nutritional intake, food security or disease outcome^{1,126} Allergen intake has been used as a marker for diet diversity.¹²⁹ The study found no consistent association between timing and diversity of allergenic solid food introduction and allergic sensitization, physician-diagnosed food allergy or eczema up to 10 y of age. "Food biodiversity is defined as the diversity of plants, animals and other organisms used as food, covering the genetic resources within species, between species and provided by ecosystems" Food biodiversity therefore measures food intake based on their scientific classifications and may be useful to determine nutritional intake.⁴⁴ Microbial diversity of food: Studying foods with a high biodiversity of microbial content such as unpasteurized milk (atopic dermatitis and atopy)¹³⁰ and fermented foods such as cheese or yoghurt (food allergy and atopic dermatitis)¹³¹ as an indicator of intake of microbial diversity, and a source of short chain fatty acids, gives an indication that these foods may be associated with allergy prevention. Studies focusing on Westernized diets^{116,117,132} (also high in advanced glycation end products, soda, fruit juice,^{133,134} cured meats¹³⁵ and fast food¹³⁶) suggest that increased intake of advanced glycation end products (AGEs) is associated with reduced diet diversity and increased allergy outcomes. A number of studies have indicated that certain nutrients (eg antioxidants) of foods (fruit and vegetables or fish) may have a beneficial effect on prevention particularly of infant wheeze¹³⁷⁻¹⁴⁰ or eczema in the infant^{77,139}
Portion size	It is unclear if portion size should be included when measuring diet diversity and it will depend on the outcome being studied. Two points are of particular importance:^{1,126,142} 1) Should portion size be included to better describe nutritional intake. 2) What is the minimum portion size to include as including foods eaten in small amounts (<15 g of the food) can falsely inflate diet diversity, particularly if nutritional intake is being studied?
Frequency of intake	Whether frequency of intake should be measured, will depend on the question asked ^{1,126,142}
Scoring system	For simple diet diversity, the number of foods or food groups consumed over a given time is usually stated. Weighted scores can be assigned to indicate how often a food or food groups were consumed over a given period of time. More complex scoring systems that include more detailed information such as the number of portions or portion size, usually form part of a dietary index as opposed to indicating diet diversity ^{58,60,143}

Recommendations regarding measuring diet diversity based on current literature

Diet Diversity, diet quality and diet patterns are distinct entities of food intake and these terms should not be used interchangeably

The age group studied must be clearly specified.

The diet diversity tool should preferably be validated in that age group, and sociodemographic information should also be collected.

The diet diversity tools required may be different depending on the populations studied.

Either foods or food groups can be studied to measure diet diversity.

Foods and/or food groups that are studied should be clearly specified and identifiable, for example fresh fruit vs. fruit juice.

Food groups chosen should be selected based on the outcome to be studied.

Practice points regarding measuring diet diversity based on Delphi consensus from the EAACI task force: Voting: >80% agreement

In future, there may be an index that better describes the allergenic potential of foods or food patterns within the context of diet diversity better

Diet diversity scores should be weighted depending on the types of food being measured (eg a diverse fast-food diet is not equal to a diverse fruit and vegetable diet).

Diversity of intake of specific foods, for example range of fruits eaten, different types of cheese consumed, different types of home-cooked or processed foods cannot be used to describe diet diversity but the terms "diversity of fruit intake," "diversity of cheese intake" or "diversity of processed food intake" can be used. These foods can, however, be included in combination with other foods to determine overall diet diversity.

For allergy (asthma, food allergy, eczema, rhinitis, allergic sensitization), there is the opportunity to measure allergenic food diversity, which relates to the number and/or amount of food allergens introduced in a given period of time, for example the first year of life. It is important to understand that allergenic food diversity may not reflect diet diversity, as an emphasis on allergenic food intake may lead to an overall reduced diet diversity.

There is the opportunity to measure food biodiversity, which relates to the taxonomic classification of food intake, for example classifying tomatoes as *Solanum* (genus) opposed to vegetables.

There is the opportunity to measure food microbial diversity which relates to the microbial content of foods.

Diversity of intake of foods containing specific nutrients or ingredients, for example foods containing advanced glycation end products or foods containing omega-3 fatty acids cannot be used to describe diet diversity but the terms "diversity of advanced glycation end products intake" or "diversity of foods containing omega-3 fatty acid intake" can be used. These foods can however be included in combination with other foods to determine overall diet diversity. In these instances, diversity may have a positive (fruit and vegetables) or a negative (advanced glycation end products) connotation. This list may continue to grow as we gain more knowledge about foods/nutrients with immunomodulatory potential, for example bovine trans fatty acids which are isomers of linoleic acid¹⁴¹

Portion size should be defined and measured using quantitative or semi-quantitative questionnaires when required to describe diet diversity

It is not possible at present to define the minimum amount of allergenic protein that should be consumed in order to be sufficient within the allergenic food diversity measure

Frequency of specific food or food group exposures should be measured in diet diversity studies

Scoring systems for diet diversity are simple and measure the number of foods or food groups consumed over a given timeframe

TABLE 1 (Continued)

Current state of knowledge	
Cut-off values	It is difficult to define what constitutes high or low diversity of foods or food groups and cut-off points should be determined in the context of why and in which population the diet diversity is measured. In terms of determining nutrient adequacy, it is recommended that cut-offs should take local food systems and dietary patterns into account. In some instances, sensitivity-specificity analysis ³⁰ or receiver-operating characteristics (ROC) curves ¹⁴⁴ can be used to determine cut-off points
Recall period	The optimal recall period required to assess dietary diversity will depend on daily variety of intake, risk of recall errors, and for intake data can be used at individual or population level. On an individual level, the number of foods being eaten reaches a plateau after 10-15 d.¹⁴⁵ In addition, as the curve increases steeply for the first 3 d, measuring diet diversity based on a 1-day recall may underestimate dietary diversity. On a household or population level, the reference period is still unclear, but seems to be shorter than measuring nutrient intake at an individual level. Ultimately, the number of days included in the recall period should take participant burden and feasibility into account^{1,146-148}
Primary source of food procurement and food preparation	Information about the primary source of food procurement may be important to determine intake of either for the whole or certain specified foods/food groups (fruit, vegetables, dairy), for example.¹⁴² 1 = Own production, gathering, hunting, fishing. 2 = Purchased. 3 = Borrowed, bartered, exchanged for labour, gift from friends or relatives. 4 = Food aid. 5 = Other. Food preparation can also affect the microbial content of food. Food preparation can therefore potentially affect the allergy preventative potential of foods^{9,62,149-151}
Consumption of fortified foods	If digestion of fortified foods is important for the outcome studied, then the questionnaire may need to address this or at least consider the local availability of these ^{126,142}
Mixed dishes or foods with multiple ingredients	As with foods consumed in small amounts, it is important to err on the side of caution and not inflate what was eaten ^{126,142}
Open recall methods or predefined list of food	There is anecdotal evidence that predefined lists of food eaten may collect less complete information than when food intake is determined in an open/unstructured fashion ^{126,142}
Age of weaning and introduction of infant formula	Data suggest that age of introduction of solid foods,¹⁵² food allergens^{24,25} and infant formula¹⁵³ may affect allergy outcomes. Introduction of solid foods during the weaning period increase the diversity of the gut microbiome¹⁸
Other factors that may affect allergy outcomes	Studies looking at growth, nutritional intake and health outcomes other than allergic diseases, do not need to control for other risk factors of allergic diseases, but these will need to be controlled for in diet diversity studies ¹⁵⁴

Recommendations regarding measuring diet diversity based on current literature

Cut-off values of high/low diversity can only be correctly ascertained at a population level, where the sample is robust and representative of the population to allow generalizability. Consequently, these may differ in different populations

The recall period and method of data collection should be clearly specified, but age of introduction for each food during infancy should also be reported given this may have a potential significant confounding effect

Investigators should consider ways to ensure measuring food procurement in their study design, and if/when possible, this should be detailed for both diet diversity and diet quality

If fortified foods are consumed, the study should aim to capture these data, and the amount quantified.

If any vitamin or mineral or nutritional supplements is consumed in the study, this should be reported, including brand and the amount consumed. Detail of probiotic and prebiotic supplements should also be recorded. Foods already supplemented with any of the above should also be clearly recorded.

If mixed dishes are consumed, this should be clearly specified, and the method for how individual food or allergen content quantification was achieved should be fully detailed for both diet quality and diet diversity.

Open recall, for example 24-h recall, is the preferred method of ascertaining foods or diet quality index. Predefined lists are less preferable, but if used, these should be clearly defined in the methods or in a File S1

Practice points regarding measuring diet diversity based on Delphi consensus from the EAACI task force: Voting: >80% agreement

When possible, studies reporting diet diversity data should include sensitivity, specificity, true and false positive/negative values to assist future meta-analyses and comparisons. They should also de-emphasize reporting of a cut-off value for a sample

For pregnant women, we recommend a minimum recall period of 2 weekdays and 1 weekend day (ie 3 d), measured at repeated intervals throughout pregnancy. When possible, portion sizes should be collected and reported. For infants, we recommend food recall periods within the first year of life. These periods may include the first four months of life, the first six months of life or the first year of life. Repeated measure of intake is recommended to improve the quality of data, rather than just recording consumption of a particular food/food group once. When possible, portion sizes should be collected and reported and data should ideally be recorded prospectively

Investigators should consider ways to ensure measuring how food is prepared/cooked (eg Raw, home cooked, processed, ultra-processed and fermented) is recorded in their study design, and if/when possible, this should be detailed for diet diversity. Ideally, foods should be defined as raw, home-cooked, processed or ultra-processed

Age of introduction of solid foods, allergenic foods and infant formula should be clearly indicated in studies investigating the association between diet diversity and allergy outcomes.

Introduction of infant formula cannot be classified on its own as diet diversity but should be included in measuring diet diversity of food and food groups. Introduction of infant formula may in fact reduce diet diversity as breastmilk potentially exposes an infant to the diversity of the maternal diet, whereas formula is uniform

There is a nonexhaustive list of factors that may affect allergy outcomes, but potential confounders should be corrected for analysing associations between diet diversity and allergy outcomes

Diet diversity can be measured by counting individual foods,^{31,37,42-46} food groups^{30,34-36,38,39,41,43,47-54} or foods within a group,^{32,33,55,56} and can be measured over a time period ranging from the previous 24 hours (24-hour recalls)^{31-35,38,40,44,46,48} or over a 7-day period^{33,39,42,47,53,55-57} to intake over one year. Food intake data may be collected once^{32-34,38,40,44,48} or a number of times^{31,35,46} as summarized in Table S1a-d. Factors that should be considered when measuring diet diversity are summarized in Table 1.

2.2 | Section 2: Overview of the use of diet quality in measuring nutrition intake

The term diet quality is broadly used as an umbrella term to describe a healthy, balanced, nutritious diet for optimal health characterized by limited amounts of fat, saturated fat, cholesterol, sodium and refined sugars, and meeting the recommended amounts of fruits, vegetables and whole grain products.⁵⁸ Diet quality is often described using a nutrition index, although food patterns, for example the Mediterranean diet, are also often referred to as indicators of diet quality. The purpose of diet indices is to synthesize a large amount of dietary information into a single useful indicator.⁵⁹ Over the years, various indices have been developed to measure diet quality, amended and validated to evaluate healthy dietary patterns such as the healthy eating index (HEI) score,⁶⁰ the Mediterranean diet score⁶¹ and more complex indices.⁶²⁻⁶⁴ Scoring is typically based on consumption of nutrients, foods or both⁶⁵ though there is wide heterogeneity in methods used. Table S2 summarizes the most commonly used dietary indices in pregnancy, infancy and childhood.

2.3 | Section 3: Diet diversity and diet quality (indices and diet patterns) during pregnancy and allergy outcomes in the infant

Diet diversity and diet quality may be used to find associations between dietary intake and allergy outcomes in either pregnancy or infant's early life or both. We conducted a systematic review of the literature to identify relevant studies, investigate the measures used and describe any associations found with allergy outcomes.

2.3.1 | Diet diversity in pregnancy and allergy outcomes

While this is an important relationship to understand, no studies have been identified exploring an association between diet diversity in pregnancy and allergy outcomes.

2.3.2 | Diet quality in pregnancy and allergy outcomes

Studies on diet quality in pregnancy and allergic diseases have used the Mediterranean diet score⁶⁶⁻⁷⁰ or a modified version of the HEI in pregnancy^{71,72} to investigate an association with allergic outcomes.

2.3.3 | Mediterranean diet in pregnancy and allergy outcomes

Four papers from longitudinal birth cohort studies^{66-68,71} (two from Spain, one from Greece and one from the USA) studied the association between Mediterranean diet patterns and atopic outcomes in the offspring (Table S3). Typically, a diet score is developed and dietary information, obtained from food recalls (food diaries, 24-hour recalls, food diaries), is used to calculate the Mediterranean diet score.⁶¹ In two studies, dairy intake^{67,68} was added to the Mediterranean diet score. All studies adjusted their analyses for common confounders, though these varied between studies. Two studies included the use of vitamin/mineral supplements in their dietary analysis^{66,71}; in one study, it was unclear if the use of supplements was included in the analyses⁶⁷ and one study adjusted for mineral/vitamin intake only in the statistical analyses.⁶⁸

Outcomes reported in the infants were wheeze in all studies,^{66-68,71} asthma in one study,⁷¹ and rhinitis, atopic dermatitis and/or eczema in three studies.⁶⁶⁻⁶⁸ Sensitization to food/aero-allergens was determined in two studies.^{68,71} None of these studies reported on food allergy as an outcome, highlighting a true deficiency in the literature. All outcome measures were parental reported and/or doctors diagnosed.

In 3 of the 4 studies,^{66,67,71} a Mediterranean diet pattern during pregnancy was not associated with the development of atopic diseases in the offspring. However, one study⁶⁸ indicated that the Mediterranean diet was associated with reduced prevalence of persistent wheeze, atopic wheeze and atopy.

2.3.4 | Other dietary patterns or indices used in pregnancy

Investigating dietary patterns other than the Mediterranean diet, we found four longitudinal birth cohort studies:⁷²⁻⁷⁵ three studies using semi-quantitative FFQs, from which the diet patterns were analysed, and one used a 24-hour recall⁷³ (Table S4). In three studies, the use of vitamin/mineral supplements was not reported, and in one, the use of supplements was excluded.⁷²⁻⁷⁵ All studies adjusted their analyses for common confounders, although confounders varied widely between studies.

In one study, the Alternate Healthy Eating Index modified for pregnancy (AHEI-P) developed by Rifas et al⁷⁶ was used to examine associations with allergic outcomes,⁷² and in three studies, food patterns were studied.⁷³⁻⁷⁵ In these three studies, principal component analysis was used to assess individual food intake and the following food patterns emerged as associated with allergic outcomes:

- Seafood and noodle pattern (noodle soup, noodles with sauce, fish, seafood and seafood products);
- Vegetable, fruit and white rice pattern (vegetables, fruit, whole grain bread and white rice with minimal processed foods/meats);
- Pasta, cheese and processed meat pattern (pasta, processed grains, cheese and processed meats)⁷³;

- Healthy pattern (high consumption of green and yellow vegetables, seaweed, mushrooms, white vegetables, pulses, potatoes, fish, sea products, fruit, and shellfish and low intake of confectioneries and soft drinks);
- Western pattern (high consumption of vegetable oil, salt-containing seasonings, beef and pork, processed meat, eggs, chicken, and white vegetables and low intake of fruit, soft drinks, and confectioneries);
- Japanese pattern (high consumption of rice, miso soup, sea products, and fish and low intake of bread, confectioneries and dairy products)⁷⁴;
- Health conscious pattern (salad, fruit, fruit juices, rice, pasta, oat/bran, fish);
- Traditional pattern (vegetables, red meat and poultry);
- Processed pattern (meat pies, sausages, burgers, fried food);
- Vegetarian pattern (meat substitutes, pulses, nuts, herbal tea);
- Confectionary (chocolate, sweets, biscuits, cakes and puddings).⁷⁵

Outcomes measured were asthma,^{73,75} eczema,^{73,74} rhinitis⁷³ and sensitization to food/aero-allergens.^{72,73,77} The only positive associations reported were reduced sensitization due to the seafood and noodle pattern⁷³ and reduced wheeze due to the Western diet pattern.⁷⁴ The seafood and noodle pattern⁷³ was associated with a reduced risk of developing allergen sensitization at both 18 months [odds ratio (95% confidence interval): 0.7 (0.5-0.9)] and 36 months [odds ratio (95% confidence interval) 0.7 (0.6-0.9)]⁷³; the maternal Western diet pattern was associated with a reduced risk of wheeze, and in adjusted analysis, the OR between extreme quartiles was 0.59 (95% CI: 0.35-0.98, *P* for trend = 0.02).^{74,75} Once again, no study looked at food allergy as an outcome.

2.4 | Section 4: Diet Diversity during infancy and allergy outcomes in the infant

2.4.1 | Diet diversity and allergen sensitization

IgE sensitization is a commonly used (but limited and imprecise) marker of clinical allergy. Roduit et al¹⁶ investigated the association between diet diversity and allergic disease and collected sensitization data based on specific IgE (Table 2) in the Protection Against Allergy Study in Rural Environments (PASTURE) prospective cohort study, which enrolled children from Austria, Finland, France, Germany and Switzerland. Diet diversity in this study was defined as the 15 foods commonly eaten by 80% of the children in the study in the first year of life: any cow's milk, yogurt, other milk product; eggs; nuts; vegetables or fruits; cereals; bread; meat; fish; soya; margarine or butter; cake; and chocolate. A second definition was also used, including the 6 major foods introduced in the first 6 months or first 12 months of life: vegetables or fruits; cereals; bread; meat; cake; and yogurt. Children with a low-diet diversity, as defined as above, had an increased risk of sensitization to food allergens at age 4.5 or 6 years, but no significant associations were found with sensitization to inhalant allergens. The association remained significant,

albeit weaker, in a subgroup analysis of children without food allergy, respiratory disorders or both. Subgroup analysis was carried out to consider the potential risk of reverse causality, given early-onset allergy or family history of allergy could lead to low-diet diversity due to different feeding practices in those infants. The German LISAPlus study assessed the impact of diet diversity on allergic disease.⁷⁸ That study concluded that children in the highest quartile of food group diversity had lower odds of allergic sensitization to aeroallergens. This finding was also supported when food group diversity was treated as a continuous variable. Similarly, in a Finnish birth cohort of over 3500 children, Nwaru et al⁷⁹ studied the association between diet diversity (defined as the number of foods introduced at 3, 4 and 6 months of age) and sensitization to food and aeroallergens at the age of 5 years (see Table 3 for definitions used). After adjustment for several demographic and parental factors, they found that reduced diet diversity as early as 3 months was associated with an increased risk of sensitization to specific food and aeroallergens. While the adverse risk estimates became much stronger with increased diet diversity at 4 and 6 months, the authors found that, compared to non-high-risk children, the at-risk children (ie those with atopic eczema by 6 months of age or those with a parental with history of allergy) had a greater risk of allergic sensitization.

2.4.2 | Diet diversity and food allergy

Only one study has focused on the potential association of the diversity of food intake and the development of food allergy (Table 3). In the aforementioned PASTURE study, Roduit et al¹⁶ showed that children with a more diverse diet had a lower prevalence of food allergy, measured as a report of a doctor-diagnosed food allergy but not necessarily an allergy proven by oral food challenge. In this study, the inclusion of 0-6 items from vegetables/fruits, cereals, bread, meat, cake and yogurt within the first 6 months or first year of life, respectively, was recorded. The study showed that children with a low-diet diversity score (consumed fewer of the items listed above) had an increased risk of food allergy up to six years of age, compared to children having more food items in their diet.

2.4.3 | Diet diversity and atopic dermatitis

A limited number of studies have investigated the association between diversity of complementary foods and the risk of atopic dermatitis (AD) in children. In all studies, diet diversity was defined as the sum of the number of complementary foods that had been introduced into the child's diet (even if eaten only once) up to a specified time point, usually within the first year of life. We identified eight unique studies (seven birth cohorts and one matched case-control study), reporting their data in 12 publications originating from Germany, Italy, New Zealand, Finland, Austria, France and Switzerland (Table 4). The pooled data from the GINIPlus and LISA studies revealed that the early introduction of solids with a high diversity before the end of the fourth month was associated with an increased risk of AD at two and six years, but

TABLE 2 The association between diet diversity and sensitization to food and aero-allergens

Study and country	Definition and assessment of diet diversity	Results	Comments
Roduit et al (2014) ¹⁶ Prospective birth cohort study Protection Against Allergy Study in Rural Environments (PASTURE/ EFRAIM).	Intervention/Exposure: Parental administered questionnaires for asthma, rhinitis and food allergy within the third trimester of pregnancy and when the children were 2, 12, 18 and 24 mo of age and then yearly up to age 6 y Asthma: at least one either doctor-diagnosed asthma or at least 2 doctor-diagnosed episodes of obstructive bronchitis in the last 12 mo in the year 4, 5, or 6 questionnaires independent of a diagnosis reported in the first 3 y of life. Food allergy: at least once been given a diagnosis of food allergy by a doctor up to age 6 y. Allergic rhinitis: Reported presence of symptoms (itchy, runny, or blocked nose without a cold and associated with red itchy eyes) or doctor-diagnosed allergic rhinitis in the 6-year questionnaire. DD was assessed through food items in monthly food diaries from 3rd-12th months. DD scores were calculated as follows: (1) using major food items introduced in the first year of life (including vegetables or fruits, cereals, bread, meat, cake and yogurt); (2) with the same major food items but introduced in the first 6 mo of life; and (3) with all food items introduced in the first year of life (including any cow's milk, yogurt, other milk product, eggs, nuts, vegetables or fruits, cereals, bread, meat, fish, soy, margarine, butter, cake and chocolate) Assessment Methods: parent self-administered questionnaire on dietary intake. Levels of allergen-specific IgE antibodies (Dermatophagoides pteronyssinus, Dermatophagoides farinae, alder, birch, hazel, grass pollen, rye, mugwort, plantain, cat, horse, dog, Alternaria species, hen's egg, cow's milk, peanut, hazelnut, carrot and wheat flour) were measured in blood among children at age 4.5 and 6 y. Sensitization was defined as ≥ 3.5 kU/L Assessment of DD age: at 6 and 12 mo of age	Complementary food introduction associated with asthma, food allergy, allergic rhinitis and atopic sensitization up to 6 y of age Assessment Methods: DD score and parent reported asthma, rhinitis and food allergy. Specific IgE levels to indicate sensitization Results Sensitization to any allergen at age 4.5 and/or 6 y was present in 25.5% of children, sensitization to food allergens was present 10.7%, and sensitization to inhalant allergens was present in 22.1%, as measured at 4.5 or 6 y. Increased DD within the first year of life was negatively associated with sensitization to food allergens at 4.5 or 6 y of age. The children with a low DD had an increased risk of sensitization to food allergens at age 4.5 or 6 y. The analysis with children having doctor-diagnosed food allergy combined with positive food sensitization showed an even stronger negative association with DD (adjusted OR for each additional food item: 0.55, 95%CI: 0.40-0.76). Children with a low DD, had an increased expression of marker for antibody isotype switching to IgE and a reduced expression of the regulatory T cell-associated gene Foxp3 measured at 6 y of age	Confounders: Confounders adjusted for in this publication. (in particular atopic dermatitis) Limitations: Study population were selected from rural Europe and may not reflect general population. Outcomes of asthma, food allergy and rhinitis were based on parental reports. Reverse causality cannot be ruled out in this study DD score used was not validated and made use of allergens and foods like chocolate and margarine as part of the diversity score, which may not be representative of true DD.
Markevych et al (2017) ⁷⁸ Population-based German birth cohort LISAPlus (Influences of Lifestyle related Factors on the Immune System and the Development of Allergies in Childhood) Sample Size: Baseline N: 3097 Analytic N: 2518 Attrition: 81% Sex: See original LISAPlus study Race/Ethnicity: See original LISAPlus study Atopic Disease Risk Status: 57.2% had atopic family history	Intervention/Exposure: Impact of DD within the first 6 mo of life on 5 allergic outcomes: doctor-diagnosed eczema, asthma and allergic rhinitis and sensitization to aeroallergens and food allergens. Assessment Methods: Self-administered biannual parental questionnaires on the children's health and on life-style factors from birth to 2 y and at 4 y and 6 y. Blood samples for specific IgE at 2 and 6 y, levels > 0.35 KU/L were defined as sensitization. At 12 mo of age, parents were asked about breastfeeding practices and about the timing of solid food introduction. Possible answer choices included: "1st until 4th month," "5th/6th month," "7th to 12th month," and "solid food item not yet introduced." Forty-eight food items were grouped into 8 food groups: (1) vegetables (avocado, cauliflower, beans, broccoli, peas, cucumbers, carrots, potatoes, white cabbage, turnip, cabbage, lentils, celery, asparagus, spinach, tomatoes, onion, vegetable juices); (2) fruit (apples, pineapples, apricots, bananas, pears, strawberries, peaches, citrus fruit, fruit juices); (3) cereal (bread/pretzels/rolls, cookies/cakes/rusk, rolled oats, muesli, millet, cornmeal/corn starch, wheat semolina/starch, noodles, rice/rice starch, spelt); (4) meat (poultry, lamb, veal/beef, pork, sausages); (5) egg; (6) dairy products (cow milk/cream, yoghurt/quark/cheese); (7) fish; and (8) other (nuts, soy products, cocoa/ chocolate). Assessment of DD age: DD at 6 mo and 12 mo of age	Allergic outcomes at 2 and 6 and 15 y of life Assessment Methods: Several definitions of DD (food group and food item diversity, each treated in quartiles and continuously) during the first year of life. All analyses were stratified by the presence of a wide range of early skin symptoms to test the impact of reverse causality. Allergic outcomes were assessed at 6, 12 and 18 mo and age 2, 4, 6, 10 and 15 y. Results Children in the highest quartile of food group diversity had lower odds 0.61 (0.44-0.85) of allergic sensitization to aeroallergens. When food group diversity was treated as a continuous variable, those with a higher DD had statistically significantly less allergic sensitization to aeroallergens in the total population and in children with early skin symptoms. 0.88 (-0.80-0.95) When food item diversity was used as an exposure variable instead of food group diversity, similar associations for allergic sensitization to aeroallergens were observed. Highest quartile 0.82 (0.52-0.98); Continuous variable 0.99 (0.97-1.00)	Confounders: Confounders adjusted for: atopic eczema Limitations: Information on frequency and amount of food intake not available. Reverse causality could not completely be ruled out DD score used not validated

(Continues)

TABLE 2 (Continued)

Study and country	Definition and assessment of diet diversity	Results	Comments
Nwaru et al (2013) ⁷⁹ Finnish Type 1 Diabetes Prediction and Prevention study Prospective Cohort Study Finland Sample Size: Baseline N: 4074 Analytic N: 3781 Attrition: 93% Sex: 1646 boys (52%), 1496 (48%) girls Race/Ethnicity: not mentioned Atopic Disease Risk Status: 16% and 62% of parents had asthma and rhinitis respectively	Intervention/Exposure: The child's diet was assessed by using age-specific dietary questionnaires at ages 3, 4, 6 and 12 mo and a follow-up "age at introduction of new foods" form for recording the age at introduction of complementary foods. Looked at the number of complementary foods introduced at 3, 4 and 6 mo of age. 4 categories of food diversity at each time point were defined based on the distribution of the data at each time point: at 3 mo, these were "no food item," "1-2 food items," and ">2 food items"; at 4 mo, these were "no food item," "1-2 food items," "3-4 food items," and ">4 food items"; at 6 mo, these were "0-4 food items," "5-6 food items," "7-8 food items," and ">8 food items". Food groups used as DD definition: cow's milk and formula (as a combined variable); potatoes; carrots; turnip; fruits and berries (as a combined variable); cereals (rye, wheat, oats and barley as a combined variable); other cereals (maize, rice, millet and buckwheat as a combined variable); meat; fish; egg; cabbage; spinach; and lettuce. Assessment Methods: Prospective Parent questionnaires Assessment of DD age: birth to 12 mo of age	Sensitization to the following food and aeroallergens were analysed at the age of 5 y: egg, cow's milk, fish, wheat, house dust mite, cat, timothy grass and birch. These out- comes were based on analysis of IgE concentration using ImmunoCAP fluoroenzyme immunoassay. Atopic sensitiza- tion was defined as IgE $\geq$ 0.35 kU/L. Less DD as early as 3 mo was associated with an increased risk of allergic sensitization at 5 y. The associations were stronger with DD at 4 and 6 mo and more prominent in at- risk children compared to no-high-risk children. Less DD as early as 3 mo was associated with an increased risk of allergic sensitization at 5 y. Food Allergen sensitization ⁷⁹ : No food at 3 mo vs > 3 foods 1.39 (1.07-1.81); 1-2 foods at 3 mo vs > 3 foods 1.36 (1.06-1.74) P value .021	Confounders: Confounders adjusted for: sex of the child, number of siblings, parental asthma, parental rhinitis, delivery hospital and maternal smoking during pregnancy. Limitations: The study recruited children carrying genetic risk (HLA-conferred susceptibility) for type 1 diabetes. Therefore, may reduce generalizability of findings to general population The number of statistical tests performed could mean that the type 1 error rate might not be at the 0.05 level. DD definition was not validated and could be improved with increasing the variety

TABLE 3 The association between diet diversity and food allergy

Study and country	Definition and assessment of diet diversity	Results	Comments
Roduit C et al JACI 2014 ¹⁶ Prospective birth cohort study Protection Against Allergy Study in Rural Environments (PASTURE/EFRAIM). Stratified in farm and nonfarm children See—food sensitization	See—food sensitization	Food allergy: parental report of ever doctor-diagnosed food allergy up to 6 y of life (overall proportion: 7.4%). Food diversity score (0–6 items): 0–3: FA 21.9% 4–5: FA 9.2% 6: FA 5.7% Food diversity score (0–6 items): 0–3: food sens. 26.9% 4–5: food sens. 13.1% 6: food sens. 8.5% Increased diet diversity in the 1st year of life: reduced risk of reported doctor-diagnosed food allergy up to 6 y (adjusted OR for each additional food items: 0.70, 95%CI: 0.57–0.86) and food sensitization at 4.5/6 y (adjusted OR for each additional food items: 0.72, 95%CI: 0.57–0.90)	Outcome assessment mainly based on parental reports of doctor-diagnosis. Adjustment for the potential confounders was performed: farmer, centre, duration of breastfeeding, parents with allergy, maternal education, sex and number of siblings. Reverse causality was taken into account to some extent, that is—analysis with exclusion of children with FA within the 1st year of life analysis with exclusion of children with AD within the 1st year of age. However did not account for lactose/food intolerances as lack of information and also lack of information on subclinical manifestations of food allergy (colic, gastroesophageal reflux etc)

interestingly not at four years.⁸⁰ Why this statistical anomaly was seen is not clear, and diversity before four months might be highly influenced by breast/formula feeding practices. Conversely, the delayed introduction of solids and reduced diversity beyond 6 months of age was not beneficial for allergy prevention. Prior to the pooling of the GINIplus and LISAPlus studies, the LISAPlus study reported an increased risk of AD at the age of 2 years associated with less diet diversity at four months of age, but they found no association between diet diversity at four months of life and AD at six years.^{81,82} Data from the 15-year follow-up of the LISAPlus birth cohort indicated that children in the highest quartile of diet diversity who were introduced to all 8 food groups during the first year of life had lower odds of developing eczema up to age 15 years when compared with children in the lowest quartile.⁷⁸

A birth cohort from New Zealand found that a more diverse diet during the first 4 months of life was associated with an increased risk of developing AD both at 2 and 3 years and an increased risk of recurrent AD at the age of 10 years.^{83–86} In this study, diet diversity was defined as the sum of six food groups (cereals, vegetables, dairy products, meat, fruits, and egg or related products). The Finnish birth cohort showed that lower diet diversity at six months was associated with an increased risk of AD at 5 years and a same tendency was observed with the diet diversity at 12 months of age.⁸⁷ In the European PASTURE study, an increased diet diversity within the 1st year of life was associated with a reduced risk of developing AD through 4 years of age (even after excluding children with AD onset within 1st year of life).⁸⁸ This finding was supported by the outcomes from the matched case-control study from Italy, in which the authors reported that more diverse diet at 4 and 5 months was associated with a reduced risk of AD by 2 years of age.⁸⁹

2.4.4 | Diet diversity and asthma and allergic rhinitis

Data investigating these relationships were limited to two large European prospective birth cohorts (Table 5), the PASTURE study¹⁶ and the Finnish Type I Diabetes Prediction and Prevention Study Prospective Cohort Study.⁸⁷ While these cohorts were recruited for different purposes, similar assessment of diet diversity was recorded during the first year of life, as a variable to help predict allergic outcomes at either ages 5 (Finnish Type I Diabetes Prediction and Prevention Study) or 6 (PASTURE). In the PASTURE cohort, Roduit et al¹⁶ noted that increasing diet diversity in first year of life was associated with a linear protective trend against the development of reported asthma, resulting in a 26% reduction for the introduction of each successive food. However, no protective association was noted for allergic rhinitis or inhalant sensitization. In the Finnish Type I Diabetes Prediction and Prevention Study, Nwaru et al⁸⁷ noted less diversity at 12 months of life was associated with a greater risk of development of any form of asthma at age 5 for 0–7 foods incorporated in the diet and for 8–9 foods incorporated into the diet compared to > 11 foods ($P < .001$), as well as increased risk for any wheeze for 0–7 foods vs. > 11 foods ($P = .004$). For allergic rhinitis, lower diet diversity at both 6 and 12 mo of life was significantly associated with later risk of developing allergic rhinitis. At 6 months, the risk of developing allergic rhinitis was significantly greater with incorporation of 0–4 foods and 5–6 foods vs. > 8 foods ($P = .02$). Similarly, at 12 months the risk was significantly higher with incorporation of 0–7 foods and 8–9 foods vs. > 11 foods ($P < .001$) (see Table 6 for a summary of all allergy outcomes).

TABLE 4 The association between diet diversity and atopic dermatitis

Study and country	Definition and assessment of diet diversity	Results	Comments
Zutavern A et al <i>Pediatrics</i> (2006) ⁸¹	Solids diversity was defined by the total number of different food groups (48 single food items were asked in a questionnaire) and classified in 8 groups of solid food: vegetables, cereal, fruit, meat, dairy products, egg, fish and others (like soybean, nuts, cacao, chocolate) introduced in the child's diet at 4 and 6 mo of age	Assessment of AD: parental reports on doctor-diagnosis and symptoms of AD, questionnaires at birth, 0.5, 1, 1.5, 2, 4 and 6 years	Families with higher educational background and high proportion of atopic parents were included.
Zutavern A et al <i>Pediatrics</i> (2008) ⁸²	Assessment method: parental interview on infant's diet at 6 mo and parental interview on infant's diet at 12 mo	Introduction of a high number of different solid foods by 6 mo of age reduced the risk for doctor-diagnosed AD up to 2 y in all children (aOR 5-8 food groups versus no solid food: 0.66, 95%CI: 0.46-0.94) and also in the children having early skin or allergic symptoms	Reverse causality was taken into account: separate analysis with AD children with and without early skin symptoms
Germany LISA study N = 2612 up to 2 years		Increased diet diversity within first 6 mo: reduced risk of AD at 2 y (no significant association with DD at 4 mo and AD)	Confounding factors due to the children included in the analysis; recall bias due to retrospective information regarding introduction of solids—misclassification of feeding history possible; Information on eczema from questionnaire
LISA study N = 2073 up to 6 y		No association between diet diversity at 4 mo and AD at 6 y, for all population. Exclusion of children with early skin or allergic symptoms: increased DD was associated with an increased risk of doctor-diagnosis of AD, but not symptoms of AD at 6 y	
Filipiak B et al <i>J Pediatrics</i> (2007) ¹⁵⁵	Solids diversity was defined by the total number of different food groups (48 single food items were asked in a questionnaire) and classified in 8 groups of solid food (vegetables, cereal, fruit meat, dairy products egg, fish, others like soybean, nuts, cacao, chocolate) introduced in the child's diet at 4 and 6 mo of age	Assessment of AD: parental reports on doctor-diagnosis and symptoms of AD, yearly up to 4 y	Selection bias due to loss of follow-up (nonintervention subgroup 25%, intervention subgroup 14%); Misclassification due to recall bias (exposure was assessed retrospectively at 1 y of age)
Germany GINI study N = 4753	Assessment method: parental interview on infant's diet at 12 mo	No association between doctor-diagnosed or symptomatic AD and time point of solid food introduction and diversity of solids	
		Intervention group: family history of allergy, prospectively and randomly assigned to either hydrolysed formula or cow's milk formula; Nonintervention group: no family history of allergy or parents did not wish to participate in intervention trial	
		No association between diet diversity at 4 or 6 mo and AD up to 4 y	
Sausenthaler S et al <i>Am J Clin Nutr</i> (2011) ⁸⁰	Solids diversity was defined by the total number of different food groups (48 single food items were asked in a questionnaire) and classified in 8 groups of solid food (vegetables, cereal, fruit meat, dairy products egg, fish, others like soya bean, nuts, cacao, chocolate) introduced in the child's diet at 4 and 6 mo of age; high diversity of solid foods: 3-8 groups	Assessment of AD: LISA study: parental reports on doctor-diagnosis and symptoms of AD, up to 4 y in GINI study and up to 6 y in LISA study	Reverse causation was not controlled for as in the GINIplus study early symptoms of eczema was not assessed; results on association between high diversity of solids in infants within the first 4 mo and increased risk of eczema was not consistent throughout different outcome measures and different time points
Germany GINIplus and LISA plus study N = 9088	Assessment method: parental report	No association between diversity of solid foods at the age of 4 mo and 6 mo and doctor-diagnosed AD during first 4 y of life. At 6 y of age significant association between AD and high diversity of solid foods. Symptomatic eczema at 2 y of age was associated with high diversity of diet at 4 mo → conclusion: early introduction of solid foods and high diversity before 17 wk of age may increase allergy risk. Increased diet diversity at 4 mo: associated with increased risk of symptoms of AD at 2 y and doctor-diagnosed AD at 6 y, but not at 4 y	

(Continues)

TABLE 4 (Continued)

Study and country	Definition and assessment of diet diversity	Results	Comments
Markevych et al (2017)⁷⁸ Population-based German birth cohort LISAPlus (Influences of Lifestyle related Factors on the Immune System and the Development of Allergies in Childhood) Sample Size: Baseline N: 3097 Analytic N: 2518 Attrition: 81% Sex: See original LISAPlus study Race/Ethnicity: See original LISAPlus study Atopic Disease Risk Status: 57.2% had atopic family history	Intervention/Exposure: Impact of DD within the first 6 mo of life on 5 allergic outcomes: doctor-diagnosed eczema, asthma and allergic rhinitis and sensitization to aeroallergens and food allergens. Assessment Methods: Self-administered biannual parental questionnaires on the children's health and on lifestyle factors from birth to 2 y and at 4 y and 6 y. Blood samples for specific IgE at 2 and 6 y, levels > 0.35 KU/L were defined as sensitization. At 12 mo of age, parents were asked about breastfeeding practices and about the timing of solid food introduction. Possible answer choices included: "1st until 4th month," "5th/6th month," "7th to 12th month," and "solid food item not yet introduced." Forty-eight food items were grouped into 8 food groups: (1) vegetables (avocado, cauliflower, beans, broccoli, peas, cucumbers, carrots, potatoes, white cabbage, turnip, cabbage, lentils, celery, asparagus, spinach, tomatoes, onion, vegetable juices); (2) fruit (apples, pineapples, apricots, bananas, pears, strawberries, peaches, citrus fruit, fruit juices); (3) cereal (bread/pretzels/rolls, cookies/cakes/rusk, rolled oats, muesli, millet, cornmeal/corn starch, wheat semolina/starch, noodles, rice/rice starch, spelt); (4) meat (poultry, lamb, veal/beef, pork, sausages); (5) egg; (6) dairy products (cow milk/cream, yoghurt/quark/cheese); (7) fish; and (8) other (nuts, soy products, cocoa/ chocolate). Assessment of DD age: DD at 6 mo and 12 mo of age	Allergic outcomes at 2 and 6 and 15 y of life Assessment Methods: Several definitions of DD (food group and food item diversity, each treated in quartiles and continuously) during the first year of life. All analyses were stratified by the presence of a wide range of early skin symptoms to test the impact of reverse causality. Allergic outcomes were assessed at 6, 12 and 18 mo and age 2, 4, 6, 10 and 15 y. Results Children in the highest quartile who were introduced to all 8 food groups during the first year of life had lower odds of developing eczema up to age 15 y compared with children in the lowest quartile with a maximum of 5 food groups. When food group diversity was treated as a continuous variable, those with a higher DD had statistically significantly less eczema	Confounders: Confounders adjusted for: atopic eczema Limitations: Information on frequency and amount of food intake not available. Reverse causality could not completely be ruled out DD score used not validated
Turati F et al <i>Allergy</i> (2016)⁸⁹ Italy Matched case-control study on incident physician-diagnosed AD (451 cases and 451 controls)	The total number of food items included in the infant's diet at 4 and 5 mo of age; no solids, 1-2 foods, 3-22 foods Assessment method: face to face questionnaire	Diagnosis of AD by dermatologist, at the age of 3-24 mo Weaning at age 4-5 mo was inversely associated with AD risk. Introduction of a high number of different solid foods at 4 and 5 mo was associated with a reduced risk of AD (OR: 0.30, 95% CI: 0.11-0.81 $\geq$ 3 foods vs 0 foods at 4 mo; OR: 0.44, 95% CI: 0.21-0.91 $\geq$ 8 foods vs 0 foods at 5 mo)	Maternal recall bias, reverse causation by prolonged exclusive breastfeeding due to mothers considering children at risk for allergies; lack of information on maternal diet during pregnancy and lactation.

(Continues)

TABLE 4 (Continued)

Study and country	Definition and assessment of diet diversity	Results	Comments
Nwaru et al (2014) ⁸⁷ Finnish Type 1 Diabetes Prediction and Prevention study Prospective Cohort Study Finland Sample Size: Baseline N: 4074 Analytic N: 3781 Attrition: 93% Sex: 1646 boys (52%), 1496 (48%) girls Race/Ethnicity: not mentioned Atopic Disease Risk Status: 16% and 62% of parents had asthma and rhinitis respectively	Intervention/Exposure: The child's diet was assessed by using age-specific dietary questionnaires at ages 3, 4, 6 and 12 mo and a follow-up "age at introduction of new foods" form for recording the age at introduction of complemen- tary foods. Looked at: the number of complementary foods in- troduced at 3, 4, 6 and 12 mo of age. 4 categories of food diversity at each time point were defined based on the distribution of the data at each time point: at 3 mo, these were "no food item," "1-2 food items," and ">2 food items"; at 4 mo, these were "no food item," "1-2 food items," "3-4 food items," and ">4 food items"; at 6 mo, these were "0-4 food items," "5-6 food items," "7-8 food items," and ">8 food items"; at 12 mo, these were "0-7 food items," "8-9 food items," "10-11 food items," and ">11 food items" Food groups used as DD definition: cow's milk and formula (as a combined variable); potatoes; carrots; turnip; fruits and berries (as a combined variable); ce- reals (rye, wheat, oats and barley as a combined vari- able); other cereals (maize, rice, millet and buckwheat as a combined variable); meat; fish; egg; cabbage; spinach; and lettuce. Assessment Methods: Prospective Parent questionnaires Assessment of DD age: birth to 12 mo of age	Asthma, wheeze, atopic eczema and allergic rhinitis were analysed. AD: parental reports of doctor-diagnosis ever up to 5 y. International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire for assessment of allergy symptoms No association between diet diversity at the age of 3, 4 mo and AD up to 5 y. Reduced diet diversity at 6 mo: increased risk of AD up to 5 y (OR and 95% CI: 0-4 food items vs > 8 items: 1.39, 0.88-2.19; 5-6 items vs > 8 items: 1.32, 0.96-1.81; 7-8 items vs > 8 items: 1.38, 1.11-1.71)	Confounders: Confounders adjusted for: sex of the child, number of siblings, parental asthma, parental rhinitis, delivery hospital and maternal smoking dur- ing pregnancy. Limitations: The study recruited children carrying genetic risk (HLA-conferred susceptibility) for type 1 diabetes. Therefore, may reduce general- izability of findings to general population The number of statistical tests performed could mean that the type 1 error rate might not be at the 0.05 level. DD definition was not validated and could be improved with increasing the variety
Roduit C et al JACI (2012) ⁸⁸ Prospective birth cohort study Protection Against Allergy Study in Rural Environments (PASTURE/ EFRAIM). Stratified in farm and non- farm children Sample Size: Baseline N: 1133 Analytic N: 1041	Diversity of diet in 1st year of life: summing the number of different types of solid food, which were introduced within the 1st year of life -> 2 scores were measured: 1. Diversity score (score 0-6) including food items, which were introduced among about 80% of the children, in total 6 groups: vegetables/fruits, cere- als, bread, meat, cake and yogurt. Score used as a continuous variable and a categorized variable (0-3, 4-5, 6 food groups) 2. Diversity score (score 0-15), including all food items: any cow's milk, yogurt, other milk products, eggs, nuts, vegetables or fruits, cereals, bread, meat, fish, soy, margarine, butter, cake and chocolate	AD: parental report of doctor-diagnosis up to 4 y and/or posi- tive SCORAD score during medical examination at the age of 1y (total: 27.1% with AD up to 4 y). Increased diet diversity within 1st year of life: reduced risk of AD up to 4 y of age (exclusion children with onset within 1st year of life) (for each additional food introduced in 1st year, reduction of 25% of AD) (aOR for each additional food item: 0.75, 95% CI 0.62-0.91)	Outcome assessment mainly based on pa- rental reports of doctor-diagnosis. To take into account reverse causality: analysis with exclusion of children with AD within the 1st year of age

(Continues)

TABLE 4 (Continued)

Study and country	Definition and assessment of diet diversity	Results	Comments
Fergusson et al (1981) ⁸³ New Zealand Baseline N: 1265 Analytic N: 1156 Atopic Disease Risk Status: 24% parental history of atopy Background Diet: 19% exclusively breastfed at 4 mo	Diet diversity assess at 4 mo: Food groups used as DD definition: cereals, vegetables, dairy products, meat, fruits, egg or related products, other solid foods Food groups categorized as: 0, 1-2, 3-4, 5+ Assessment methods: Parent interview and food diary	Atopic Dermatitis assessed at 2 y. Assessment Methods: Maternal report; some with physician follow-up Increased diet diversity at 4 mo was associated with increased eczema at 2 y (0 food groups: 13%; 1-2 food groups: 17%; 3-4 food groups: 17%; 5+ food groups: 33%; $P < .05$) Increased diet diversity at 4 mo was associated with an increased risk for AD at 2 y	Adjusted for: Parental history of allergic disease Limitations: No info on similarity of groups at baseline. No blinded/validated assessments of outcome. Key confounders not taken into account (education, SES, sex, race/ethnicity, feeding practices, birth size, gestational age, smoking, pets) Timing of DD assessment (most children don't eat by 4 mo)
Fergusson et al <i>J Epidemiol Community Health</i> (1982) ⁸⁴ New Zealand Birth cohort of New Zealand N = 1143	Diet diversity assess at 4 mo: DD definition: sum of food groups (cereals, vegetables, dairy products, meat, fruits, egg or related products), which the child had been given during the first 4 mo. Categorized as follows: 0, 1-3, 4+ food groups Assessment method: Parent interview and food diary	Atopic Dermatitis: maternal report or directly from the child's doctor information on doctor-diagnosis of AD, up to 3 y Increased diet diversity within the first 4 mo of age: increased risk of AD up to 3 y (proportion of AD by numbers of solid food: 0:18.4%; 1-3:20.6%; 4+: 24.3%)	Adjusted for parental AD and/or asthma, infant milk diet. Analyses stratified depending on infant milk diet (breastfeeding, bottle only or both)
Fergusson D et al <i>Pediatrics</i> (1990) ⁸⁵ New Zealand Birth cohort of New Zealand N = 1067	Diet diversity assess at 4 mo: DD definition: sum of food groups (cereals, vegetables, dairy products, meat, fruits, egg or related products), which the child had been given during the first 4 mo. Categorized as follows: 0, 1-3, 4+ food groups Assessment method: Parent interview and food diary	Atopic Dermatitis: maternal report on doctor-diagnosis of AD, up to 10 y of age (31% at least once report of medical attendance for AD). Definition of a subgroup with recurrent or chronic AD (at least 3 medical visit for AD, condition has lasted at least 3 consecutive years and regular treatment for AD) (7.5%) Increased diet diversity within the first 4 mo of age: increased risk of recurrent/chronic AD up to 10 y (2.9 times increased risk: 4+ food groups versus no foods)	Adjusted for age at onset of AD, parental and siblings history of allergy, SES, maternal education, age of mother, ethnic status, breastfeeding
Fergusson D et al <i>PAI</i> (1994) ⁸⁶ New Zealand Birth cohort of New Zealand N = 1141 (data on AD up to 2 y) N = 1067	Diet diversity assess at 4 mo: DD definition: sum of food groups (cereals, vegetables, dairy products, meat, fruits, egg or related products), which the child had been given during the first 4 mo. Categorized as follows: 0, 1-3, 4+ food groups	Atopic Dermatitis: maternal report or directly from the child's doctor information on doctor-diagnosis of AD, up to 2 and 10 y of age Increased diet diversity within the first 4 mo of age: increased risk of AD up to 2 y (1.6 times increased risk: 4+ food groups versus no foods), increased risk of recurrent/chronic AD up to 10 y (2.5 times increased risk: 4+ food groups versus no foods)	Analyses adjusted for child's milk diet (breastfeeding vs bottle), parental history of AD or asthma, maternal education

2.4.5 | Food patterns during infancy and allergy outcomes in the infant

In children, all studies focused on *current* intake vs. allergy outcomes, which does not give an indication of early intake (infancy) vs. later (childhood) outcomes. These studies therefore are not designed to inform us regarding the role of the Mediterranean diet as a proxy measure of diet quality in infancy on allergy outcomes in childhood. Nonetheless, an overview is provided of the Mediterranean diet pattern in childhood and its influence on current allergy outcomes. The majority of childhood studies have used either the KIDMED Mediterranean score^{68,90-95} or the adult EPIC score.^{69,96-99} While the KIDMED index reflects what is commonly interpreted as a "healthy and diverse" diet, many Mediterranean diet studies use an index which was developed in a time when saturated fatty acids were believed to increase the risk of cardiovascular disease. Thus, dietary intake is categorized into "pro-Mediterranean diet" (fruit, vegetables, fish, cereals, pasta, rice and potatoes) and "anti-Mediterranean diet" (milk, meat, fast foods). There is, however, growing evidence that the "pro-" and "con-" assignment is not only out of date, but that it is not evidence-based, and some of the "anti-Mediterranean diet" foods were actually found to decrease the risk of wheeze/asthma (eg meat^{66,91,100,101} and milk^{67,97,101}).

2.4.6 | Mediterranean diet in infancy and childhood

While this is an important relationship to understand, no studies have been identified exploring an association between the Mediterranean diet in infancy and allergy outcomes. Four systematic reviews focussing on nutrients and foods associated with asthma and allergy outcomes investigated the impact of the Mediterranean diet in childhood¹⁰¹⁻¹⁰⁴ and found an inverse relationship between eating according to the Mediterranean diet and a range of reported symptoms such as wheeze and asthma. Papamichael et al¹⁰³ summarized twelve studies reporting an inverse association between adherence to a Mediterranean dietary pattern and asthma in children. Nurmatov et al¹⁰² reported that adherence to a Mediterranean diet was protective for persistent wheeze (OR, 0.22; 95% CI, 0.08-0.58) and atopy (OR, 0.55; 95% CI, 0.31-0.97). Garcia-Marcos et al¹⁰¹ found a significant negative association between the highest tertile of Mediterranean diet score (OR 0.85, 95% CI 0.75-0.98; $P = .02$) and "current wheeze." Lv et al¹⁰⁴ concluded that the Mediterranean diet in children may be associated with prevention of asthma or wheeze, but that randomized controlled trials are required.

Ten original papers were also identified (Table S5) from cross-sectional studies,^{66,68,90-92,95,97,98,105,106} three papers from two (birth) cohorts from Mediterranean regions^{68,94,107}; five cross-sectional studies from non-Mediterranean regions^{69,99,108-110} and one paper on using the International Study on Asthma and Allergy in Children (ISAAC) data from 29 centres in 20 countries.¹⁰⁰ These publications focused on a range of allergy outcomes: most of the studies investigated the impact of the Mediterranean diet on risk of wheeze/asthmatic symptoms,^{68,69,90-96,99-101,106-108,110} sometimes including the development

of other allergic outcomes. Only a few studies focussed on atopic dermatitis,⁹⁷ and allergic rhinitis.^{94,98,105} However, as with the maternal studies, none of the studies focused on food allergy as an outcome.

The majority of studies used FFQs completed by parents^{69,90,93,95,97} and semi-quantitative questionnaires^{68,91,94,98,99} to calculate either the KIDMED index⁹⁰⁻⁹⁵ or another index to assess adherence to a Mediterranean diet.¹⁰⁶ The analysis of the ISAAC study¹⁰⁰ assessed adherence to a Mediterranean type diet using their own food categorization. Selected food items with either positive (+) or negative scoring (-) included were meat (-), fish (+), fresh fruit (+), raw green vegs (+), cooked green vegs (+), burgers (-), fruit juice (+) and fizzy drinks (-).

Adherence to the Mediterranean diet was primarily evaluated by using two different indices. While the KIDMED index, used in six studies,⁹⁰⁻⁹⁵ reflects what is commonly interpreted as a "healthy and diverse" diet, the other Mediterranean diet studies used the EPIC index^{69,96-99} (developed by Psaltopoulou/Trichopoulou^{61,111}). The EPIC score allowed a total of 10 points from incorporation of the following foods into the diet: vegetables, legumes, fruit, dairy products, cereals, meat and meat products, fish and seafood, olive oil, monounsaturated: saturated lipids, and alcohol intake.

Summarizing the available data on the association between the Mediterranean diet and childhood allergy outcomes is difficult, primarily due to different definitions of the Mediterranean diet and allergy outcomes assessed. Some studies showed a small but positive effect on current severe asthma in girls¹⁰⁵ and a protective effect on asthma/wheeze.^{69,96,100,110} Alternatively, some studies showed no protective effect on asthma and/or rhinitis symptoms^{98,99,108,109} or atopic dermatitis.⁹⁷ None of the studies reported on food allergy as an outcome.

2.4.7 | Other dietary patterns in infants and childhood allergy outcomes

Dietary patterns other than the Mediterranean diet were also studied in children. Three birth cohorts were identified,¹¹²⁻¹¹⁵ two cross-sectional in design^{116,117} and three papers on a case-control study within a cohort.^{114,118,119} Some of the identified publications on the Mediterranean diet also studied other dietary patterns.^{91-94,97-99} Dietary intake was assessed using FFQs,^{73,116,117} 24 hour recalls,¹¹³ semi-quantitative questionnaires¹¹² and prospective food diaries.^{114,118,119} (Table S5).

Two studies showed that food intake relating to a Western dietary pattern was associated with an increased prevalence of wheeze/asthma.^{116,117} A study from Singapore identified the pattern "noodles and seafood" as protective against the development of allergen sensation in Asian infants in the second half of the first year of life.¹¹⁵ Grimshaw et al^{114,118,119} found that a diet pattern obtained from principal component analysis on prospective food diary data described as "predominantly home cooked" (fruit, vegetable, fish and poultry consumption) in UK infants was associated with a reduced prevalence of food allergy. In contrast to other studies, analysis of the dietary data of the Dutch Generation R cohort did not find that a

TABLE 5 The association between diet diversity and asthma/allergic rhinitis

Roduit et al (2014) ¹⁶ Protection Against Allergy Study in Rural Environments (PASTURE/EFRAIM) Prospective Cohort Study Austria, Finland, France, Germany, Switzerland Sample Size: Baseline N: 1133 Analytic N: 848 (asthma) 806 (rhinitis) Attrition: 25% asthma 29% rhinitis Sample Size Calculation: NR Sex: 49.5% female Race/Ethnicity: NR Atopic Disease Risk Status: 53.6% parental history of atopy Background Diet: 47.4% nonexclusively breastfed at least 6 mo	Asthma/Allergic Rhinitis assessed at 6 y Assessment Methods: Questionnaires were administered in interviews or self-administered to the mothers within the third trimester of pregnancy and when the children were 2,12, 18 and 24 mo of age and then yearly up to age 6 y. Findings: <i>Asthma</i> : Increased diet diversity in first year of life was associated with linear trend in protection against development of reported asthma, 26% reduction for the introduction of each successive food. <i>Allergic Rhinitis</i> : No significant relationship noted between diversity and the development of allergic rhinitis (linear trend $P = .31$, $P = .29$ for inhalant sensitization)	Confounders: Confounders adjusted for: Centre, living on a farm, atopic Fhx, breastfeeding, gender, siblings, maternal education Limitations: Use of reported doctor-diagnosis and possible lack of assessment for resolved transient childhood wheezing Use of asthma medications was not part of the asthma definition While analysis was adjusted for confounders, were these the optimal ones to choose Use of 1-month recall period in assessing new food introduction
Intervention/Exposure: See table—Food Allergy		

healthy dietary pattern in early life is associated with a lower risk of allergic sensitization or atopic diseases in childhood.¹¹²

2.4.8 | Key measurement issues to address when designing studies assessing the association between diet diversity and allergy outcomes

Research into diet diversity should have three particular prerequisites; (1) The method used needs to be specific to the outcome which may include nutritional intake, growth or health outcomes; (2) The diet diversity tool needs to be able to measure food security and socio-economic status.^{120,121} This needs further clarification

as well as careful statistical guidance to disentangle the impact of socio-economic status vs. diet diversity on outcomes; and (3) Consideration should be given to healthy diet diversity vs. unhealthy diet diversity when studying disease outcomes to inform diet recommendations. Researchers must consider that diversity in diets is also strongly related to local and ethnic traditions, with regional environmental exposures leading to unmeasured/unmeasurable characteristics which could potentially impact on short-, medium- and long-term outcomes. These considerations will apply to the most studied model of diet intake, that is, the Mediterranean diet, which partly explains some “caveats” within previous paragraphs.

Allergy outcome	Increased risk with higher DD	Reduced risk with higher DD	No effect
Sensitization		+ (4.5 y) [food] ¹⁶ + (6 y) [food] ¹⁶ + (up to 15 yrs) [aero-allergens] ⁷⁸ + (year 5) ⁷⁹	+ (4.5 y) [inhalant] ¹⁶ + (6 y) [inhalant] ¹⁶
Food Allergy		+ (up to 6 y) ¹⁶	
Atopic Dermatitis	+ (2 y) ⁸⁰ + (6 y) ⁸⁰ + (2 y) ⁸³ + (3 y) ⁸⁴ + (10 y) ^{85,86,155}	+ (2 y) ^{81,82} + (1 y) ⁸⁷ + (5 y) ⁸⁷ + (4 y) ⁸⁸ + (2 y) ⁸⁹	+ (4 y) ⁸⁰ + (6 y) ^{81,82}
Asthma/Wheeze		+ (6 y) ¹⁶ + (5 y) ⁸⁷	
Rhinitis		+ (5 y) ⁸⁷	+ (6 y) ¹⁶

TABLE 6 Summary of diet diversity on Allergy Outcomes

TABLE 7 Modified delphi panel regarding diet diversity statements

Statement	Per cent Agreement between those who voted			Comments
	Agree	Disagree	who voted	
1. Diet diversity scores should be weighted depending on the types of food being measured (eg a diverse fast-food diet is not equal to a diverse fruit and vegetable diet).	23	1	95.8%	
2. Diversity of intake of specific foods, for example range of fruits eaten, different types of cheese consumed, different types of home-cooked or processed foods cannot be used to describe diet diversity but the term diversity of fruit intake, diversity of cheese intake, or diversity of processed food intake can be used. These foods can however be included in combination with other foods to determine overall diet diversity.	22	2	91.67%	1. I would suggest separating the first sentence for clarity. Anyhow, I agree with this statement. 2. The diversity of fruits and vegetables is important to quantify and acknowledge in the overall definition of diet diversity, the diversity of types of cheese and other food groups is less so. 3. Need a better explanation.
3. Diversity of intake of foods containing specific nutrients or ingredients, for example foods containing advanced glycation end products or foods containing omega-3 fatty acids cannot be used to describe diet diversity but the terms diversity of advanced glycation end products intake or diversity of food containing omega-3 fatty acid intake can be used. These foods can however be included in combination with other foods to determine overall diet diversity. Following comments we have changed the wording to: In these instances, diversity may have a positive (fruit and vegetables) or a negative) (advanced glycation end products) connotation. This list may continue to grow as we gain more knowledge about foods/nutrients with immunomodulatory potential, for example bovine trans fatty acids which are isomers of linoleic acid.	21	3	87.5%	1. We do not have any data to suggest that diversity of high AGE foods has a positive effect on dietary diversity. 2. There is a need for high level of knowledge and intellectual capacity to appropriately understand and answer this question. I do not think there is many people who can talk about diversity of advanced glycation end products.
4. For allergy (asthma, food allergy, eczema, rhinitis, allergen sensitivity), there is the opportunity to measure food microbial diversity which relates to the microbial content of foods. Following comments we have changed the wording to: There is the opportunity to measure food microbial diversity which relates to the microbial content of foods.	20	3	87%	The formulation of the question is unclear as to what is the relation to "For allergy" (to determine the sensitization capacity of the food? To use the food as microbiome-modulating agent? To treat allergy with microbes on the food?) It is unclear what "For allergy" means here. Also, the whole question is unclear. Is it technically possible, but not very feasible at the point of care. Is it a general question what we should recommend to pursue more in the future? I would assume that this can be extended to other food related clinical entities, not only allergies.
5. For allergy (asthma, food allergy, eczema, rhinitis, allergen sensitivity), there is the opportunity to measure food biodiversity which relates to the taxonomic classification of food intake, for example classifying tomatoes as Solanum (genus) opposed to vegetables. Following comments we have changed the wording to: There is the opportunity to measure food biodiversity which relates to the taxonomic classification of food intake, for example classifying tomatoes as Solanum (genus) opposed to vegetables.	21	1	95.5%	1. This is still a magic area surrounded by echo chambers even among experts. 2. Solanum—Wow—you picked a good one here. Tomatoes are a fruit, and other members of the genus include potato—vegetable and aubergine—fruit. I believe that in the US data potato (fries) and tomato (sauce) account for about 40% of fruit and vegetable intake in children. 3. why would this be only true for allergy? what would be the advantage over diversity of vegs? 4. It is unclear what "For allergy" means here. Please see my comment above.

(Continues)

TABLE 7 (Continued)

Statement	Per cent Agreement between those who voted			Comments
	Agree	Disagree		
6. For allergy (asthma, food allergy, eczema, rhinitis, allergen sensitivity), there is the opportunity to measure food allergen diversity which relates to the number and/or amount of food allergens introduced in a given period of time, for example the first year of life. It is important to understand that allergic food diversity may not reflect diet diversity as an emphasis on allergic food intake, may lead to an overall reduced diet diversity. Following comments we have changed the wording to: For allergy (asthma, food allergy, eczema, rhinitis, allergen sensitivity), there is the opportunity to measure allergenic food diversity which relates to the number and/or amount of food allergens introduced in a given period of time, for example the first year of life. It is important to understand that allergenic food diversity may not reflect diet diversity as an emphasis on allergenic food intake, may lead to an overall reduced diet diversity.	22	0	100%	1. This point is not clear. precisely, food allergen means are h 1, cor a 9 etc what you mean is foods which a lot of children are allergic to. there is hardly a food which cannot elicit allergic reactions. 2. Please consider also contact with food allergens other than by the oral route- this can be exposure by inhalation or via skin—so the measurement of allergen intake maybe not sufficient if control of exposure is the question.
7. It is not possible at present to define the minimum amount of allergenic protein that should be consumed in order to be sufficient within the food allergen diversity measure. Following comments we have changed the wording to: It is not possible at present to define the minimum amount of allergenic protein that should be consumed in order to be sufficient within the allergenic food diversity measure. In future, there may be an index that could described the allergenic potential of foods within the context of diet diversity better.	21	2	91.3%	1. Basically agreed, maybe in a short time we will be able to develop a sort of "index" specific by any specific protein, that, in combination with the food allergen diversity measure, could give a more precise idea of the allergenic potential of that protein with in a measure of an allergen diversity patterns. A sort of "diet allergen index" conceptually similar to the glycemic index and again similarly, with two definitions as "allergenic index" and an "allergenic load". Finally (I have a dream) this could lead to a "personalized allergenic diet" based on the individually defined numbers, on the way of the personalized diet depicted by Elinav and co. at the Weizman one doubts: has someone already described this pathway? Sufficient for allergy prevention? 2. Agree—may be a question of present/absent or the amount and frequency and timing of that. 3. I don't understand "to be sufficient within the food allergen diversity measure."
8. When possible, studies reporting data of diet diversity should include sensitivity, specificity, true and false positive/negative values to assist future meta-analyses and comparisons but should de-emphasize reporting of a cut-off value for a sample.	20	1	95.2%	1. Differentiating between sensitization and allergy would be more helpful 2. Getting this into practice will depend on cut-off values that are clinically meaningful. So, need them. Paper would though present the basic data to allow later meta-analysis. 3. Again, not very clear to me. There are two questions within one sentence. I agree with the first part. 4. But I do not understand clearly the second part. 5. Not sure how this can be done in reality during a study? 6. Sensitivity, specificity, true and false positive/negative values are values used for validation studies. it is unclear what their purpose here would be and how they can be derived.

(Continues)

TABLE 7 (Continued)

Statement	Agree	Disagree	Per cent Agreement between those who voted	Comments
9. For pregnant women we recommend a minimum recall period of 2 weekdays and 1 weekend day, measured at repeated intervals throughout pregnancy. When possible, portion sizes should be collected and reported.	20	2	90.9%	1. Agree with the need to measure dietary exposure at more than one interval & record portion sizes, but not necessarily the use a recall period of 2 week days and 1 weekend day—this rules out the use of FFQs and 24 h recalls, which may be more practical methods than a food diary method. 2. Any standard used to define the 2-week period? If mothers can recall up to several months for the child (as question 2 below), then they can also give recall of their own diet over several months. Is there any evidence that 2 wks is an acceptable period of time?
10. For infants, we recommend food recall periods within the first year of life. These recall periods may include the first four months of life, the first six months of life or the first year of life. Repeated measure of intake is recommended to improve the quality of data, rather than just consuming a particular food/food group once. When possible, portion sizes should be collected and reported. Following comments we have changed the wording to: For infants, we recommend food recall periods within the first year of life. These periods may include the first four months of life, the first six months of life or the first year of life. Repeated measure of intake is recommended to improve the quality of data, rather than just consuming a particular food/food group once. When possible, portion sizes should be collected and reported, and data should be recorded prospectively.	21	2	91.3%	1. "Vidiotape" techniques should be developed (either at an institution or at home—parents are not reliable. 2. Again, not sure how this can be provided by the participants for practical reasons. 3. How far back can parents really remember. Certainly not a year.

11. Investigators should consider ways to ensure measuring how food is prepared/cooked in their study design, and if/when possible, this should be detailed for diet diversity. Ideally foods should be defined as raw, home-cooked, processed or ultra-processed.	22	1	95.7%	1. Methodologies should be carefully defined and agreed, step by step. Caregivers (especially mothers) are extraordinarily able to mix different concentrations all these dines of preparations to get their final purpose. That infants eat somethings and/or anything whichever the source. 2 What about home-cooked foods that include some processed ingredients eg casserole containing canned chickpeas alongside other fresh vegetables. Perhaps a 4th category? 3. Water quality and milk quality are also important points to consider? 4. I agree with the first part of this statement, but not with the need for categorization. These categories are difficult as they are not mutually exclusive, a food could be processed AND home cooked (ie canned/frozen vegetables/fruit/fish used in a home cooked recipe). 5. I do not see a big difference between home cooked and processed since cooking per se is a way of processing foods.
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(Continues)

TABLE 7 (Continued)

Statement	Per cent Agreement between those who voted			Comments
	Agree	Disagree		
12. Age of introduction of solid foods, food allergens and infant formula should be clearly indicated in studies investigating the association between diet diversity and allergy outcomes. Following comments we have changed the wording to: Age of introduction of solid foods, allergenic foods and infant formula should be clearly indicated in studies investigating the association between diet diversity and allergy outcomes.	22	0	100%	1. Difficult tasks for the same reasons explained before. Parents should not perceive these surveys as a sort of "drug-us" indication. 2. Agree but the term "food allergens" should be changed as commented before.
13. Introduction of infant formula cannot be classified on its own as diet diversity but should be included in measuring diet diversity of food and food groups. Following comments we have changed the wording to: Introduction of infant formula cannot be classified on its own as diet diversity but should be included in measuring diet diversity of food and food groups. Introduction of infant formula may in fact reduce diet diversity as breastmilk potentially exposes an infant to the diversity of the maternal diet, whereas formula is uniform.	23	0	100%	1. This is difficult. Perhaps this statement needs a caveat? Using this definition, it would mean that an infant who is formula fed would be classified as having a more diverse diet than an infant who is exclusively breastfed? Breastmilk potentially exposes an infant to the diversity of the maternal diet, whereas formula is uniform.

^aThreshold for consensus was set at 18 votes in favour of the statement (75% of the 24 panel members).

2.4.9 | Delphi consensus

The EAACI task force agreed that the systematic review was unable to answer a number of key questions. Given the complexities and confusion/inconsistencies of the concept and terminology in the existing literature for diet diversity, the organizing members of this taskforce initiated methods to provide an expert consensus regarding multiple concepts, in order to provide a pathway forward for future research into diet diversity and allergic outcomes. In the absence of established clinical trials or observational research studies with agreed definitions and nomenclature, expert opinion obtained in this fashion becomes an acceptable alternative.^{28,122-124} The panel used the modified Delphi Method (written questionnaire was not used) technique to reach consensus on outstanding issues identified in these literature searches regarding diet diversity in relation to various allergic outcomes. A single-group, single-round method was chosen for developing consensus on all statements. Feedback was given on each statement. Questions were written by 4 committee members based on identified gaps in each subsection in this document and refined in an iterative manner among these individuals (CV, LM, RM, MG) until there was consensus, and then, the questions were formatted into an electronic survey software (RedCAP) and emailed to the group. Responses were gathered over a 2-week period of time, then tallied and discussed among the wider group. The tally was then either confirmed or revised based on panel member insights from the discussion. Consensus threshold was defined a priori as agreement on a given statement by 75% of the committee members. This threshold was chosen based on existing literature and agreed upon as an appropriate level by the experts. The questions, vote tally and final responses are summarized in Table 7, and the final recommendations noted in Table 1. Threshold for consensus was set at 18 votes in favour of the statement (75% of the 24 panel members).

3 | CONCLUSION

We have performed a systematic review particularly investigate the association between diet diversity and allergy outcomes in infancy and childhood. Currently, we suggest that diet diversity in infancy may be associated with reduced allergy outcomes, but additional studies are required to define more clearly the role of diet diversity and diet patterns, while clearly adjusting for appropriated confounders. There are no data on diet diversity in pregnancy and allergy outcomes in the offspring. Data on diet quality in pregnancy are not consistent, but usually indicate an inverse association with asthma/wheeze in the offspring. There are no data on diet quality in infancy, but studies in childhood, show a possible association with reduction in wheeze/asthma and perhaps used different definitions of diet diversity, and different instruments to measure diet diversity.

In line with the European Food Safety Authority (EFSA),¹²⁵ we endorse a "complementary approach to traditional monitoring

and surveillance programmes of dietary intake, which instead of focusing on compliance is designed to provide a solid basis for calculating population dietary exposure and assessing potential impact on public health. Harmonizing the total diet study methodology, focused on specifically allergy outcomes, will enhance the value of these programmes by improving the comparability at international level."

CONFLICT OF INTEREST

Dr Nwaru, Dr Maslin, Remo Frei, Dr Pali-Schöll, Dr Garn, Dr Untersmayr, Dr Lunjani, Dr Sokolowska, Dr Agache, Dr Renz, Dr Feeney, Dr Stanton, Dr Smith, Dr Roberts, Dr Ben-Abdallah, Dr Muraro, Dr Agostoni, Dr Roduit and Dr Poulsen have nothing to disclose. Dr O'Mahony reports personal fees from Alimentary Health, grants from GSK, outside the submitted work. Dr Hoffmann-Sommergruber reports other from EAACI, during the conduct of the study. Dr Meyer reports grants from Danone, personal fees from Nutricia, personal fees from Mead Johnson and personal fees from Nestle, during the conduct of the study. Dr Grimshaw reports other from Nutricia Speakers fees, other from Abbott Speakers fees, other from Mead Johnson, outside the submitted work. Dr Reese reports personal fees from Nestlé Deutschland AG, personal fees from Nutricia GmbH, personal fees from Sanomega GmbH, personal fees from DAAB e.V., personal fees from Schweizer Milchproduzenten SMP, personal fees from Bofrost GmbH, personal fees from Milchwirtschaftlicher Verein BW, personal fees from Hans Karrer GmbH, personal fees from GMF GmbH, outside the submitted work. Dr Vlieg-Boerstra reports grants from Nutricia Early Life Nutrition, during the conduct of the study; personal fees from for Marfo Food Group, Lelystad, The Netherlands (Producer of commercially prepared test materials for Oral Food Challenge tests), personal fees from Nutricia, personal fees from Mead Johnson, grants from Nutricia Research, personal fees from Thermofisher, outside the submitted work;. Dr Bischoff reports personal fees from Hexal, personal fees from Nestle, personal fees from Wild Foundation, personal fees from SymbioPharm, other from Ardeypharm, personal fees from Cemet, personal fees from Pfizer, personal fees from Janssen, personal fees from ZKES, outside the submitted work. Dr Venter reports personal fees from Danone, personal fees from Nestle, personal fees from Mead Johnson, personal fees from Abbott, personal fees from DBV technologies, personal fees from Lil Mixins, outside the submitted work. Dr Akdis reports grants from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission's Horizon's 2020 Framework Programme, Cure, other from Sanofi-Aventis_Regeneron, grants from Novartis Research Institutes, Astra Zeneca, Scibase, outside the submitted work. Dr Du Toit reports grants from MRC & Asthma UK Centre, grants from UK Dept of Health through NIHR, grants from Action Medical Research, grants from National Peanut Board, personal fees from Scientific Advisory Board member Aimmune., outside the submitted work..

Dr reports grants from MRC & Asthma UK Centre, grants from Action Medical Research, grants from National Peanut Board, personal fees from Scientific Advisory Board member Aimmune, grants from National Institute of Allergy and Infectious Diseases (USA), outside the submitted work. Dr Greenhawt has received fees from Annals of Allergy, DBV technologies, Thermo Fisher Scientific; Florida Society of Allergy and Immunology; Eastern Allergy Society; Northern California Allergy Society Medscape; California Society of Allergy and Clinical Immunology; Kentucky Allergy Society; EAACI; Canadian Society of Allergy and Clinical Immunology; Before Brands; Vindico; Clinical Mind; Hybrid Health; Symbiotix; Allergy and Asthma Network.

AUTHOR CONTRIBUTIONS

LOM, CV, CA and MG wrote the introduction and the section; CV wrote the methods and the overview section on diet diversity (Section 1) with support of MBA; KM wrote the overview section on diet quality (Section 2); BV wrote the section on maternal diet patterns/quality in pregnancy and allergy outcomes (Section 3); RM, GdT and MF wrote the section on allergy sensitization and diet diversity (Section 3); CR and BN wrote the section on food allergy and diet diversity (Section 3); EU and IP wrote the section on atopic dermatitis and diet diversity (Section 3); MG and GR wrote the section on allergic rhinitis and asthma and diet diversity (Section 3); IR wrote the section on diet patterns/quality in infancy and childhood (Section 3); CV and CAg wrote the section on key measurement issues (Section 4); MG and CV wrote the section on Delphi consensus; and LOM, CV, CAg and RM wrote the conclusion. CV, RM, MBA, LOM and MG developed and distributed the Delphi questionnaires, and MG analysed the Delphi consensus data. MG, CAg, RM, IR, PS and LOM reviewed the first draft of the paper. All authors actively reviewed and commented on the paper and Delphi questions and edited the final version of the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Venter C, Greenhawt M, Meyer RW, et al. EAACI position paper on diet diversity in pregnancy, infancy and childhood: Novel concepts and implications for studies in allergy and asthma. *Allergy*. 2019;75:497-523. <https://doi.org/10.1111/all.14051>

Supplementary file 1: Search terms

A search was performed on Medline

Section 1 and 2: Diet Diversity and Diet Quality

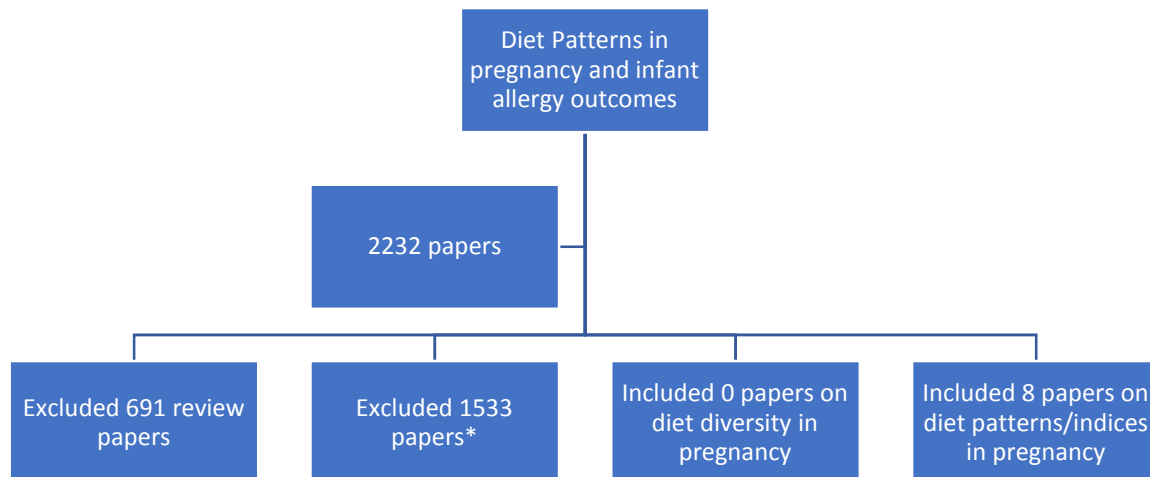
Search terms used: Diet Diversity or Food Diversity or Diet Variety or Food Variety or Diet

Quality or Food Quality and pregnant or pregnancy OR antenatal or ante-natal or ante natal OR prenatal or pre-natal or pre- natal OR mother or maternal or Exp pregnancy or infant or toddler or infancy or child or childhood OR household OR toddler

Section 3: Diet diversity and diet patterns during pregnancy and allergy outcomes in the infant

Search terms used:

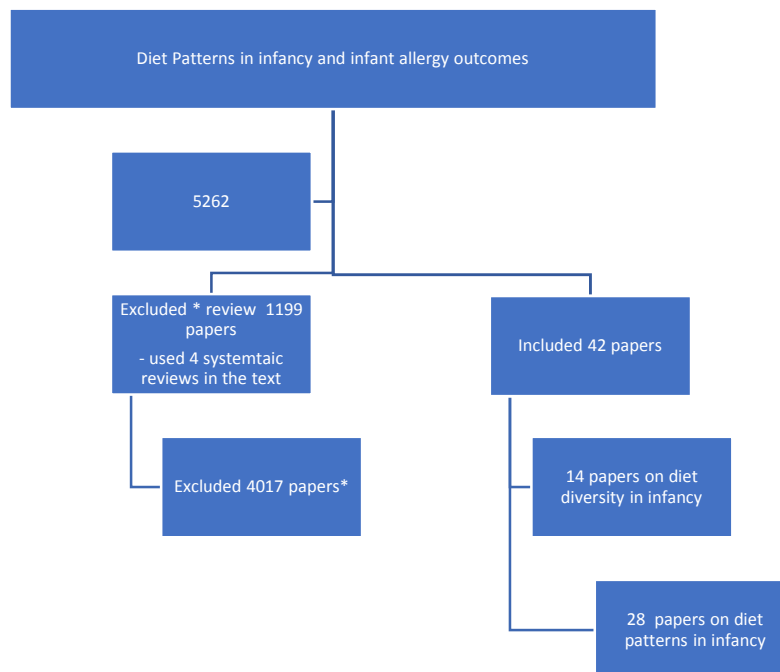
((pregnan* OR antenatal* or ante-natal* or ante natal* OR prenatal* or pre-natal* or pre natal* OR mother* or maternal*).tw,kf. or Exp Pregnancy/ OR exp "Prenatal Nutritional Physiological Phenomena"/ OR exp Mothers/) and ((allerg* or atop* or dermatitis or eczema OR asthma OR wheez* OR food hypersensitivit* or food intolerance* OR sensitiz* OR sensitiz* OR rhinitis OR hay fever OR seasonal allerg*).tw,kf. or exp Hypersensitivity/ OR exp Rhinitis, Allergic/ OR exp Dermatitis, Atopic/ OR exp Immunoglobulin E/ OR exp Eczema/ OR exp Asthma/) and (((Diet or diets or dietary or food or eating OR meal* or snack* or nutrition*) adj5 (diversity or variety or quality or pattern*)) or healthy eating or healthy diet).tw,kf. or Exp "Diet, Food, and Nutrition"/)



* excluded mainly because the papers focused on one nutrient such as vitamin D etc or food or single foods were studied

Section 4: Diet Diversity and food patterns during infancy and childhood and allergy outcomes in the infant

A search was performed on medline using the (infant* OR baby OR babies OR toddler OR early childhood OR early year OR young child/) and ((allerg* or atop* or dermatitis or eczema OR asthma OR wheez* OR food hypersensitivit* OR sensit* OR sensitiz* OR rhinitis OR hay fever OR seasonal allerg*).tw,kf. or exp Hypersensitivity/ OR exp Rhinitis, Allergic/ OR exp Dermatitis, Atopic/ OR exp Immunoglobulin E/ OR exp Eczema/ OR exp Asthma/) and (((Diet or diets or dietary or food or eating OR meal* or snack* or nutrition*) adj5 (diversity or variety or quality or pattern*)) or healthy diet).tw,kf. or Exp "Diet, Food, and Nutrition"/)



*one review paper included in the discussion¹

* excluded mainly because the papers focused on one nutrient such as vitamin D etc.

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Supplementary file 2:

Supplementary table S1a: Studies on diet diversity in pregnancy, infancy or childhood measured using simple count of food

Author	Year	Foods	Population	Scoring	Outcome
Roche ²	2008	20 Traditional Foods	Mothers and Children (3-6 years)	One point given to each unique local food in the diet reported in two 24-hour recalls, and an individual's total food diversity score was the sum of points given.	Nutrient adequacy
LaChat ³	2018	234 species	Women and children	Number of different species consumed by an individual from 24-hour diet recalls. Minimum cut-offs were set for species richness and diet diversity.	Nutrient adequacy
Remans ⁴	2011	Number of species grown on each farm	Household/Adult women	Measured food diversity based on 17 nutrients from 77 crops during the growing season and ranked them based on level of nutrients provided by each species	Nutritional diversity provided by species grown on farms (Household)
Bezerra ⁵	2011	27 foods or groups	Household/Adults	One point given for each of the 27 foods or food groups during a one-week period. First 4 foods/groups not considered healthy: Diet diversity score varied from 0 to 23, depending on the number of groups/foods.	Obesity
Onyango ⁶	1998	Simple foods	Toddlers	Number of different foods consumed	Anthropometry
Ntwenya ⁷	2017	Simple foods	Households	Number of foods consumed per day at beginning and end of rainy season	Food diversity vs. biodiversity

Supplementary table S1b: Studies on diet diversity measured in pregnancy, infancy or childhood using simple count of food groups

Author	Year	Food group	Population	Scoring	Outcome
Jones ⁸	2017	10 food groups based on 124 food items	Household	One point per food group eaten over a 7 day period	Crop series richness vs. diet diversity
Chomat ⁹	2015	10 predefined food groups	Pregnancy	Sum of all groups consumed eaten the day before	Resilience or increase vulnerability of the mother–infant dyad.
Rukundo ¹⁰	2016	12 groups consisting of 72 foods commonly eaten in Rwanda	Household/Adults	1 point for each food group consumed in 30 days based on intake and frequency of intake, food insecurity based ['never' = 0; one to two times = 1; three to ten times = 2 and more than ten times = 3 points]. Maximum score of 33 points given if the household often reported 'yes' to all the eleven questions, indicative of a high level of food insecurity; total score > 0 food insecure.	Food security
Christian ¹¹	2016	Household diet diversity 14 Food groups Child Adversity score Child (ASF) = 10 groups	Household food security vs. Children (2-5 years) diet quality	One point given per food group 0 = if no household member consumed any item in that food group in the past 7 days; 1 = if a member consumed something in the food group. The dietary diversity score had a maximum score of 14 (eating from all fourteen food groups). SDF: 0 = did not consume any form of ASF, maximum = 10 (consumed from all ten groups of ASF).	Socio-economic status and childhood diet quality
Ey Chua ¹²	2012	15 food groups	Children (1-6 years)	1 point per each food group	Anthropometry
Wright ¹³	2015	7 food groups +/- breast feeding at birth and bimonthly till 2 year.	Infants (6-24 months)	Any consumption of 10g or more of a given food group was awarded 1 point, for a maximum of 7 points. A 10g threshold was used because a previous study in this cohort imposed this cut-off point. Foods consumed in very small quantities and improved correlations of the DDS with nutrient intake. A dietary diversity score based on seven food groups was classified as low (<4) or high (≥4). The breast- feeding variable was a dichotomous indicator (yes/no) of whether the infant was breast-fed in the past 24h, which is also the same time period of reference for the 24h dietary recall.	Length and weight for age
Woo ¹⁴	2015	7 food groups	Infants (6-12 months)	Minimum diet diversity was defined as by 4/7; dietary intake assessed weekly with 24-hour recall from 6 – 12 months	Increase in diet diversity from 6 – 12 months
Chandrasekhar ¹⁵	2017	7 food groups consisting of 21 foods	Infant (6-23 months)	One point per food group for diet from the 24 hours preceding the survey.	Anthropometry

Agize ¹⁶	2017	7 food groups	Children	One point given per food group. Those who fed their child with 4 or more food groups were categorised as practicing good dietary diversity (minimum acceptable diet) and below 4 groups were categorised as not practicing good dietary diversity.	Mother's knowledge on diet diversity and child feeding vs social factors (mother's age, husbands education level, marital status)
Gewa ¹⁷	2014	9 food groups	Children (7 years)	3 scoring schemes: (1) 1 point given based on 1 gram of food in food group (2) 1 point given based on 15g food in food group (3) 1 point given based on minimum required amount eaten for food eaten over the past 24 hours	Minimum intakes required
Shamim ¹⁸	2016	9 food groups	Pregnancy	One point per food group eaten in past 24 hours	Sociodemographic status
Leroy ¹⁹	2008	9 food groups	Household diet diversity vs. child outcomes (9-36 months)	Number of 9 all-inclusive food groups used in preparing the communal household meals over a 7 day period	Intra-household allocation and gender differences
Msaki ²⁰	2013	Food count and count of 5 food groups	Household/Adults (15-50 years)	Number of foods or number of food groups consumed over a 14 day period	Seasonality variation in food quality.
Hatloy ²¹	1998	Counted individual foods and food groups	Children (13-58 months)	Food Variety. simple count of food items, and Dietary Diversity Score , a count of food groups eaten over 2 or 3 days	Nutrient adequacy
Mok ²²	2017	Seven food groups	Infants (6-36 months)	Diet diversity score = number of food groups consumed at least once over a period of 3 days from the diet record (at 6, 9 and 12 months of age), giving a potential score between 0 and 7	Adiposity and consumption of home cooked foods

Supplementary table S1c: Studies on diet diversity measured in pregnancy, infancy or childhood using count of foods within food groups

Author	Year	Foods within good group	Population	Scoring	Outcome
Hatloy ²³	2000	The food variety score (FVS) was the number of food items from the list of 104 food items. Diet diversity score: the number of food groups consumed	Household and Children (6-59 months)	FVS, where high > 18, medium = 14-18 and low 4-13 food items. The DDS was divided into tertiles, which gave the categories: high = 3 =8, medium=6-7 and low = 2-5. Based on food intake the previous day and the week before	Anthropometry
Motbainor ²⁴	2015	The number of food items grouped into specific food groups	Mother and Infants (0-35 months)	Number of different foods or food groups consumed over 24 hours	Stunting and underweight

Supplementary table S1d: Studies on diet diversity measured in pregnancy, infancy or childhood and used within an index

Author	Year	Within an index	Population	Scoring	Outcome
Vadiveloo ²⁵	2014	5 food groups weighted based on health values used in a modified Berry Index	Household	US house hold food diversity (HFD) index giving a score between zero and 1 based on 24 hour recall	Weight control

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Supplementary file 3:

Supplementary table S2: Diet Quality Indices for Pregnant Women
Diet Quality Index Adapted for Pregnant Women ²⁶
Dutch Health Diet Index ²⁷
Mediterranean Diet Score in Pregnancy ²⁸
Complementary Feeding Utility Index ²⁹
Healthy Eating Index-2010 (HEI-2010) ³⁰
Obesity Protective Dietary Index ³¹
Chinese Children's Dietary Index (CCDI) ³²
Food Diversity Index (FDI) ³³
Protein to Non-protein ratio ³⁴
Healthy Eating Index ³⁵⁻³⁹
Dietary glycaemic index (GI) ⁴⁰
Mediterranean Diet Index ²⁸
Alternative Healthy Eating Index-Pregnancy ⁴¹

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Supplementary file 4:

Supplementary table S3 Mediterranean diet/ pattern in pregnancy			
Castro-Rodriguez et al.⁴² Longitudinal Spain Sample Size: 2396 invited Analytic N: 1694 completed survey 1.5, 1000 completed both surveys Sex: m 54.7% Race/Ethnicity: NR Atopic Disease Risk Status:	Intervention/Exposure: The MedDiet score employed in the present study was previously developed Assessment Methods of MD: Questionnaires of epidemiological factors and food intake by the mother during pregnancy and later by the child were filled in by parents in two surveys at two different time points (1.5 yrs and 4 yrs of life) in 1000 preschoolers Used MedDiet as quartiles of score and also as raw score. Supplements: NR	Outcomes studied: Current wheezing 18.8%, rhinitis 10.4%, and dermatitis 17.2% MD consumption by the mother during pregnancy was not a protective factor for current wheezing, rhinitis, or dermatitis in preschoolers. Pattern (mothers) While consumption by the mother during pregnancy of meat 1 or 2 times/week, and never or occasionally pasta, remained as independent protective factors for <u>current wheezing</u> in the offspring For <u>current dermatitis</u>, high fast food consumption by mothers in pregnancy was associated to higher prevalence.	Confounders taken into account: age; gender; race; type of delivery; number of siblings; birth weight and height(by parental report); low birth weight (<2000 g or <2500 g);exclusive breastfeeding for six months (without any formula feeding or infant food); air pollution (living near to factories or roads with heavy traffic); mould stains on the house-hold walls; dogs and cats at home, during pregnancy and at present; maternal age and educational level; oral contraceptive used before pregnancy; paracetamol used during pregnancy; number of colds during the first year of life; maternal smoking during pregnancy; paternal current smoking; parental asthma, rhinitis and eczema Limitations: Data not corrected for energy intake
Chatzi et al. 2013⁴³ 2 population-based birth cohorts, Longitudinal Spain, Greece Sample Size: Analytic N: 1771 mother–newborn pairs from the Spanish multi-centre ‘INMA’ (INfancia y Medio Ambiente) study (Gipuzkoa, Sabadell and Valencia) and 745 pairs from the ‘RHEA’ study in Crete, Greece Sex: NR	Intervention/Exposure: MD score based on the one used in EPIC but with a <u>positive assignment for milk</u> and without alcohol <u>Beneficial</u> components (vegetables, legumes, fruits and nuts, cereals, fish and seafood, and dairy products), women whose consumption was below the median (cohort-specific median) were assigned a value of 0 and women whose consumption was at or above the median were assigned a value of 1. <u>Detrimental</u> components (meat, including all types of meat), women whose consumption was below the median were assigned a value	Outcomes studied: Wheeze acc. to ISAAC Eczema acc. to ISAAC Food group intakes during pregnancy differed significantly across cohorts, except vegetable intake. A higher intake of fruits and nuts during pregnancy was reported in the RHEA cohort, a higher intake of meat was reported in 2 Spanish cohorts and the lowest fish and legume intake were reported in the RHEA cohort. Dairy product intake was higher in the INMA-Gipuzkoa and INMA-Valencia cohorts than in the INMA-Sabadell and RHEA cohorts, while a higher intake of MUFA was reported in the INMA-Sabadell and INMA-	Confounders taken into account: Maternal and paternal age; maternal and paternal education (low level: #6 years of school, medium level: .6 and #12 years of school and high level: university of technical college degree); maternal pre-pregnancy weight (kg); maternal pre-pregnancy and paternal BMI (kg/m2); weight gain during pregnancy (kg); maternal smoking during pregnancy (yes/no); physical activity during pregnancy (yes/no); total energy intake during pregnancy (kJ/d for the first trimester in the INMA cohort and for mid-

<u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Different for different cohorts	of 1, whereas women whose consumption was at or above the median were assigned a value of 0 The total MD score ranged from 0 (minimal adherence to the traditional MD) to 8 (maximal adherence). The score was categorised to reflect three levels of adherence: (1) ≤ 3, low; (2) 4–5, medium; (3) 6–8, high MD quality. Assessment Methods of MD: INMA: Quantitative FFQ administered by trained interviewers, with 100 food items to assess usual food and nutrient intakes during the first trimester of pregnancy with 9 frequency categories RHEA: semi-quantitative FFQ with 250 food items was administered in mid- pregnancy (14th–18th weeks of gestation) assessing dietary habits over pregnancy Use of dietary supplements included	Valencia cohorts than in the other two cohorts. The highest proportion of subjects with a low adherence to the MD (65.4 %) was observed in the INMA-Gipuzkoa cohort (mean MD score 3.0 (SD 1.3)), while the highest proportion of subjects with a high adherence to the MD was observed in the RHEA cohort (11.5 %, mean MD score 3.5 (SD 1.6)). MD adherence was not associated with the risk of wheeze and eczema in any cohort. Pattern High meat intake (relative risk (RR) 1.22, 95% CI 1.00, 1.49) and ‘processed’ meat intake (RR 1.18, 95% CI 1.02, 1.37) during pregnancy were associated with an increased risk of wheeze in the first year of life, while a high intake of dairy products was significantly associated with a decreased risk of infantile wheeze (RR 0.83, 95% CI 0.72, 0.96).	pregnancy for the RHEA cohort); parity (primiparous or multiparous); infant sex (male or female); maternal and paternal history of asthma (yes/no); maternal and paternal history of eczema (yes/ no); birth weight (g); preterm birth (yes/no); breast-feeding duration (months); damp stains or mould spots in the child’s bedroom (yes/no); pet ownership since birth (yes/no); daycare attendance in the first year of life (yes/no); exposure to passive smoking in the first year of life (yes/no). Limitations: Dietary habits related to median, not only to cut-offs Unclear if supplements are taken into account
Chatzi et al. 2008⁴⁴ Birth cohort, Longitudinal Spain <u>Sample Size:</u> 460 children included at follow-up at age 6.5 years Analytic N: 412 for SPT <u>Sex:</u> NR 228 f, 232 m <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> General population	Intervention/Exposure: Mediterranean diet (MD) score based on the one used in EPIC but with a <u>positive assignment for milk</u> and without inclusion of alcohol See ref 6 The total Mediterranean Diet Score ranged from 0 (minimal adherence) to 7 (maximal adherence). The score was divided into two levels: (1) 4–7, high and (2) ≤ 3 low Beneficial components (vegetables, legumes, fruits and nuts, cereals, fish and seafood, and dairy products) Assessment Methods of MD: semi-quantitative FFQs of 42 food items Use of dietary supplements included	Outcomes studied: Persistent wheeze (≥ 1 episodes over past 12 months or preceding years) 13.8% Atopic wheeze (current wheeze and atopy) 5.8% Atopy (sensitization to $\geq 1/6$ common aeroallergens) 17% Adherence to MD: low 36.1%, high 63.9% High adherence to MD was negatively associated with persistent wheeze OR 0.23 (0.09 – 0.60), atopic wheeze OR 0.34 (0.12-0.97) and atopy OR 0.55 (0.32 – 1.97)	Confounders taken into account: Gender, maternal age at pregnancy, maternal social class and education, maternal smoking during pregnancy, supplement use during pregnancy, breastfeeding, lower track resp. infection at 1 year, birth weight, gestational age, birth order, number of siblings, BMI at 6.5 years Controlled for energy intake Limitations: Dietary habits related to median, not to cut-offs

Lange et al. ⁴⁵ <u>Type of study:</u> longitudinal prebirth cohort <u>Country</u> USA: multispecialty suburban/urban group practice in eastern Massachusetts. <u>Sample Size:</u> Baseline N: 2128 mother-infant pairs – 752 pairs excluded Analytic N: 1376 mother-infant pairs (infant age 3 years) Sample Size Calculation: NR <u>Sex:</u> Female <u>Race/Ethnicity:</u> Black 160 (11.6%) Hispanic 82 (6.0 %) Other 134 (9.8%) White 999 (72.7%) <u>Atopic Disease Risk Status:</u> Seventeenpercent of mothers and 15% of fathers had a history of asthma	Intervention/Exposure: Overall dietary pattern was examined by using Mediterranean diet score (Trichopoulou, NEJM 2003), Alternate Healthy Eating Index modified for pregnancy (AHEI-P) (Rifas), and principal components analysis to look at Western and Prudent diets Assessment Methods of MD: FFQs in the first and second trimester: 166-item semi-quantitative food frequency questionnaire modified for pregnancy Supplements us not reported	Outcomes studied: <u>Primary:</u> <u>Recurrent wheeze</u>, parental report None of these dietary patterns, including MD, was associated with the primary outcome of recurrent wheeze in children in either the crude or the multivariable model (multivariable model, odds ratio per 1-point increase in Mediterranean diet, 0.98 [95% CI, 0.89-1.08]; AHEI-P, 1.07 [0.87-1.30]; Prudent, 1.02 [0.83-1.26]; Western, 0.98 [0.81-1.19]). <u>Secondary outcomes:</u> parental report of: doctor's diagnosis of asthma, eczema, lower respiratory tract infections, or atopy at any time (0-3 years); Atopy (sigE) at age 3 years (N5721): either total IgE levels at the 75th percentile or greater of the distribution (>75.6 IU/mL) or at least 1 detectable allergen-specific IgE level (>0.35 IU/mL): dust mite (Dermatophagoides farina), cat dander, dog dander, egg white, cockroach, and mold (Alternaria tenuis). In the adjusted models, neither diet score was associated with any of the secondary outcomes	Confounders taken into account: Adjusted for child's sex, maternal race, maternal education level, household income, maternal and paternal history of asthma, presence of children <12 years of age at home, maternal pre-pregnancy BMI, breast-feeding duration, and passive smoke exposure. Limitations: Possible misclassification of wheezers as children with asthma. Information in questionnaires did not distinguish between wheezing with and without concomitant infection. Supplement use not reported
OTHER DIETARY PATTERNS			
Loo et al. ⁴⁶ <u>Type of study</u> Longitudinal birth cohort: Growing Up in Singapore Towards Healthy Outcomes (GUSTO)	Assessment Methods : 24 hr recalls and food diaries at 26-28 weeks of pregnancy. During repeated visits in the first 36 months of life, questionnaires were administered to	Outcomes studied: Parental reported asthma, eczema, rhinitis in the offspring SPT to inhalant allergens (house dust mites Dermatophagoides pteronyssinus, Dermatophagoides farinae, and Blomia tropicalis)	Confounders taken into account: Adjusted for sex, ethnicity, maternal education levels and family history of allergy Limitations: incomplete response rates to

<u>Country</u> Singapore <u>Sample Size:</u> Baseline N: NR Analytic N: 735 mother-infant pairs Sample Size Calculation: NR <u>Sex:</u> Male: 52.5% Female: 47.5% <u>Race/Ethnicity:</u> Chinese: 56.5% Malay: 26.9% Indian: 16.5% <u>Atopic Disease Risk Status:</u> Neg. fam. History atopy: 48.5% Pos. fam. History atopy: 48.5%	ascertain allergic symptoms, namely, eczema, rhinitis and wheezing. At ages 18 and 36 months, skin prick testing to inhalant and food allergens. Supplement use: NR	and food allergens (egg, peanut and cow's milk) was carried out at both 18 and 36 months. Three maternal dietary patterns: emerged: Seafood and Noodle (SfN) pattern was associated with a reduced risk of developing allergen sensitization at both 18 months [odds ratio (95% confidence interval): 0.7 (0.5-0.9)] and 36 months [odds ratio (95% confidence interval) 0.7 (0.6 - 0.9)]. No associations between (Vegetable, Fruit and white Rice)and(Pasta, Cheese and Processed meat) patterns were observed with any of the allergic outcomes in the first 18 and 36 months of life. No association with allergic symptoms	questionnaires parental reported disease outcomes No information on breast feeding Supplement use: not recorded
Miyake et al. 2011⁴⁷ Type of study: Longitudinal birth cohort: Osaka Maternal and Child Health Study (OMCHS) Country: Japan Sample Size: Baseline N: 1002 women between the 5th and 39th wk of pregnancy Analytic N: 763 Japanese mother–child pairs Sample Size Calculation: NR Sex: NR Race/Ethnicity: NR	Assessment Methods: In the baseline survey, dietary habits during the preceding month were assessed using a self-administered diet history questionnaire (DHQ). Estimates of daily intake for 150 food and beverage items, energy, and selected nutrients were calculated using an ad hoc computer algorithm for the DHQ based on the Standard Tables of Food Composition in Japan. According to similar nutrient profiles and culinary usage of the food items, 145 food items on the DHQ were grouped into 33 predefined food groups to extract dietary patterns (23): Healthy, Western and Japanese pattern ; Excluded supplements	Outcomes studied: Wheeze and eczema The maternal Western, but not the healthy or Japanese, pattern during pregnancy was significantly associated with a reduced risk of wheeze in the offspring After adjustment for the confounding factors under study, the inverse relationship with the Western food pattern was strengthened: the adjusted OR between extreme quartiles was 0.59 (95% CI: 0.35–0.98, p for trend = 0.02). Neither the maternal healthy pattern nor the Japanese pattern during pregnancy was related to childhood wheeze or eczema.	Confounders taken into account: Adjustment was made for maternal age, gestation, residential municipality, family income, maternal and paternal education, maternal and paternal history of allergic disorders, changes in maternal diet in pregnancy, seasonal baseline, maternal smoking during pregnancy, baby's older siblings, sex, birth weight, age at the third survey, household smoking, and breastfeeding duration. Limitations: DHQ was designed to assess recent dietary intake

Atopic Disease Risk Status: Maternal history of: -asthma (%) 80 (10.5) - atopic eczema (%) 120 (15.7) - allergic rhinitis (%) 256 (33.6) Paternal history of -asthma (%) 64 (8.4) - atopic eczema (%) 72 (9.4) -allergic rhinitis (%) 143 (18.7)	‘Healthy’, characterised by high intake of green and yellow vegetables, seaweed, mushrooms, white vegetables, pulses, potatoes, fish, sea products, fruit, and shellfish; ‘Western’, characterised by high intake of vegetable oil, salt-containing seasonings, beef and pork, processed meat, eggs, chicken, and white vegetables; ‘Japanese’, characterised by high intake of rice, miso soup, sea products, and fish During repeated visits in the first 36 months of life, questionnaires were administered to ascertain allergic symptoms, namely, eczema, rhinitis and wheezing. Data on symptoms of wheeze and eczema were based on criteria of the International Study of Asthma and Allergies in Childhood (ISAAC).		
Moonesinghe et al. 2016⁴⁸ Type of study: whole population birth cohort (FAIR). Country: Isles of White Sample Size: 969 pregnant women Baseline N: 937 pregnant women Sample Size Calculation: NR Sex: female Race/Ethnicity: see Venter 2009 Atopic Disease Risk Status: see Venter 2009	Method of assessment: Validated FFQ was completed at 36 weeks’ gestation. At 3, 6, and 9 months, as well as 1, 2, 3, and 10 years, information regarding feeding practices and reported symptoms of allergic disease in the offspring was obtained using an adapted Alternative Healthy Eating Index (AHEI-P) suited for pregnancy for our study. Supplements use: NR (not checked in the original paper) For the purpose of this study, an allergy-focused healthy eating indicator with a score of 70 was devised using the same scoring system as above for the following intake of nutrients, which influence allergy outcomes.^{1,7}: (wheat and fiber= 10, fruit and vegetables = 10,	Outcomes studies: Sensitization Allergic symptoms at 3 and 10 years of age Maternal food intake (AHEI-P) and the consumption of white fish and shellfish were not found to be associated with sensitization or allergic disease during childhood. However, maternal consumption of oily fish was found to be a risk for atopy at 3 years of age and allergic disease at 10 years of age; this finding remained significant after controlling for the presence of allergic history in the mother	Confounders: Maternal allergic history Limitations: Only one confounder taken into consideration Supplement use: NR

	calcium =10, iron =10, white fish= 10, oily fish = 10, omega 3 fatty acids = 10).		
Shaheen et al. 2009⁴⁹ Type of study Population-based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) Country: UK Sample Size: Baseline N: NR Analytic N: 14 541 pregnant women; 14 062 Sample Size Calculation: NR Sex: NR Race/Ethnicity: NR Atopic Disease Risk Status: NR	Assessment Methods: 32 weeks of pregnancy: FFQ comprising 110 questions: current weekly frequency of consumption of 43 food groups and food items, and about daily consumption of a further eight basic foods, (Yarnell) and modified in the light of a more recent weighed dietary survey (Emmett) Additional questions about the types of certain foods used and about food preparation and eating methods. Information on portion size was not collected. Supplements: NR Dietary patterns in pregnancy previously identified using principal components analysis: “Health conscious”: salad, fruit, fruit juices, rice, pasta, oat/bran based breakfast cereals, fish, pulses, cheese, non-white bread. “Traditional”: vegetables, red meat, poultry. “Processed”: meat pies, sausages, burgers, fried foods, pizza, chips, crisps, white bread, eggs, baked beans. “Vegetarian”: meat substitutes, pulses, nuts, herbal tea. “Confectionery”: chocolate, sweets, biscuits, cakes, puddings. “health conscious”, “traditional”, “processed”, “vegetarian” and “confectionery”)were related to early wheezing phenotypes and eczema; wheezing, hay fever, eczema, doctor-diagnosed asthma,	Outcomes studied: Primary outcome measure: asthma Early wheezing phenotypes and eczema; Parental reported / doctor’s diagnosed wheezing, hay fever, eczema, asthma, atopy and total IgE at 7; Lung function and bronchial responsiveness at 8–9 years: FEV1, FVC, FEF25–75 and the FEF25–75/FVC ratio (proposed as a measure of dysynaptic lung growth²⁷), adjusted for gender, age and height and expressed in standard deviations (SDs).²⁸ Bronchial responsiveness (BR) to methacholine was measured Dietary patterns in pregnancy did not predict asthma and related outcomes in the offspring after controlling for confounders.	Confounders taken into account: Controlling for energy intake, maximum smoked, infections, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, pre-pregnancy body mass index, ethnicity, age, parity, history of asthma, eczema, rhinoconjunctivitis, migraine; sex of child, gestational age, breast fed in first 6 months, day care at 8 months, multiple pregnancy, pets in infancy, damp/condensation/mould, child exposed to environmental tobacco smoke at weekends, season of birth, season of food frequency questionnaire completion, birth weight, head circumference, birth length. Limitations: Use of dietary supplements not included

	atopy and total IgE at 7 years; lung function and bronchial responsiveness at 8–9 years		
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Supplementary table S4 Mediterranean diet and dietary patterns in infancy and childhood

Single studies on Mediterranean Diet

KIDMED Mediterranean score

Calatayud-Saez et al. 2016 ⁵⁰ prospective (cohort) study Spain <u>Sample Size:</u> Baseline N: 104 asthmatic children (1-5 year old) Sample Size Calculation: Significance level of 0.05 and a power of 85% were used, assuming a decrease in the mean number of childhood asthma attacks of 1 unit/patient/yr, with a standard deviation of 4 units, adjusted for a 25% loss. The resulting sample size was 115 patients. <u>Sex:</u> 50 girls and 54 boys <u>Atopic Disease Risk Status:</u>	Intervention/Exposure: Definition of mediterranean diet (MD) Characterised by a high intake of unrefined plant-based foods such as fruits and fresh vegetables, whole grains, legumes, olive oil and nuts; low to moderate consumption of foods of animal origin such as fermented milk, fish, eggs and lean meats; and by a low intake of sugar, refined flour and fast food Assessment Methods of MD: At start of 1-year program "Learning to Eat from the Mediterranean": 7-day recall questionnaire, KIDMED test Nutritional counselling, after 4 months KIDMED test 1-year follow-up: adherence to MD by KIDMed test	Outcomes studied: Asthma control Adherence to MD improved during programme, but not statistically analysed The adoption of a traditional Mediterranean diet could contribute significantly to the improvement of patients diagnosed with childhood asthma.	Confounders taken into account: Limitations: Inappropriate statistical analysis (comment in ref 50: "suffered from inappropriate statistical analysis and lack of consideration of potential bias such as nonresponse and dropout bias that led to unreliable results and ambiguity in study population characteristics which made it difficult to compare the results against other studies.")
Grigoropoulou et al. 2011 ⁵¹ Cross-sectional survey, same cohort (extended PANACEA study) Greece <u>Sample Size:</u> Baseline N: 1125 children 10 to 12 years old Participation rate: 83,5% The total number of enrolled children (<i>n</i> = 1125) was deemed	Intervention/Exposure: Definition of mediterranean diet (MD): KIDMED Assessment Methods of MD: KIDMED food frequency questionnaire	Outcomes studied: Asthma by standardised ISAAC questionnaire Any asthmatic symptom 23.7% urban-residing children vs 14.6% living in rural areas (<i>p</i><0.001) Mean adherence to MD 5.3% rural vs 4.7% urban High adherence to MD 4,8 % rural vs 2,4 % urban (different from ref 36 13,4 vs 11,6) The analysis showed that 1-unit increase in the KIDMED score was associated with 16% lower likelihood of having asthma symptoms	Confounders taken into account: Adjusted for age, sex, BMI, physical activity status, and energy intake Limitations: Cross-sectional study, limitations such as recall bias and reverse causality bias

adequate to evaluate odds ratios (ORs) between various groups of study equal to 1.20, at probability level < 0.05, and achieving statistical power equal to 77% Sex: m 529, 596 f Race/Ethnicity: NR Atopic Disease Risk Status:		greater adherence to MD was inversely associated with ever had wheeze (OR _ 0.88; 95% CI, 0.78, 0.98) and exercise wheeze (OR _ 0.79; 95% CI, 0.67, 0.93).	
Chatzi et al. 2008 ⁴⁴ Birth cohort, prospective Spain Sample Size: 460 children included at follow-up at age 6.5 years Analytic N: 412 for SPT Sex: NR 228 f, 232 m Race/Ethnicity: NR Atopic Disease Risk Status: General population	Intervention/Exposure: Mediterranean diet (MD) assessed by modified KidMed index Assessment Methods of MD: Semi-quantitative FFQs of 96 food items based on KidMed index, modified ≥ 7 optimal MD ≤ 3 low level MD	Outcomes studied: Persistent wheeze (≥1 episode over past 12 months or preceding years) 13,8% atopic wheeze (current wheeze and atopy) 5.8% Atopy (sensitization to ≥1/6 common aeroallergens) 17% Adherence to MD 9.3% low level 53.7% medium level 37 % high level High adherence to MD was negatively associated with persistent wheeze OR 0.46 (0.10 – 2.17) and atopy =R 0.49 (0.18 – 1.32), but did not reach statistical significance Atopic wheeze OR 0.64 (0.10 – 4.06)	Confounders taken into account: Gender, maternal age at pregnancy, maternal social class and education, maternal smoking during pregnancy, supplement use during pregnancy, breastfeeding, lower track resp. infection at 1 year, birth weight, gestational age, birth order, number of siblings, BMI at 6.5 years Control for energy intake Limitations: Variability in choosing cut-off points Different distribution of selected foods in different populations
Alphantonogeorgos et al. 2014 ⁵² Cross-sectional study (extended PANACEA study ref 37) Greece, urban (Athens, n = 700) or rural environment (n = 425) Sample Size: Baseline N: 1125 children 10 to 12 years old	Intervention/Exposure: Hypothesis: living environment could affect asthma prevalence, with MD and physical activity as mediators Definition of mediterranean diet (MD): KIDMED Assessment Methods of MD: KIDMED food frequency questionnaire	Outcomes studied: Asthma by standardised ISAAC questionnaire Any asthmatic symptom 23.7% urban-residing children vs 14.6% living in rural areas (p<0.001) Mean adherence to MD 5.3% rural vs 4.8% urban High adherence to MD 12,3% (13.4% rural vs 11.6% urban) different from ref 46 (4,8% rural	Confounders taken into account: Adjusted for several confounders Limitations: Cross-sectional study, limitations such as recall bias and reverse causality bias

Partician rate: 83,5% Sample Size Calculation: NR <u>Sex:</u> m 529, 596 f <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Parental atopy 34% urban vs 27,3 rural		vs 2,4% urban) data concerning diet more detailed in Grigoropoulou et al.⁵¹ Adherence to the Mediterranean diet was related negatively with asthma symptoms (standardised beta = -0.224, p<0.001). An inverse mediating effect of the Mediterranean diet was observed for the urban environment – asthma relation (standardised beta=-0.029, p<0.001) while physical activity had no significant contribution (p=0.62), adjusted for several confounders																																				
Arvaniti et al. 2011 ⁵³ Cross-sectional study (PANACEA study) Athen, Greece <u>Sample Size:</u> Baseline N: 700 (10-12 years old) Partician rate 83,5% <u>Sex:</u> m 323, f 377	Intervention/Exposure: MD adherence measured by KidMed sore Assessment Methods of MD: semi-Quantitative FFQ on consumption of 63 food items on daily or weekly basis completed by parents during face-to-face interviews Assessment of dietary pattern of breakfast, but answers not different between asthma and no asthma	Outcomes studied: Asthma acc. to ISAAC II criteria 23.7% Adherence to MD (mean 4.8) Low n=213, Moderate n=413, high n=74 Greater adherence to MD inversely associated: <table><tr><td></td><td>Bad (0-3)</td><td>Moderate (4-7)</td><td>Good (8-12)</td><td>p</td></tr><tr><td>N</td><td>213</td><td>413</td><td>74</td><td></td></tr><tr><td>Ever had wheeze (%)</td><td>29</td><td>19</td><td>8</td><td>0.001</td></tr><tr><td>Exercise wheeze (%)</td><td>11</td><td>7</td><td>0</td><td>0.004</td></tr><tr><td>Night cough (%)</td><td>17</td><td>11</td><td>6</td><td>0.07</td></tr><tr><td>Ever had diagn. Asthma (%)</td><td>16</td><td>9</td><td>3</td><td>0.002</td></tr><tr><td>Any asthma symptoms (%)</td><td>34</td><td>22</td><td>5</td><td><0.001</td></tr></table> One-unit increase in KidMed score was associated with 14% lower likelihood of having asthma Pattern: No sign. associations with single food groups except fish and meat (increased intake, less asthma symptoms)		Bad (0-3)	Moderate (4-7)	Good (8-12)	p	N	213	413	74		Ever had wheeze (%)	29	19	8	0.001	Exercise wheeze (%)	11	7	0	0.004	Night cough (%)	17	11	6	0.07	Ever had diagn. Asthma (%)	16	9	3	0.002	Any asthma symptoms (%)	34	22	5	<0.001	Confounders taken into account: Various factors considered as potential confounders and effect mediators Limitations: Cross-sectional study Recall bias not excluded
	Bad (0-3)	Moderate (4-7)	Good (8-12)	p																																		
N	213	413	74																																			
Ever had wheeze (%)	29	19	8	0.001																																		
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Arvaniti et al. 2011 ⁵⁴ Cross-sectional study (PANACEA study) Athen, Greece <u>Sample Size:</u> Baseline N: 700 (10-12 years) Participation rate 83,5% <u>Sex:</u> m 323, f 377	Intervention/Exposure: MD adherence measured by KidMed score Assessment Methods of MD: see Arvaniti et al. ⁵³ Including salty-snack consumption (pattern)	Outcomes studied: Asthma acc. to ISAAC II criteria 23.7% Pattern: 48% reported salty-snack consumption (SSC) ≥1 times/week SSC was inversely associated with the KidMed score. SSC >3 times/ week vs never was associated with a 4.8 times higher likelihood of having asthma symptoms	Confounders taken into account: see Arvaniti et al. ⁵³ Limitations: see Arvaniti et al. ⁵³
Chatzi et al. 2007 ⁵⁵ Cross-sectional survey Crete, Greece <u>Sample Size:</u> Baseline N: 690 (age: 7-18 years) Analytic N: 537 (incl. information about allergic manifestations) <u>Sex:</u> m 331, f 359 <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> 6.8% parental asthma	Intervention/Exposure: Adherence to MD measured by modified KidMed score (left out questions on fast food, sweets and legumes, optimum reduced from 8 to 6) Assessment Methods of MD: FFQ (58 items) usual weekly food consumption during previous 12 months with a 6-level-scale (never, <1 times per week, 1-2 times, 3-4 times, once per day, > once per day) ≥ 6 optimal MD ≤ 3 low level MD Degree of adherence based on KidMed index, modified + MD Sore (EPIC), modified Definition of mediterranean diet (MD) KidMed Index, more red than white meat per week -1, margarine more than once a week -1	Outcomes studied: Questionnaires on respiratory and allergic symptoms over the past 12 months by parents, SPT 10 aeroallergens Any wheezing in the past 16.8%, atopic wheeze 5.4%, current wheezing 4.6%, nocturnal dry cough (last 12 months) 10.9% Any rhinitis in the past 18.7% (atopic rhinitis 6.7%, current AR 13.3, current seasonal AR 5.1) Atopy 22.3% <u>adherence to MD</u> 27.9 % low level 43.8 % medium level 28.3 % high level After multivariate logistic regression analysis high level of adherence to MD was inversely related to AR ever OR 0.34 (0.18 – 0.64) p<0.01 AR with atopy OR 0.39 (0.13-0.97) Current AR OR 0.49 (0.24 – 0.99) p<0.05 Nocturnal cough apart from cold in the last 12 months OR 0.49 (0.23-0.96) Protective trend but not significant for	Confounders taken into account: Age, sex, BMI, parental asthma number of older siblings Limitations: Cross sectional design Self-administered questionnaire Non-validated FFQ

		wheezing and atopy Pattern: Nuts ≥ 3 times/w reduced wheezing ever OR 0.54 (0.34-0.86) and current wheeze OR 0.46 (0.20-0.98) Margarine > once/w increased current wheezing OR 2.19 (1.01-4.82), AR ever OR 1.99 (1.32-3.00), current AR OR 2.10 (1.31-3.37)	
Chatzi et al. 2007 56 Birth cohort, prospective Spain <u>Sample Size:</u> 460 children included at follow-up at age 6.5 years Analytic N: 412 for SPT <u>Sex:</u> NR 228 f, 232 m <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> General population Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	Intervention/Exposure: Mediterranean diet (MD) assessed by modified KidMed index (questions regarding breakfast left out, optimum reduced from 8 to 7) Assessment Methods of MD: Semiquantitative FFQs of 96 food items based on KidMed index, modified ≥ 7 optimal MD ≤ 3 low level MD	Outcomes studied: prevalence of current wheeze, atopic wheeze, and atopy at age 6.5 yr were 8.7%, 5.8%, and 17.0% pattern: A high consumption (>40 g/day) of fruity vegetables were found to have beneficial effect on current wheeze (OR, 0.38; 95% CI, 0.15–0.95, $p < 0.05$), and atopic wheeze with a significant decreasing trend with increasing intake (OR, 0.19; 95% CI, 0.04–0.95, p for trend = 0.04). Atopy was negatively associated with a high fish intake (>60.5 g) (OR, 0.43; 95% CI, 0.21–0.90, $p < 0.05$).	Confounders taken into account: Gender, maternal and parental asthma, maternal and paternal atopy, maternal smoking, BMI at age 6.5 yr, maternal and paternal education and social class, breastfeeding, fish intake during pregnancy, and number of siblings at age 6.5 yr. In addition, analyses including specific food intake were adjusted for total energy intake using the standard multivariate method
<u>Adult EPIC score/ Mediterranean diet pattern</u>			
Castro-Rodriguez et al. 2017 57 Cross-sectional Spain <u>Sample Size:</u> Baseline N: 2922 pre-school	Intervention/Exposure: Definition of mediterranean diet (MD) Pro: Fruit, fish, vegs, legumes, cereals, pasta, rice, potatoes Anti: meat, milk, fast food	Outcomes studied: Current wheezing cw (episodes over the past 12 months) 20% Highest quartile of MD cw 42.9, cnw 53.2 After multivariate analysis: highest quartile of	Confounders taken into account: Children with current wheeze were more often born by cesarean section, lower birth weight, lower proportion of breast-feeding, higher antibiotic and acetaminophen consumption in first year of life,

children invited Analytic N: 1784 (mean age 4.08 ± 0.8) completed questionnaire, 1757 answered questions regarding current wheezing Sex: male cw 53.3, cnw 51.1 Race/Ethnicity: caucasian cw 91.5, cnw 94.3 Atopic Disease Risk Status: General population, Paternal asthma cw 6.3, cnw 3.1, maternal asthma cw 8.0, cnw 4.0	3 answers (0-2 and 2-0 pts, respectively) Based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸ Range in study group 14-36, adherence by quartiles Assessment Methods of MD: Environmental questionnaires including questions on consumption and allergic manifestations (based on ISAAC phase III)	MD aOR 0.54 (0.33 – 0.88)	more acetaminophen consumption in previous 12 months, More parental asthma, more smoking, heavier truck traffic in front of house, more cat owners, lower rate of vigorous physical activity, significantly more margarine consumption Limitations: Questionable MD score, Adherence by quartiles not by cut-off values – highest quartile does not mean high adherence (e.g. only 30% of children ate vegs more than 3 times per week)
de Batlle et al. 2008⁵⁹ Cross sectional study Mexico Sample Size: Baseline N: random sample of 3125 children Analytic N: 1476 children (6-7 years) Attrition: Sample Size Calculation: NR Sex: NR Race/Ethnicity: NR Atopic Disease Risk Status: General population	Intervention/Exposure: Mediterranean diet (MD) Based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸ Assessment Methods of MD: Parental FFQ with 70 food items, usual diet in the last 12 months (8 food groups: vegs (+), legumes (+), fruit and nuts (+), dairy products (-), cereals (+), meat (-), fish (+), junk food and fat (-) with minimum (0) to maximum (8) Adherence measure in tertiles	Outcomes studied: Asthma/rhinitis related outcomes by ISAAC questionnaire Asthma ever 170 (12%) Wheezing ever 354 (25%) Current wheezing n=147 (11%) Rhinitis ever n=100 (7%) Sneezing ever n=419 (30%) Current sneezing n=370 (25%) Current itchy-watery eyes n=166 (11%) high consumption of fruits and nuts, vegetables, and junk food and fat -> mean MD 3.7 Adherence to MD (2nd and 3rd tertile compared with 1st tertile) inversely associated with Asthma ever OR 0.60 (0.40-0.91) Wheezing ever OR 0.64 (0.47-0.87) Sneezing ever OR 0.79 (0.59-1.07), current Sneezing OR 0.71 (0.52-0.96) Current itchy-watery eyes OR 0.63 (0.42-0.95)	Confounders taken into account: Gender, number of older sisters or brothers, birth weight, body mass index (BMI), maternal breastfeeding, parental educational level, children's exercise, smoking exposure (while in the womb, during the first year of life, or currently in the home), parental medical history of asthma and allergic rhinitis, animals at home during pregnancy, animals at home during first year of life, living in a ranch during pregnancy, premature birth, respiratory infections during early life, silhouette, changes from the silhouette they had at 4-year old, type of combustible used for cooking at home, sleeping alone in a room, and mould or dampness at home. Limitations: Cross-sectional study Adherence to MD by tertiles not

			cut-offs, Diet score questionable
Garcia-Marcos L et al. 2007⁶⁰ Cross sectional study Spain <u>Sample Size:</u> Baseline N: 20106 children (6-7 years old) Mean participation rate: 78.7% Complete data on consumption: 17145 children <u>Sex:</u> NR <u>Race/Ethnicity:</u> only Spanish children <u>Atopic Disease Risk Status:</u> General population	Intervention/Exposure: Relationship of MD with asthma/ rhinoconjunctivitis adjusting for obesity and exercise Based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸ Definition of mediterranean diet (MD): fruit, fish, vegetables, pulses, cereals, pasta, rice and potatoes were considered “pro-Mediterranean” foods and rated 0, 1 or 2 points from less frequent to more frequent intake. Meat, milk and fast food were considered “anti-Mediterranean” foods and rated 0, 1 or 2 points from more frequent to less frequent consumption	Outcomes studied: Asthma/ rhinoconjunctivitis acc. to ISAAC questionnaire Current occasional asthma (COA) 1379 (8%) Current severe asthma (CSA) 390 (2.3%) Rhinoconjunctivitis 1446 (8.4%) Independent of the amount of exercise, each Mediterranean score unit had a small but protective effect on CSA in girls (adjusted OR 0.90, 95% CI 0.82 to 0.98). Diet Pattern <u>Protective factor for COA:</u> frequent intake of nuts (1–2 times/week and >3 times/week vs never/occasionally) aOR 0.82 (0.73-0.94) and aOR 0.68 (0.51-0.90) p<0.001 <u>protective factors for CSA:</u> of seafood (adjusted ORs 0.63 (95% CI 0.44 to 0.91) and 0.53 (95% CI 0.35 to 0.80)) and cereals (adjusted OR 0.56 (95% CI 0.30 to 1.02) and 0.39 (95% CI 0.23 to 0.68)), trend for meat, fruit, vgs, cereal, milk) <u>risk factor for CSA:</u> fast food (adjusted ORs 1.64 (95% CI 1.28 to 2.10) and 2.26 (95% CI 1.09 to 4.68)) <u>protective factors for rhinoconjunctivitis:</u> seafood (adjusted ORs 0.74 (95% CI 0.60 to 0.92) and 0.67 (95% CI 0.53 to 0.85)) and fruit (adjusted ORs 0.76 (95% CI 0.60 to 0.97) and 0.71 (95% CI 0.57 to 0.88)), trend for meat	Confounders taken into account: Limitations: No adjustment of food consumption to energy intake Questionable MD score
Suarez-Varela et al. 2010⁶¹ Cross-sectional study ISAAC phase III Spain <u>Sample Size:</u> Baseline N: 20106 (6-7 years of age)	Intervention/Exposure: Definition of mediterranean diet (MD) based on⁶² which was again based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸ Range 0-22 Assessment Methods of MD:	Outcomes studied: Atopic dermatitis assessed acc. to ISAAC questionnaire 5.92% Mean MDS 13.26 Good adherence 9.43% Bad adherence 90.57%	Confounders taken into account: Gender, obesity, exposure to tobacco smoke in the first year of life, younger and older siblings, and exercise. Limitations: Questionable MD Definition, especially with regard to outcome

Analytic N: 13153 Participation rate 76.5% <u>Sex:</u> m 6621, f 6512 <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	FFQ on 16 foods and food groups with 3 answers (never, 1-2 times/ wk, ≥3 times/wk)	No association between MDS and AD Pattern Milk was negatively associated with AD (aOR 0.42 (0.22-0.79) when eaten 1-2 times/wk, aOR 0.50 (0.33-0.75) when consumed ≥3 times/wk). Butter aOR 0.70 (0.50-0.97) when consumed ≥3 times/wk) Nuts aOR 0.51 (0.33-0.80) when consumed ≥3 times/wk)	
Tamay et al. 2014 ⁶³ Cross-sectional study Turkey <u>Sample Size:</u> Baseline N: 11483 (6-7 years of age) Analytic N: 9875 Attrition: Sample Size Calculation: NR <u>Sex:</u> m 50.7%, f 49.3% <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	Intervention/Exposure: Definition of mediterranean diet (MD) MDS based on⁶² which again was based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸ Range: 0 to 22 Assessment Methods of MD: Semiquantitative FFQ with 30 food items assessing diet in the past 12 months completed by parents Consumption of protective foods such as potatoes, rice, cereals, pasta, vegetables, tomatoes, broad bean fish and other sea foods, fruits, nuts, olive oil, fish oil, and some traditional foods made from grapes and mulberries, fermented drinks made from millets and various seeds, pickle; aggravating foods including fast-food, potato chips and crackers, chocolates, lollipops and candies, cookies and muffins, margarine; and other foods including eggs, animal fats, milk and dairy products, meat, polyunsaturated fatty acids (butter), sun-flower oil, corn oil, tea, and olive were asked. (3 answers possible)	Outcomes studied: Allergic rhinitis acc. to ISAAC protocoll Lifetime rhinitis 44.3% Current rhinitis 29.2% Current rhinoconjunctivitis 8.5% Physician-diagnosed AR 8.1% No protective effect of MD Pattern <u>physician-diagnosed allergic rhinitis:</u> Consumption of rice, and cereals ≥3 times/wk protective effect (aOR = 0.53, 95% CI = 0.32-0.87 and aOR = 0.58, 95% CI = 0.36-0.92). <u>current rhinoconjunctivitis:</u> pasta, and Chocolates ≥3 times/ wk protective effect (aOR = 0.45, 95% CI = 0.25-0.79 and aOR = 0.50, 95% CI = 0.29-0.86). <u>current rhinoconjunctivitis</u> Eating lollipops, candies and animal fats ≥3 times per week was positively associated with (aOR = 1.47, 95% CI = 1.00-2.17 and aOR = 2.25, 95% CI = 1.11-4.56).	Confounders taken into account: Gender, parental education level and exercise Limitations: Questionable MDS
Akçay et al. 2014 ⁶⁴ Cross-sectional study	Intervention/Exposure: Definition of mediterranean diet (MD): MD score based on the work of García-Marcos et al. 2016 et al. which again was based	Outcomes studied: Wheeze ever 17.4%, wheezing in last 12 months 9.0%, and lifetime doctor diagnosed	Confounders taken into account:

Turkey <u>Sample Size:</u> Baseline N: 10894 adolescents (13-14 years of age) Analytic N: 9991 Response rate: 91.7% Sample Size Calculation: NR <u>Sex:</u> 4746 boys (47.9%) and 5166 girls (52.1%) <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸ Ranging from 0 to 22 Assessment Methods of MD: Dietary intake was estimated by a semi-quantitative food frequency questionnaire. Consumption of foods including potatoes, rice, cereal, pasta, vegetables, fish, other sea foods, fruits, tomatoes, nuts, olive oil, fish oil, boiled grape juice, fermented drinks made from millets and various seeds, hamburger, potato chips, crackers, chocolates, lollipops, candies, cookies, muffins, margarine, eggs, animal fats, milk and dairy products, meat, PUFAs (butter), sun-flower oil, corn oil, tea, broad bean and olives were asked. (3 answers possible)	asthma prevalence 11.8% The mean MD scores for children with asthma and children without asthma were 12.51 and 12.53 The Mediterranean-style diet was not associated with the prevalence of asthma. Pattern: Asthma prevalence in children consuming fruits and animal fats ≥ 3 times a week was lower than in those with these foods consumed never or occasionally (aOR = 0.66, 95% CI = 0.48-0.93; and aOR = 0.58, 95% CI = 0.35-0.93, respectively. When animal fats or olive were consumed three or more times a week, asthma prevalence was lower than it was in those who consumed these foods once or twice per week (aOR = 0.48, 95%CI = 0.28-0.84; and aOR = 0.79, 95% CI = 0.66-0.94, respectively). When fermented drinks made from millets and various seeds, mix pickles and margarine were consumed ≥ 3 times a week, asthma prevalence was higher than it was in those who consumed these foods never or occasionally, or once to twice per week. When meat was consumed three or more times a week, asthma prevalence was higher than it was in those who consumed these foods once to twice per week (aOR = 1.26, 95% CI = 1.04---1.52)	Limitations: Asthma based on a questionnaire, without confirming the diagnosis according to their medical histories or to lung function tests. Another limitation of this study was that ISAAC protocol questions have not been validated in Turkey.
Rice et al. 2015⁶⁵ Case-control study Peru <u>Sample Size:</u> Baseline N: 287 asthmatic (physician diagnosed) children (9-19 years of age, mean 13.5) + 96 controls without asthma <u>Sex:</u> m 165, f 112 (controls m 40, f 56) <u>Race/Ethnicity:</u> NR	Intervention/Exposure: Definition of mediterranean diet (MD): MDS based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸, except milk (+) range 0-22 Assessment Methods of MD: FFQ with 170 food items assessed usual dietary intake over previous 2 weeks (6 answers possible)	Outcomes studied: Asthma status (asthma control, FEV1), AR, atopy 86% with controlled asthma Being above the median MDS scores was associated with decreased odds of asthma [OR = 0.55, 95 % CI (0.33, 0.92), p = 0.02]. Among children whose mothers completed secondary education, being above the median MDS significantly decreased the odds of asthma [OR = 0.31, 95 % CI (0.14, 0.71), p<0.01], whereas among those whose mothers did not complete secondary education there	Confounders taken into account: Maternal education, age, sex, BMI Limitations: No correction for energy intake Questionable MDS, but better than in other studies

<u>Atopic Disease Risk Status:</u> No information on parental allergy		was no protective effect [OR = 0.86, 95 % CI (0.43, 1.7), p = 0.66]. No association between MDS scores and asthma control, FEV1, allergic rhinitis, or atopic status	
Silveira et al. 2015 ⁶⁶ Cross-sectional study Brazil <u>Sample Size:</u> Baseline N: 268 (3-12 years of age) with persistent asthma, 126 age-matched controls with intermittend asthma <u>Sex:</u> m 159, f 109 (controls m 61, f 65) <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> FA asthma 59.5% (controls 56%) FA AR 72.8% (controls 67.2%)	Intervention/Exposure: Definition of mediterranean diet (MD) (Criteria adapted from the literature) pro-MD pattern (fruit, vegetables, fish, fruit juices, root vegetables and tubers and grains) and a contra-MD diet (milk, meat, eggs, processed foods, soft drinks, butter). The Mediterranean diet was classified as “yes” when intake of at least 5 foods in each group was frequent (≥3 times per week) Assessment Methods of MD: Interview with parents/ guardians using a pre-coded questionnaire several outcomes including dietary habits food consumption over the past 12 months assessing frequent and infrequent consumption (never or <3 times/week)	Outcomes studied: No significant association between frequency of consumption of specific foods, food groups or dietary pattern (pro- vs anti-MD) and <u>severity</u> of asthma (not risk!)	Confounders taken into account: Multivariate analysis was applied to control for potential confounding factors, with inclusion of variables according to the pre-established hierarchical levels as follows: level 1: gender, skin colour, maternal schooling, income, paternal schooling, and smoking during pregnancy; level 2: allergens in the home, gestational age, birth weight, family history of allergic rhinitis, exposure to passive smoking; level 3: dietary variables; and level 4: obesity. Only the variables with <i>P</i> ≤0.20 remained in the model. Limitations: Statistical power insufficient Brought range of age – food consumption varies with age
Romieu et al. 2009 ⁶⁷ Cohort study Mexico <u>Sample Size:</u> Baseline N: 158 asthmatic children (6-14 years of age), 50 non-asthmatic children Analytic N: Attrition:	Intervention/Exposure: Definition of mediterranean diet (MD) based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou) ⁵⁸ Assessment Methods of MD: Dietary intake was evaluated using a 108-item validated quantitative FFQ completed by mothers with 8 possible answers regarding frequency and a fruit and vegetable index (FVI) and a Mediterranean	Outcomes studied: Pulmonary function was measured and nasal lavage collected and analysed every 2 weeks The impact of these indices on lung function and interleukin-8 (IL-8) and their interaction with air pollutants were determined using mixed regression models with random intercept and random slope. No significant difference between the asthmatic and the non-asthmatic children. We observed a high frequency of intake of	Confounders taken into account: 5-day accumulated moving average O3 (ppb), 5-day accumulated average (maximum) PM2.5 (µg/m3), Previous day minimum temperature, gender, body mass index, calories and chronological time Limitations:

Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	diet index (MDI) were constructed. FVI: based on intake of fruits and vegetables and the consumption of vitamins or supplements reported on the questionnaire and were scored on a scale of 0 to 3 MDI adapted from that by Trichopoulou/ Psaltopoulou used in adults (EPIC)⁵⁸ with regard to cardiovascular risk modifications: 1) without alcohol ii) without high monounsaturated/saturated consumptions iii) introduction of junk food In the case of fruits, vegetables, cereals, legumes, dairy products and fish, a value of 1 was assigned if consumption was above of the median value and 0 otherwise. For meat and junk food, the scoring was reversed.	fruit or fruit juices, vegetables and dairy products as well as junk food, while the intake of fish was low FVI was inversely related to IL-8 levels in nasal lavage ($p < 0.02$) with a significant inverse trend (test for trend $p < 0.001$), MDI was positively related to lung function ($p < 0.05$), and children in the highest category of MDI had a higher FEV1 (test for trend $p < 0.12$) and FVC (test for trend $p < 0.06$) than children in the lowest category. A significant interaction was observed between FVI and ozone for FEV1 and FVC as was with MDI and ozone for FVC. No effect of diet was observed among healthy children.	
Nagel et al. 2010⁶⁸ Cross-sectional studies of 29 centres in 20 countries ISAAC <u>Sample Size:</u> Baseline N: 50004 schoolchildren (8-12 years) Analytic N: 29579 with SPT Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	Intervention/Exposure: Definition of mediterranean diet (MD) “score of MD derived according to consumption frequency of food items” Selected food items: meat (-), fish (+), fresh fruit (+), raw green vegs (+), cooked green vegs (+), burgers (-), fruit juice (+), fizzy drinks (-) Assessment Methods of MD: FFQ When was dietary intake assessed and how often? E.g. twice during pregnancy at 24 and 36 weeks.	Outcomes studied: <u>Effect on current wheeze:</u> Fruit intake (ORadj 0.86, 95% CI 0.73 to 1.02) and consumption of fish (ORadj 0.85, 95% CI 0.74 to 0.97) was associated with low prevalence in affluent countries. Burger consumption aOR 0.76 (0.61-0.95), fruit (ORadj 0.71, 95% CI 0.57 to 0.88) and fruit juice intake aOR 0.80 (0.68-0.94) and consumption of cooked green vegetables (ORadj 0.78, 95% CI 0.65 to 0.95) was associated with a lower prevalence of current wheeze in non-affluent countries. <u>Association with lower lifetime prevalence of asthma:</u> more frequent consumption of fruit, vegetables and fish <u>Association with higher lifetime asthma prevalence asthma:</u> high burger consumption ≥ 3 times/week aOR 1.42 (1.08-1.87) (comment: obviously driven by affluent countries - in non-affluent countries, an inverse relationship was found between burger consumption and wheeze aOR 0.76 (0.61-0.95). <u>allergic sensitisation:</u> no sign. association of any food item	Confounders taken into account: Age, sex, environmental tobacco smoke, parental atopy, exercise, number of siblings Limitations: Questionable definition of MD No adjustment for total energy intake and BMI

		atopic wheeze no sign. associations “Food selection according to the ‘Mediterranean diet’ was associated with a lower prevalence of current wheeze and asthma ever (ptrend=0.03).”	
Gonzalez et al. 2010 ⁶⁹ cross-sectional study Spain Sample Size: Baseline N: 14700 Analytic N: 7454 children (6-7 years of age), 7391 adolescents (13- to 14-yr olds) Response rate: 75% in the 6- to 7-yr age group and 85% in the 13- to 14-yr-old age group Sex: NR Race/Ethnicity: NR Atopic Disease Risk Status: Not assessed	Intervention/Exposure: Definition of mediterranean diet (MD): Fruit, fish, vegetables, pulses, cereals, pasta, rice and potatoes were considered pro-Mediterranean foods and rated 0, 1 or 2 points from less frequent to more frequent intake (0 points = never or occasionally; 1 point = 1 or 2 times/wk; 2 points = ≥3 times/wk). Meat, milk and fast food were considered anti-Mediterranean foods and rated 0, 1 or 2 points from more frequent to less frequent consumption (0 points = ≥3 times/wk; 1 point = 1 or 2 times/wk; 2 points = never or occasionally). MDS developed by Garcia-Marcos⁶² to be added based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁵⁸	Outcomes studied: Based on ISAAC questionnaire The prevalence of asthma in children was 39.9%, current asthma 13.8%, severe asthma 4.7% and exercise-induced asthma 6.5%. In adolescents, this prevalence was 22.2%, 12.4%, 5.2% and 19.5%, respectively MDS range 3-21 (mean 13.1) in children and 4-20 (mean) 12 in adolescents Greater adherence to the MD is associated with a higher risk of severe asthma (odds ratios = 2.26, 95% CI: 1.21–4.22 in the 2nd quartile, but not in the 3rd and 4th) in girls of 6–7 yr. There was no significant relationship for the other asthma categories in the population studied.	Confounders taken into account: Limitations: Questionable MDS “As regards individual foods, it was noted that in the lower age group, more than 2/3 of the children ate meat (-), fruit, cereals, potatoes and milk (-) more than three times per week.” Adherence by quartiles not by cut-off values – highest quartile does not mean high adherence
Other dietary patterns			
de Cassia et al. 2014 ⁷⁰ Cross-sectional study Brazil Sample Size: Baseline N: 1500 children (6-12 year old) Analytic N: 1187 Attrition: Sample Size Calculation: NR Sex: male 53.3% Race/Ethnicity: NR	Intervention/Exposure: Dietary pattern: Western Diet vs prudent Assessment Methods of MD: Validated quantitative food frequency questionnaire of 97 food items adapted to take local dishes into account administered to mothers by nutritionists The frequency of consumption of these items were divided into the following 4 categories: never consumes = 0; consumed 1–3 times a month = 1; once a week = 2; 2–4 times a week = 3; and ≥ 4 times in weeks = 4. Afterward, the scores of the frequency of	Outcomes studied: Asthma by ISAAC questionnaire 10.6% From this analysis, 2 components (patterns) were extracted that accounted for 45.7% of the total variance. The eating patterns that were extracted were named as Western and Prudent. The first component was positively correlated with the intake of sugars, typical Brazilian dishes, pastries, fast food, oils, milk, cereals, cakes, and sauces. The second component was positively correlated with roots, legumes, fruits, and leafy vegetables. The indices relating to internal consistency (α > 0.60) ensured an acceptable level of accuracy of	Confounders taken into account: BMI, physical activity, pubertal development, gender (male, female reference category), age (< 10 years, ≥ 10 years reference category), education of caregiver (£ 4th grade, 5th grade ± reference category), household location (urban, rural reference category), per capita income [as minimum salary (MS); £ 1 MS, > 1 MS reference category], number of people living in the household (> 3, £ 3 reference category), and

<u>Atopic Disease Risk Status:</u>	consumption were calculated as weighed proportion consumption where the numerator is the sum of the categories of all food items into in food cluster multiplied by 4 and the denominator the number of food items into food cluster multiplied by 4. This score or weighed proportion consumption represents a summary measure of the food consumption	measurement for the 2 patterns, ensuring internal consistency for the dimensions of the questionnaire. Certain foods and food groups were not considered in the analysis due to the low communality presented ($h^2 < 0.30$): soft drinks, beef, chicken, fish, eggs, processed meat products, bread, baked beans, and artificial sweeteners. We found a positive statistically significant association of the Western pattern with wheeze (odds ratio = 1.77, 95% confidence interval: 1.10–2.84) after adjustment for total energy intake and controlling for potential confounders	presence of smokers in the house (no reference category, Yes)
Lee et al. 2012 ⁷¹ Cross-sectional study Taiwan <u>Sample Size:</u> Baseline N: 2,419 schoolchildren Analytic N: 2082 Response rate: 78.8%. Sample Size Calculation: NR <u>Sex:</u> m 1111, f 971 <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Parental asthma: 3,7%	Intervention/Exposure: Dietary pattern identified by reduced rank regression (RRR) Assessment Methods of DP: FFQ with 21 food groups to assess dietary intake (at home) Average intake in days/wk in the past month Food groups included vegetables, fruits, milk, yogurt, Yakult (lactic acid beverages with low dairy protein and high sugar), cheese, meat, fish, shellfish, organ meat (e.g. heart, liver, kidney and stomach of poultry and livestock), soybean milk, soy products, eggs, fast foods (e.g. hamburgers, pizza, French fries, fried chicken, and fried Asian delicacies), high-fat snacks (e.g. potato chips, flour based and rice flour-based crisps), sweet drinks (e.g. cola and soda), candy (e.g. chocolate and candy), desserts (e.g. cakes, cookies and sweet pastries), instant noodles, rice and flour.	Outcomes studied: Asthma assessed by ISAAC questionnaire by face-to-face interviews Asthma ever 5.4% Current asthma 3.5% Current severe asthma 2.3% Exercise-induced wheeze 3.1% Nocturnal cough 6.9% More prevalent in boys The RRR derived dietary pattern was characterised by high consumption of fast foods, high-fat snacks, candy, and cheese; and low consumption of fruit, vegetables and rice. The RRR-derived dietary pattern was associated with an increased risk of current asthma (OR [95% CI]) (2.42 [1.19-4.93] for Q4/Q1, p-for-trend=0.01), current severe asthma (3.21 [1.11-9.25] for Q3/Q1, 4.45 [1.59-12.5] for Q4/Q1; p-for-trend=0.003), and nocturnal cough (1.79 [1.06-3.05] for Q2/Q1, 1.74 [1.02-2.97] for Q3/Q1, 1.82 [1.07-3.11] for Q4/Q1; p-for-trend=0.049).	Confounders taken into account: Age, sex, BMI z-score, older sibling number (0, 1 and 2+), parental education level (<high school, high school, and college+), parental asthma status (yes and no), ambient NOx concentration and Seasonal effect (spring and summer versus fall and winter) Limitations: Cross-sectional design -> no causal relationship
Jonsson et al. 2016 ⁷² Birth cohort	Intervention/Exposure: Dietary differences in relation to allergy outcomes	Outcomes studied: AR, asthma, FA, AD (pediatrician diagnosed at year 1.5 and 3): 1 farm child with eczema	Confounders taken into account:

Sweden <u>Sample Size:</u> Baseline N: 65 children, 28 living on a farm, 37 controls from a rural area but not farm (10-14 months of age) <u>Sex:</u> farm: m 36%, f 64% Control: m 62%, f 38% <u>Atopic Disease Risk Status:</u> Farm: mother 25%, father 4% Controls mother 30%, father 32%	Assessment Methods of MD: 24-h dietary recall by pre-decided interview protocol + 24-h food diary at 1 year of age	(4%), 10 controll children (32%): 6 AD, 4 A, 2 FA, 1 AR Farm children had a higher intake of farm milk (comment: median intake was 0g), whole cream (comment: median intake was 1g, energy-adjusted 0g), cholesterol, saturated fat, and fat in total and tended to eat more butter, while controls consumed more carbohydrates and poultry (comment: median intake was 0g) and tended to eat more margarine (comment: median intake was 2g, energy-adjusted 0g). Farm children also had higher intakes of homemade porridge/gruel (comment: median intake was 0g), oily fish (comment: median intake was 0g), and iodine. A weak negative association was found between seafood intake and allergy development, while allergy was positively associated with the intake of pork as well as zinc in the control group; these intakes also correlated with each other.	Limitations: Numbers too small for statistical analysis
Loo et al. 2017 ⁷³ cohort study (GUSTO study) Singapore <u>Sample Size:</u> Baseline N: 486 infants Analytic N: Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> Chinese, Malays and Indians <u>Atopic Disease Risk Status:</u>	Intervention/Exposure: Influence of infant dietary pattern on allergic outcomes until 5 yr of age Assessment Methods of DP: Analysis of dietary data from 6-12 months revealed 4 patterns: <i><u>Predominantly breastmilk</u></i>—mainly breastmilk and less formula milk; <i><u>according to Guidelines</u></i>—rice porridge, vegetables, fruits and low-fat fish and meat; <i><u>Easy-to-prepare foods</u></i>—infant cereals, juices, cake and biscuits; <i><u>Noodles (in soup) and seafood</u></i>—rice and wheat noodles and common accompaniments such as fish and shellfish. A fifth pattern emerged at age 12 months: <i><u>Pulses and grains</u></i>—characterised by high intake of nuts and seeds, grains, legumes and lentils and high energy-dense confectionaries	Outcomes studied: Allergic outcomes (sensitization, eczema, rhinitis, wheeze with use of nebulizer) by modified ISAAC questionnaire at 3,6,9,12,18,24,36,48,60 months <i>“Noodles and seafood”</i> dietary pattern at month 12 which consists of consumption of rice and wheat noodles, prawn, scallop and cuttlefish was associated with reduced odds of developing allergen sensitization at ages 18 months [adjusted OR (95% CI): 0.5 (0.3-0.98)] and at 60 months [adjusted OR (95% CI): 0.7 (0.4-0.98)] Further analysis showed that a <i>“Noodles and seafood”</i> dietary pattern at month 12 was also associated with reduced odds of developing house dust mite allergen sensitization at ages 18 months [adjusted OR (95% CI): 0.4 (0.2-0.9)] and 60 months [adjusted OR (95% CI): 0.7 (0.4-0.99)]. There were no associations between a <i>“Noodles and seafood”</i> dietary pattern at month 12 and development of food allergen sensitization at 18, 36 and 60	Confounders taken into account: Sex, ethnicity, maternal education level, FA, eczema Limitations: Regular collection of information at multiple time points. The collection of infant dietary patterns also reduces recall and response bias as this information is collected prior to the assessment of infant allergic outcomes. To further reduce misrepresentation of day-to-day variation of infant diet, a high correlation of dietary pattern scores across the 3 days of the food diaries was observed, signifying good reproducibility of 1-day dietary records

		months. In addition, no associations were observed between a “<i>Noodles and seafood</i>” dietary pattern at month 12 and eczema, rhinitis and wheeze with use of nebulizer. “Predominantly Breastmilk” dietary pattern at months 6 and 9 was associated with increased odds of developing allergen sensitization at 18 months [adjusted OR (95% CI): 1.6 (1.01-2.5) and adjusted OR (95% CI): 1.5 (1.01-2.1) after adjusting for sex, ethnicity, maternal education levels, family history of allergy and eczema. There were no changes in trend upon performing sensitivity analysis.	
Nguyen et al. 2017⁷⁴ Population-based cohort (Generation R) see also Tromp 2012⁷⁵ Netherlands <u>Sample Size:</u> Baseline N: 5225 Analytic N: 2796 at infancy, 4066 at childhood for diet assessment <u>Sex:</u> m 49.2%, f 50.8% <u>Race/Ethnicity:</u> 63.7% Dutch background <u>Atopic Disease Risk Status:</u> Maternal history of atopic disease 40.5%	Intervention/Exposure: Impact of diet quality on allergic outcomes Assessment Methods of DP: Diet assessed during (pregnancy)*, infancy (mean age 12.9 months), childhood (mean age 8.1 yr) by validated semi-quantitative FFQ filled out by parents *not relevant in this table Food-based diet quality scores reflecting adherence to guidelines with 10 components representing a healthy diet	Outcomes studied: Sensitization with 10 years of age by SPT 26% Information on physician-diagnosed inhalant (10.6%) and food allergies (1.9%), eczema 20%, asthma (8.3%) by questionnaires Max diet quality score not reached by any participant diet quality in infancy (mean 4.3 of 10) or childhood (4.5 of 10) were not associated with atopic outcomes in childhood in any of the models. The findings did not support the hypothesis that a healthy dietary pattern in early life is associated with a lower risk of allergic sensitization or atopic diseases in childhood	Confounders taken into account: All associations were analysed in three models with stepwise adjustment for potential confounders based on previous evidence. 1. Model: adjusted for child’s ethnic background, sex, age at outcome assessment, and total energy intake. 2. Model: additionally, adjusted for several socioeconomic and lifestyle factors, including maternal BMI at enrolment, maternal educational level, household income, parity, prenatal pet exposure, alcohol intake during pregnancy, smoking during pregnancy, folic acid supplements during pregnancy, and maternal history of atopic disease. 3. Model: associations of diet quality in pregnancy, infancy, or childhood with allergic sensitization and atopic diseases were independent of diet at the other two time points by additionally adjusting them for each other. Breastfeeding, child’s sex, child’s ethnic background, and maternal history of atopic diseases were separately

			examined as potential effect modifiers by including interaction terms in the models
Grimshaw et al. 2015⁷⁶ Nested, case-control within a cohort study (PIFA) UK <u>Sample Size:</u> Baseline N: 41 food-allergic infants (DBPCFC+), 82 controls <u>Sex:</u> FA: male 58.5% Control: male 52.4% <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Maternal asthma 26.8% (FA), 13.4 % (controls), maternal allergy 53.7% (FA), 37.8% (controls)	Intervention/Exposure: Characterisation of Dietary Patterns using PCA across hole cohort ad then seen if identified patterns were related to FA Assessment Methods of DP: Sets of 4 weekly dietary intake sheets for all nutritional intake (without amounts) were sent out every 2 months for the 1st year of life (prospectively collected) The first PCA looked at characteristics of the early infant diet, such as duration and exclusivity of breast-feeding, infant formula use, and timing and types of solid food introduced into the infant diet. The second PCA looked at the diet from solid introduction to 1 year of life and was termed the ongoing infant diet (did not included common allergenic foods).	Outcomes studied: No difference between the study groups for the early infant diet pattern, but significant difference for the ongoing diet pattern (P = .001). PCA for ongoing infant diet produced a pattern in which the first 3 components accounted for 50% of the variance, with the first component accounting for 32% of the variance. Component 1 depicted a dietary pattern with high positive values associated with fruit, vegetable, fish, and poultry consumption, “predominantly home cooked”. Highly processed adult foods and commercial baby foods were not important in the component. It was named “healthy infant diet”. Component 2 was a pattern defined by finger foods. Within the analysis, highest positive values were allocated to healthy finger foods, and the low/negative values were allocated to pureed baby foods and unhealthy finger foods. The third component had high values allocated to highly processed adult foods. The PCA assigned a score to each infant in the analysis according to how his or her diet corresponded to each of the dietary components. These scores were significantly different between the symptomatic and control infants (P = .002) for component 1 but not for components 2 or 3. Control infants having a significantly higher healthy infant diet dietary pattern score than children who had a food allergy.	Confounders taken into account: Age at solid introduction, maternal asthma, maternal allergy, maternal smoking, maternal education, maternal age, pet ownership, female sex, any siblings Allergenic foods not included in the on-going analysis to avoid food allergy confounding the outcomes

Grimshaw et al. 2014 ⁷⁷ Nested, case-control within a cohort study (PIFA) UK <u>Sample Size:</u> Baseline N: 41 food-allergic infants (DBPCFC+), 82 controls <u>Sex:</u> FA: male 58.5% Control: male 52.4% <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Maternal asthma 26.8% (FA), 13.4 % (controls), maternal allergy 53.7% (FA), 37.8% (controls)	Intervention/Exposure: Timing of solid food introduction Assessment Methods of DP: Sets of 4 weekly dietary intake sheets for all nutritional intake (without amounts) were sent out every 2 months for the 1st year of life (prospectively collected) Descriptive analysis of baseline characteristics	<u>Outcomes studied:</u> Infants who were diagnosed with food allergy by the time they were 2 years of age were introduced to solids earlier (≤16 weeks of age) and were less likely to be receiving breast milk when cow's milk protein was first introduced into their diet	Confounders taken into account: Age at solid introduction, maternal asthma, maternal allergy, maternal smoking, maternal education, maternal age, pet ownership, female sex, any siblings
Tromp et al. 2012 ⁷⁵ Prospective cohort study (Generation R) Netherlands <u>Sample Size:</u> Baseline N: 5088 mothers received FFQ Analytic N: 2173 preschool children (≤4 years of age) Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> only children of Dutch origin were included in the analyses (n=2443). Siblings within the Generation R cohort were randomly selected and excluded (n =270)	Intervention/Exposure: Dietary patterns related to asthma-related symptoms Assessment Methods of DP: Validated quantitative FFQs at 14 months of age The frequency of consumption of a food item was to be recorded per day, per week, or per month over the past 4 weeks. Prinzipal component analysis (PCA)	Outcomes studied: Asthma-related symptoms by ISAAC questionnaire at age 2,3 and 4 Questionnaire regarding respiratory tract infections at age 2,3 and 4 2 dietary patterns (DP) identified: DP 1 was associated with starchy foods, fruit, vegetables, potatoes, vegetable oils, fish, legumes and meat. This pattern was referred to "Health conscious" DP. [Comment: very similar to MD] DP 2 was associated with refined grains, soups and sauces, savoury and snacks, other fats, sugar containing beverages and meat. This pattern was referred to as the "Western" dietary pattern. High adherence to the "Western" dietary pattern was significantly associated with frequent wheeze at 3 years of age (RR: 1.39; 95% CI: 1.02-1.89) and frequent shortness of breath (RR: 1.44; 95% CI: 1.03-2.01) and respiratory tract infections (RR: 1.54; 95% CI: 1.08-2.19) at 4 years of age. However, this association was partially explained by energy	Confounders taken into account: Gender, gestational age and birth weight, maternal age, maternal socioeconomic status (SES), maternal smoking during pregnancy, Multiple parities and parental history of atopy Limitations: Several arbitrary decisions are involved in identifying dietary patterns by PCA. Decisions on combining food items into food groups, the number of factors to extract, the method of rotation, and the labelling of the components may influence the reproducibility of the findings. Potential confounders could not be fully excluded thereby final conclusions regarding the causality of the study results were precluded.

<u>Atopic Disease Risk Status:</u>		intake After adjustment for total energy intake, high adherence to the “Western” dietary pattern remained significantly associated with frequent wheeze (≥ 4) (aRR: 1.47, 95% CI: 1.04-2.07) at 3 years of age and frequent respiratory tract infections (≥ 3) (aRR: 1.46, 95% CI: 1.00-2.13) at 4 years of age, but no longer significantly associated with shortness of breath up to 4 years of age. Adherence to the “Western” dietary pattern remained not significantly associated with any respiratory symptom at age 2 years or short-term respiratory symptom up to 4 years of age. Adherence to the “Health conscious” diet was not significantly associated with respiratory symptoms up to 4 years of age, even after adjustment for total energy intake. Therefore, it does not support a protective effect of a “Health conscious” diet on respiratory outcomes in children younger than 4 years of age.	
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Supplementary file 5:

Supplementary table S5 Mediterranean diet and dietary patterns in infancy and childhood

Single studies on Mediterranean Diet

KIDMED Mediterranean score

Calatayud-Saez et al. 2016⁷⁸ prospective (cohort) study Spain <u>Sample Size:</u> Baseline N: 104 asthmatic children (1-5 year old) Sample Size Calculation: a significance level of 0.05 and a power of 85% were used, assuming a decrease in the mean number of childhood asthma attacks of 1 unit/patient/yr, with a standard deviation of 4 units, adjusted for a 25% loss. The resulting sample size was 115 patients. <u>Sex:</u> 50 girls and 54 boys <u>Atopic Disease Risk Status:</u>	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) Characterized by a high intake of unrefined plant-based foods such as fruits and fresh vegetables, whole grains, legumes, olive oil and nuts; low to moderate consumption of foods of animal origin such as fermented milk, fish, eggs and lean meats; and by a low intake of sugar, refined flour and fast food <u>Assessment Methods of MD:</u> At start of 1-year program “Learning to Eat from the Mediterranean”: 7-day recall questionnaire, KIDMED test Nutritional counselling, after 4 months KIDMED test 1-year follow-up: adherence to MD by KIDMed test	<u>Outcomes studied:</u> Asthma control Adherence to MD improved during programme, but not statistically analysed The adoption of a traditional Mediterranean diet could contribute significantly to the improvement of patients diagnosed with childhood asthma.	<u>Confounders taken into account:</u> <u>Limitations:</u> Inappropriate statistical analysis (comment in ref 50: “suffered from inappropriate statistical analysis and Lack of consideration of potential bias such as nonresponse and dropout bias that led to unreliable results and ambiguity in study population characteristics which made it difficult to compare the results against other studies.”)
Grigoropoulou et al. 2011⁷⁹ Cross-sectional survey, same cohort (extended PANACEA study) Greece <u>Sample Size:</u> Baseline N: 1125 children 10 to 12 years old Participation rate: 83,5%	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD): KIDMED <u>Assessment Methods of MD:</u> KIDMED food frequency questionnaire	<u>Outcomes studied:</u> Asthma by standardized ISAAC questionnaire Any asthmatic symptom 23.7% urban-residing children vs 14.6% living in rural areas (p<0.001) Mean adherence to MD 5.3% rural vs 4.7% urban High adherence to MD 4,8 % rural vs 2,4 % urban (different from ref 36 13,4 vs 11,6) The analysis showed that 1-unit increase in	<u>Confounders taken into account:</u> Adjusted for age, sex, BMI, physical activity status, and energy intake <u>Limitations:</u> Cross-sectional study, limitations such as recall bias and reverse causality bias

The total number of enrolled children ($n = 1125$) was deemed adequate to evaluate odds ratios (ORs) between various groups of study equal to 1.20, at probability level < 0.05, and achieving statistical power equal to 77% Sex: m 529, 596 f Race/Ethnicity: NR Atopic Disease Risk Status:		the KIDMED score was associated with 16% lower likelihood of having asthma symptoms greater adherence to MD was inversely associated with ever had wheeze (OR $_ 0.88$; 95% CI, 0.78, 0.98) and exercise wheeze (OR $_ 0.79$; 95% CI, 0.67, 0.93).	
Chatzi et al. 2008 ⁸⁰ Birth cohort, prospective Spain Sample Size: 460 children included at follow-up at age 6.5 years Analytic N: 412 for SPT Sex: NR 228 f, 232 m Race/Ethnicity: NR Atopic Disease Risk Status: General population	Intervention/Exposure: Mediterranean diet (MD) assessed by modified KidMed index Assessment Methods of MD: Semiquantitative FFQs of 96 food items based on KidMed index, modified ≥ 7 optimal MD ≤ 3 low level MD	Outcomes studied: Persistent wheeze (≥ 1 episode over past 12 months or preceding years) 13,8% atopic wheeze (current wheeze and atopy) 5.8% Atopy (sensitization to $\geq 1/6$ common aeroallergens) 17% Adherence to MD 9.3% low level 53.7% medium level 37 % high level High adherence to MD was negatively associated with persistent wheeze OR 0.46 (0.10 – 2.17) and atopy =R 0.49 (0.18 – 1.32), but did not reach statistical significance Atopic wheeze OR 0.64 (0.10 – 4.06)	Confounders taken into account: Gender, maternal age at pregnancy, maternal social class and education, maternal smoking during pregnancy, supplement use during pregnancy, breastfeeding, lower track resp. infection at 1 year, birth weight, gestational age, birth order, number of siblings, BMI at 6.5 years Control for energy intake Limitations: Variability in choosing cut-off points Different distribution of selected foods in different populations
Alphantonogeorgos et al. 2014 ⁸¹ Cross-sectional study (extended PANACEA study ref 37) Greece, urban (Athens, $n = 700$) or rural environment ($n = 425$) Sample Size:	Intervention/Exposure: Hypothesis: living environment could affect asthma prevalence, with MD and physical activity as mediators Definition of mediterranean diet (MD): KIDMED Assessment Methods of MD:	Outcomes studied: Asthma by standardized ISAAC questionnaire Any asthmatic symptom 23.7% urban-residing children vs 14.6% living in rural areas ($p < 0.001$) Mean adherence to MD 5.3% rural vs 4.8% urban	Confounders taken into account: Adjusted for several confounders Limitations: Cross-sectional study, limitations such as recall bias and reverse causality bias

Baseline N: 1125 children 10 to 12 years old Partician rate: 83,5% Sample Size Calculation: NR <u>Sex:</u> m 529, 596 f <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Parental atopy 34% urban vs 27,3 rural	KIDMED food frequency questionnaire	High adherence to MD 12,3% (13.4% rural vs 11.6% urban) different from ref 46 (4,8% rural vs 2,4% urban) data concerning diet more detailed in Grigoropoulou et al.⁷⁹ Adherence to the Mediterranean diet was related negatively with asthma symptoms (standardized beta = -0.224, p<0.001). An inverse mediating effect of the Mediterranean diet was observed for the urban environment – asthma relation (standardized beta=-0.029, p<0.001) while physical activity had no significant contribution (p=0.62), adjusted for several confounders																																				
Arvaniti et al. 2011 ⁸² Cross-sectional study (PANACEA study) Athen, Greece <u>Sample Size:</u> Baseline N: 700 (10-12 years old) Partician rate 83,5% <u>Sex:</u> m 323, f 377	<u>Intervention/Exposure:</u> MD adherence measured by KidMed sore Assessment Methods of MD: semi-Quantitative FFQ on consumption of 63 food items on daily or weekly basis completed by parents during face-to-face interviews Assessment of dietary pattern of breakfast, but answers not different between asthma and no asthma	<u>Outcomes studied:</u> Asthma acc. to ISAAC II criteria 23.7% Adherence to MD (mean 4.8) Low n=213, Moderate n=413, high n=74 Greater adherence to MD inversely associated: <table><tr><td></td><td>Bad (0-3)</td><td>Moderate (4-7)</td><td>Good (8-12)</td><td>p</td></tr><tr><td>N</td><td>213</td><td>413</td><td>74</td><td></td></tr><tr><td>Ever had wheeze (%)</td><td>29</td><td>19</td><td>8</td><td>0.001</td></tr><tr><td>Exercise wheeze (%)</td><td>11</td><td>7</td><td>0</td><td>0.004</td></tr><tr><td>Night cough (%)</td><td>17</td><td>11</td><td>6</td><td>0.07</td></tr><tr><td>Ever had diagn. Asthma (%)</td><td>16</td><td>9</td><td>3</td><td>0.002</td></tr><tr><td>Any asthma symptoms (%)</td><td>34</td><td>22</td><td>5</td><td><0.001</td></tr></table> One-unit increase in KidMed score was associated with 14% lower likelihood of having asthma Pattern: No sign. associations with single food groups		Bad (0-3)	Moderate (4-7)	Good (8-12)	p	N	213	413	74		Ever had wheeze (%)	29	19	8	0.001	Exercise wheeze (%)	11	7	0	0.004	Night cough (%)	17	11	6	0.07	Ever had diagn. Asthma (%)	16	9	3	0.002	Any asthma symptoms (%)	34	22	5	<0.001	<u>Confounders taken into account:</u> Various factors considered as potential confounders and effect mediators <u>Limitations:</u> Cross-sectional study Recall bias not excluded
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		except fish and meat (increased intake, less asthma symptoms)	
Arvaniti et al. 2011 ⁸³ Cross-sectional study (PANACEA study) Athen, Greece <u>Sample Size:</u> Baseline N: 700 (10-12 years) Participation rate 83,5% <u>Sex:</u> m 323, f 377	<u>Intervention/Exposure:</u> MD adherence measured by KidMed score <u>Assessment Methods of MD:</u> see Arvaniti et al. ⁸² Including salty-snack consumption (pattern)	<u>Outcomes studied:</u> Asthma acc. to ISAAC II criteria 23.7% Pattern: 48% reported salty-snack consumption (SSC) ≥1 times/week SSC was inversely associated with the KidMed score. SSC >3 times/ week vs never was associated with a 4.8 times higher likelihood of having asthma symptoms	<u>Confounders taken into account:</u> see Arvaniti et al. ⁸² <u>Limitations:</u> see Arvaniti et al. ⁸²
Chatzi et al. 2007 ⁸⁴ Cross-sectional survey Crete, Greece <u>Sample Size:</u> Baseline N: 690 (age: 7-18 years) Analytic N: 537 (incl. information about allergic manifestations) <u>Sex:</u> m 331, f 359 <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> 6.8% parental asthma	<u>Intervention/Exposure:</u> Adherence to MD measured by modified KidMed score (left out questions on fast food, sweets and legumes, optimum reduced from 8 to 6) <u>Assessment Methods of MD:</u> FFQ (58 items) usual weekly food consumption during previous 12 months with a 6-level-scale (never, <1 times per week, 1-2 times, 3-4 times, once per day, > once per day) ≥ 6 optimal MD ≤ 3 low level MD Degree of adherence based on KidMed index, modified + MD Score (EPIC), modified Definition of mediterranean diet (MD) KidMed Index, more red than white meat per week -1, margarine more than once a week -1	Questionnaires on respiratory and allergic symptoms over the past 12 months by parents, SPT 10 aeroallergens Any wheezing in the past 16.8%, atopic wheeze 5.4%, current wheezing 4.6%, nocturnal dry cough (last 12 months) 10.9% Any rhinitis in the past 18.7% (atopic rhinitis 6.7%, current AR 13.3, current seasonal AR 5.1) Atopy 22.3% <u>adherence to MD</u> 27.9 % low level 43.8 % medium level 28.3 % high level After multivariate logistic regression analysis high level of adherence to MD was inversely related to AR ever OR 0.34 (0.18 – 0.64) p<0.01 AR with atopy OR 0.39 (0.13-0.97) Current AR OR 0.49 (0.24 – 0.99) p<0.05 Nocturnal cough apart from cold in the last 12 months OR 0.49 (0.23-0.96) Protective but not sign. for wheezing and	<u>Confounders taken into account:</u> Age, sex, BMI, parental asthma number of older siblings <u>Limitations:</u> Cross sectional design Self-administered questionnaire Non-validated FFQ

		atopy Pattern: Nuts ≥ 3 times/w reduced wheezing ever OR 0.54 (0.34-0.86) and current wheeze OR 0.46 (0.20-0.98) Margarine > once/w increased current wheezing OR 2.19 (1.01-4.82), AR ever OR 1.99 (1.32-3.00), current AR OR 2.10 (1.31-3.37)	
Chatzi et al. 2007 85 Birth cohort, prospective Spain <u>Sample Size:</u> 460 children included at follow-up at age 6.5 years Analytic N: 412 for SPT <u>Sex:</u> NR 228 f, 232 m <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> General population Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	<u>Intervention/Exposure:</u> Mediterranean diet (MD) assessed by modified KidMed index (questions regarding breakfast left out, optimum reduced from 8 to 7) <u>Assessment Methods of MD:</u> Semiquantitative FFQs of 96 food items based on KidMed index, modified ≥ 7 optimal MD ≤ 3 low level MD	<u>Outcomes studied:</u> prevalence of current wheeze, atopic wheeze, and atopy at age 6.5 yr were 8.7%, 5.8%, and 17.0% pattern: A high consumption (>40 g/day) of fruity vegetables were found to have beneficial effect on current wheeze (OR, 0.38; 95% CI, 0.15–0.95, $p < 0.05$), and atopic wheeze with a significant decreasing trend with increasing intake (OR, 0.19; 95% CI, 0.04–0.95, p for trend = 0.04). Atopy was negatively associated with a high fish intake (>60.5 g) (OR, 0.43; 95% CI, 0.21–0.90, $p < 0.05$).	<u>Confounders taken into account:</u> Gender, maternal and parental asthma, maternal and paternal atopy, maternal smoking, BMI at age 6.5 yr, maternal and paternal education and social class, breastfeeding, fish intake during pregnancy, and number of siblings at age 6.5 yr. In addition, analyses including specific food intake were adjusted for total energy intake using the standard multivariate method <u>Limitations:</u>
<u>Adult EPIC score/ Mediterranean diet pattern</u>			
Castro-Rodriguez et al. 2017 ⁸⁶ Cross-sectional Spain <u>Sample Size:</u> Baseline N: 2922 pre-school	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) Pro: Fruit, fish, vegs, legumes, cereals, pasta, rice, potatoes Anti: meat, milk, fast food	<u>Outcomes studied:</u> Current wheezing cw (episodes over the past 12 months) 20% Highest quartile of MD cw 42.9, cnw 53.2 After multivariate analysis: highest quartile of	<u>Confounders taken into account:</u> Children with current wheeze were more often born by cesarean section, lower birth weight, lower proportion of breast-feeding, higher antibiotic and acetaminophen consumption in first year of life,

children invited Analytic N: 1784 (mean age 4.08 ± 0.8) completed questionnaire, 1757 answered questions regarding current wheezing <u>Sex:</u> male cw 53.3, cnw 51.1 <u>Race/Ethnicity:</u> caucasian cw 91.5, cnw 94.3 <u>Atopic Disease Risk Status:</u> General population, Paternal asthma cw 6.3, cnw 3.1, maternal asthma cw 8.0, cnw 4.0	3 answers (0-2 and 2-0 pts, respectively) Based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷ Range in study group 14-36, adherence by quartiles Assessment Methods of MD: Environmental questionnaires including questions on consumption and allergic manifestations (based on ISAAC phase III)	MD aOR 0.54 (0.33 – 0.88)	more acetaminophen consumption in previous 12 months, More parental asthma, more smoking, heavier truck traffic in front of house, more cat owners, lower rate of vigorous physical activity, significantly more margarine consumption <u>Limitations:</u> Questionable MD score, Adherence by quartiles not by cut-off values – highest quartile does not mean high adherence (e.g. only 30% of children ate vegs more than 3 times per week)
de Batlle et al. 2008⁸⁸ Cross sectional study Mexico <u>Sample Size:</u> Baseline N: random sample of 3125 children Analytic N: 1476 children (6-7 years) Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> General population	<u>Intervention/Exposure:</u> Mediterranean diet (MD) Based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷ Assessment Methods of MD: Parental FFQ with 70 food items, usual diet in the last 12 months (8 food groups: vegs (+), legumes (+), fruit and nuts (+), dairy products (-), cereals (+), meat (-), fish (+), junk food and fat (-) with minimum (0) to maximum (8) Adherence measure in tertiles	<u>Outcomes studied:</u> Asthma/rhinitis related outcomes by ISAAC questionnaire Asthma ever 170 (12%) Wheezing ever 354 (25%) Current wheezing n=147 (11%) Rhinitis ever n=100 (7%) Sneezing ever n=419 (30%) Current sneezing n=370 (25%) Current itchy-watery eyes n=166 (11%) high consumption of fruits and nuts, vegetables, and junk food and fat -> mean MD 3.7 (!) Adherence to MD (2nd and 3rd tertile compared with 1st tertile) inversely associated with Asthma ever OR 0.60 (0.40-0.91) Wheezing ever OR 0.64 (0.47-0.87) Sneezing ever OR 0.79 (0.59-1.07), current Sneezing OR 0.71 (0.52-0.96) Current itchy-watery eyes OR 0.63 (0.42-0.95)	<u>Confounders taken into account:</u> Gender, number of older sisters or brothers, birth weight, body mass index (BMI), maternal breastfeeding, parental educational level, children's exercise, smoking exposure (while in the womb, during the first year of life, or currently in the home), parental medical history of asthma and allergic rhinitis, animals at home during pregnancy, animals at home during first year of life, living in a ranch during pregnancy, premature birth, respiratory infections during early life, silhouette, changes from the silhouette they had at 4-year old, type of combustible used for cooking at home, sleeping alone in a room, and mould or dampness at home. <u>Limitations:</u> Cross-sectional study Adherence to MD by tertiles not

			cut-offs, Diet score questionable
Garcia-Marcos L et al. 2007⁸⁹ Cross sectional study Spain <u>Sample Size:</u> Baseline N: 20106 children (6-7 years old) Mean participation rate: 78.7% Complete data on consumption: 17145 children <u>Sex:</u> NR <u>Race/Ethnicity:</u> only Spanish children <u>Atopic Disease Risk Status:</u> General population	<u>Intervention/Exposure:</u> Relationship of MD with asthma/ rhinoconjunctivitis adjusting for obesity and exercise Based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷ Definition of mediterranean diet (MD): fruit, fish, vegetables, pulses, cereals, pasta, rice and potatoes were considered “pro-Mediterranean” foods and rated 0, 1 or 2 points from less frequent to more frequent intake. Meat, milk and fast food were considered “anti-Mediterranean” foods and rated 0, 1 or 2 points from more frequent to less frequent consumption	<u>Outcomes studied:</u> Asthma/ rhinoconjunctivitis acc. to ISAAC questionnaire Current occasional asthma (COA) 1379 (8%) Current severe asthma (CSA) 390 (2.3%) Rhinoconjunctivitis 1446 (8.4%) Independent of the amount of exercise, each Mediterranean score unit had a small but protective effect on CSA in girls (adjusted OR 0.90, 95% CI 0.82 to 0.98). Diet Pattern <u>Protective factor for COA:</u> frequent intake of nuts (1–2 times/week and >3 times/week vs never/occasionally) aOR 0.82 (0.73-0.94) and aOR 0.68 (0.51-0.90) p<0.001 <u>protective factors for CSA:</u> of seafood (adjusted ORs 0.63 (95% CI 0.44 to 0.91) and 0.53 (95% CI 0.35 to 0.80)) and cereals (adjusted OR 0.56 (95% CI 0.30 to 1.02) and 0.39 (95% CI 0.23 to 0.68)), trend for meat, fruit, vegs, cereal, milk) <u>risk factor for CSA:</u> fast food (adjusted ORs 1.64 (95% CI 1.28 to 2.10) and 2.26 (95% CI 1.09 to 4.68)) <u>protective factors for rhinoconjunctivitis:</u> seafood (adjusted ORs 0.74 (95% CI 0.60 to 0.92) and 0.67 (95% CI 0.53 to 0.85)) and fruit (adjusted ORs 0.76 (95% CI 0.60 to 0.97) and 0.71 (95% CI 0.57 to 0.88)), trend for meat	<u>Confounders taken into account:</u> <u>Limitations:</u> No adjustment of food consumption to energy intake Questionable MD score
Suarez-Varela et al. 2010⁹⁰ Cross-sectional study ISAAC phase III Spain <u>Sample Size:</u> Baseline N: 20106 (6-7 years of age)	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) based on⁹¹ which was again based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷ Range 0-22 <u>Assessment Methods of MD:</u>	<u>Outcomes studied:</u> Atopic dermatitis assessed acc. to ISAAC questionnaire 5.92% Mean MDS 13.26 Good adherence 9.43% Bad adherence 90.57%	<u>Confounders taken into account:</u> Gender, obesity, exposure to tobacco smoke in the first year of life, younger and older siblings, and exercise. <u>Limitations:</u> Questionable MD Definition, especially with regard to outcome

Analytic N: 13153 Participation rate 76.5% <u>Sex:</u> m 6621, f 6512 <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	FFQ on 16 foods and food groups with 3 answers (never, 1-2 times/ wk, ≥3 times/wk)	No association between MDS and AD Pattern Milk was negatively associated with AD (aOR 0.42 (0.22-0.79) when eaten 1-2 times/wk, aOR 0.50 (0.33-0.75) when consumed ≥3 times/wk). Butter aOR 0.70 (0.50-0.97) when consumed ≥3 times/wk) Nuts aOR 0.51 (0.33-0.80) when consumed ≥3 times/wk)	
Tamay et al. 2014 ⁹² Cross-sectional study Turkey <u>Sample Size:</u> Baseline N: 11483 (6-7 years of age) Analytic N: 9875 Attrition: Sample Size Calculation: NR <u>Sex:</u> m 50.7%, f 49.3% <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) MDS based on⁹¹ which again was based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷ Range: 0 to 22 <u>Assessment Methods of MD:</u> Semiquantitative FFQ with 30 food items assessing diet in the past 12 months completed by parents Consumption of protective foods such as potatoes, rice, cereals, pasta, vegetables, tomatoes, broad bean fish and other sea foods, fruits, nuts, olive oil, fish oil, and some traditional foods made from grapes and mulberries, fermented drinks made from millets and various seeds, pickle; aggravating foods including fast-food, potato chips and crackers, chocolates, lollipops and candies, cookies and muffins, margarine; and other foods including eggs, animal fats, milk and dairy products, meat, polyunsaturated fatty acids (butter), sun-flower oil, corn oil, tea, and olive were asked. (3 answers possible)	<u>Outcomes studied:</u> Allergic rhinitis acc. to ISAAC protocol Lifetime rhinitis 44.3% Current rhinitis 29.2% Current rhinoconjunctivitis 8.5% Physician-diagnosed AR 8.1% No protective effect of MD Pattern <u>physician-diagnosed allergic rhinitis:</u> Consumption of rice, and cereals ≥3 times/wk protective effect (aOR = 0.53, 95% CI = 0.32-0.87 and aOR = 0.58, 95% CI = 0.36-0.92). <u>current rhinoconjunctivitis:</u> pasta, and Chocolates ≥3 times/ wk protective effect (aOR = 0.45, 95% CI = 0.25-0.79 and aOR = 0.50, 95% CI = 0.29-0.86). <u>current rhinoconjunctivitis</u> Eating lollipops, candies and animal fats ≥3 times per week was positively associated with (aOR = 1.47, 95% CI = 1.00-2.17 and aOR = 2.25, 95% CI = 1.11-4.56).	<u>Confounders taken into account:</u> Gender, parental education level and exercise <u>Limitations:</u> Questionable MDS
Akçay et al. 2014 ⁹³ Cross-sectional study	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD): MD score based on the work of García-Marcos et al. 2016 et al. which again was based	<u>Outcomes studied:</u> Wheeze ever 17.4%, wheezing in last 12 months 9.0%, and lifetime doctor diagnosed	<u>Confounders taken into account:</u>

Turkey <u>Sample Size:</u> Baseline N: 10894 adolescents (13-14 years of age) Analytic N: 9991 Response rate: 91.7% Sample Size Calculation: NR <u>Sex:</u> 4746 boys (47.9%) and 5166 girls (52.1%) <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷ Ranging from 0 to 22 <u>Assessment Methods of MD:</u> Dietary intake was estimated by a semi-quantitative food frequency questionnaire. Consumption of foods including potatoes, rice, cereal, pasta, vegetables, fish, other sea foods, fruits, tomatoes, nuts, olive oil, fish oil, boiled grape juice, fermented drinks made from millets and various seeds, hamburger, potato chips, crackers, chocolates, lollipops, candies, cookies, muffins, margarine, eggs, animal fats, milk and dairy products, meat, PUFAs (butter), sun-flower oil, corn oil, tea, broad bean and olives were asked. (3 answers possible)	asthma prevalence 11.8% The mean MD scores for children with asthma and children without asthma were 12.51 and 12.53 The Mediterranean-style diet was not associated with the prevalence of asthma. Pattern: Asthma prevalence in children consuming fruits and animal fats ≥ 3 times a week was lower than in those with these foods consumed never or occasionally (aOR = 0.66, 95% CI = 0.48-0.93; and aOR = 0.58, 95% CI = 0.35-0.93, respectively. When animal fats or olive were consumed three or more times a week, asthma prevalence was lower than it was in those who consumed these foods once or twice per week (aOR = 0.48, 95%CI = 0.28-0.84; and aOR = 0.79, 95% CI = 0.66-0.94, respectively). When fermented drinks made from millets and various seeds, mix pickles and margarine were consumed ≥ 3 times a week, asthma prevalence was higher than it was in those who consumed these foods never or occasionally, or once to twice per week. When meat was consumed three or more times a week, asthma prevalence was higher than it was in those who consumed these foods once to twice per week (aOR = 1.26, 95% CI = 1.04---1.52)	<u>Limitations:</u> Asthma based on a questionnaire, without confirming the diagnosis according to their medical histories or to lung function tests. Another limitation of this study was that ISAAC protocol questions have not been validated in Turkey.
Rice et al. 2015⁹⁴ Case-control study Peru <u>Sample Size:</u> Baseline N: 287 asthmatic (physician diagnosed) children (9-19 years of age, mean 13.5) + 96 controls without asthma <u>Sex:</u> m 165, f 112 (controls m 40, f 56) <u>Race/Ethnicity:</u> NR	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD): MDS based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷, except milk (+) range 0-22 <u>Assessment Methods of MD:</u> FFQ with 170 food items assessed usual dietary intake over previous 2 weeks (6 answers possible)	<u>Outcomes studied:</u> Asthma status (asthma control, FEV1), AR, atopy 86% with controlled asthma Being above the median MDS scores was associated with decreased odds of asthma [OR = 0.55, 95 % CI (0.33, 0.92), p = 0.02]. Among children whose mothers completed secondary education, being above the median MDS significantly decreased the odds of asthma [OR = 0.31, 95 % CI (0.14, 0.71), p<0.01], whereas among those whose mothers did not complete secondary education there	<u>Confounders taken into account:</u> Maternal education, age, sex, BMI <u>Limitations:</u> No correction for energy intake Questionable MDS, but better than in other studies

<u>Atopic Disease Risk Status:</u> No information on parental allergy		was no protective effect [OR = 0.86, 95 % CI (0.43, 1.7), p = 0.66]. No association between MDS scores and asthma control, FEV1, allergic rhinitis, or atopic status	
Silveira et al. 2015 ⁹⁵ Cross-sectional study Brazil <u>Sample Size:</u> Baseline N: 268 (3-12 years of age) with persistent asthma, 126 age-matched controls with intermittend asthma <u>Sex:</u> m 159, f 109 (controls m 61, f 65) <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> FA asthma 59.5% (controls 56%) FA AR 72.8% (controls 67.2%)	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) (Criteria adapted from the literature) pro-MD pattern (fruit, vegetables, fish, fruit juices, root vegetables and tubers and grains) and a contra-MD diet (milk, meat, eggs, processed foods, soft drinks, butter). The Mediterranean diet was classified as “yes” when intake of at least 5 foods in each group was frequent (≥3 times per week) <u>Assessment Methods of MD:</u> Interview with parents/ guardians using a pre-coded questionnaire several outcomes including dietary habits food consumption over the past 12 months assessing frequent and infrequent consumption (never or <3 times/week)	<u>Outcomes studied:</u> No significant association between frequency of consumption of specific foods, food groups or dietary pattern (pro- vs anti-MD) and <u>severity</u> of asthma (not risk!)	<u>Confounders taken into account:</u> Multivariate analysis was applied to control for potential confounding factors, with inclusion of variables according to the preestablished hierarchical levels as follows: level 1: gender, skin color, maternal schooling, income, paternal schooling, and smoking during pregnancy; level 2: allergens in the home, gestational age, birth weight, family history of allergic rhinitis, exposure to passive smoking; level 3: dietary variables; and level 4: obesity. Only the variables with $P \leq 0.20$ remained in the model. <u>Limitations:</u> Statistical power insufficient Brought range of age – food consumption varies with age
Romieu et al. 2009 ⁹⁶ Cohort study Mexico <u>Sample Size:</u> Baseline N: 158 asthmatic children (6-14 years of age), 50 non-asthmatic children Analytic N: Attrition:	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou) ⁸⁷ <u>Assessment Methods of MD:</u> Dietary intake was evaluated using a 108-item validated quantitative FFQ completed by mothers with 8 possible answers regarding frequency and a fruit and vegetable index (FVI) and a Mediterranean	<u>Outcomes studied:</u> Pulmonary function was measured and nasal lavage collected and analyzed every 2 weeks The impact of these indices on lung function and interleukin-8 (IL-8) and their interaction with air pollutants were determined using mixed regression models with random intercept and random slope. No significant difference between the asthmatic and the non-asthmatic children. We observed a high frequency of intake of	<u>Confounders taken into account:</u> 5-day accumulated moving average O3 (ppb), 5-day accumulated average (maximum) PM2.5 (µg/m3), Previous day minimum temperature, gender, body mass index, calories and chronological time <u>Limitations:</u>

Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	diet index (MDI) were constructed. FVI: based on intake of fruits and vegetables and the consumption of vitamins or supplements reported on the questionnaire and were scored on a scale of 0 to 3 MDI adapted from that by Trichopoulou/ Psaltopoulou used in adults (EPIC)⁸⁷ with regard to cardiovascular risk modifications: 1) without alcohol ii) without high monounsaturated/saturated consumptions iii) introduction of junk food In the case of fruits, vegetables, cereals, legumes, dairy products and fish, a value of 1 was assigned if consumption was above of the median value and 0 otherwise. For meat and junk food, the scoring was reversed.	fruit or fruit juices, vegetables and dairy products as well as junk food, while the intake of fish was low FVI was inversely related to IL-8 levels in nasal lavage ($p < 0.02$) with a significant inverse trend (test for trend $p < 0.001$), MDI was positively related to lung function ($p < 0.05$), and children in the highest category of MDI had a higher FEV1 (test for trend $p < 0.12$) and FVC (test for trend $p < 0.06$) than children in the lowest category. A significant interaction was observed between FVI and ozone for FEV1 and FVC as was with MDI and ozone for FVC. No effect of diet was observed among healthy children.	
Nagel et al. 2010⁹⁷ Cross-sectional studies of 29 centres in 20 countries ISAAC <u>Sample Size:</u> Baseline N: 50004 schoolchildren (8-12 years) Analytic N: 29579 with SPT Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u>	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD) “score of MD derived according to consumption frequency of food items” Selected food items: meat (-), fish (+), fresh fruit (+), raw green vegs (+), cooked green vegs (+), burgers (-), fruit juice (+), fizzy drinks (-) <u>Assessment Methods of MD:</u> FFQ When was dietary intake assessed and how often? E.g. twice during pregnancy at 24 and 36 weeks.	<u>Outcomes studied:</u> <u>Effect on current wheeze:</u> Fruit intake (ORadj 0.86, 95% CI 0.73 to 1.02) and consumption of fish (ORadj 0.85, 95% CI 0.74 to 0.97) was associated with low prevalence in affluent countries. Burger consumption aOR 0.76 (0.61-0.95), fruit (ORadj 0.71, 95% CI 0.57 to 0.88) and fruit juice intake aOR 0.80 (0.68-0.94) and consumption of cooked green vegetables (ORadj 0.78, 95% CI 0.65 to 0.95) was associated with a lower prevalence of current wheeze in non-affluent countries. <u>Association with lower lifetime prevalence of asthma:</u> more frequent consumption of fruit, vegetables and fish <u>Association with higher lifetime asthma prevalence asthma:</u> high burger consumption ≥ 3 times/week aOR 1.42 (1.08-1.87) (comment: obviously driven by affluent countries - in non-affluent countries, an inverse relationship was found between burger consumption and wheeze aOR 0.76 (0.61-0.95). <u>allergic sensitisation:</u> no sign. association of any food item	<u>Confounders taken into account:</u> Age, sex, environmental tobacco smoke, parental atopy, exercise, number of siblings <u>Limitations:</u> Questionable def of MD No adjustment for total energy intake and BMI

		<u>atopic wheeze</u> no sign. associations “Food selection according to the ‘Mediterranean diet’ was associated with a lower prevalence of current wheeze and asthma ever (ptrend=0.03).”	
Gonzalez et al. 2010 ⁹⁸ cross-sectional study Spain <u>Sample Size:</u> Baseline N: 14700 Analytic N: 7454 children (6-7 years of age), 7391 adolescents (13- to 14-yr olds) Response rate: 75% in the 6- to 7-yr age group and 85% in the 13- to 14-yr-old age group <u>Sex:</u> NR <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Not assessed	<u>Intervention/Exposure:</u> Definition of mediterranean diet (MD): Fruit, fish, vegetables, pulses, cereals, pasta, rice and potatoes were considered pro-Mediterranean foods and rated 0, 1 or 2 points from less frequent to more frequent intake (0 points = never or occasionally; 1 point = 1 or 2 times/wk; 2 points = ≥3 times/wk). Meat, milk and fast food were considered anti-Mediterranean foods and rated 0, 1 or 2 points from more frequent to less frequent consumption (0 points = ≥3 times/wk; 1 point = 1 or 2 times/wk; 2 points = never or occasionally). MDS developed by Garcia-Marcos⁹¹ to be added based on score used in adults (EPIC) with regard to cardiovascular risk (Trichopoulou/ Psaltopoulou)⁸⁷	<u>Outcomes studied:</u> Based on ISAAC questionnaire The prevalence of asthma in children was 39.9%, current asthma 13.8%, severe asthma 4.7% and exercise-induced asthma 6.5%. In adolescents, this prevalence was 22.2%, 12.4%, 5.2% and 19.5%, respectively MDS range 3-21 (mean 13.1) in children and 4-20 (mean) 12 in adolescents Greater adherence to the MD is associated with a higher risk of severe asthma (odds ratios = 2.26, 95% CI: 1.21–4.22 in the 2nd quartile, but not in the 3rd and 4th) in girls of 6–7 yr. There was no significant relationship for the other asthma categories in the population studied.	<u>Confounders taken into account:</u> <u>Limitations:</u> Questionable MDS “As regards individual foods, it was noted that in the lower age group, more than 2/3 of the children ate meat (-), fruit, cereals, potatoes and milk (-) more than three times per week.” Adherence by quartiles not by cut-off values – highest quartile does not mean high adherence
Other dietary patterns			
de Cassia et al. 2014 ⁹⁹ Cross-sectional study Brazil <u>Sample Size:</u> Baseline N: 1500 children (6-12 year old) Analytic N: 1187 Attrition: Sample Size Calculation: NR <u>Sex:</u> male 53.3% <u>Race/Ethnicity:</u> NR	<u>Intervention/Exposure:</u> Dietary pattern: Western Diet vs prudent <u>Assessment Methods of MD:</u> Validated quantitative food frequency questionnaire of 97 food items adapted to take local dishes into account administered to mothers by nutritionists The frequency of consumption of these items were divided into the following 4 categories: never consumes = 0; consumed 1–3 times a month = 1; once a week = 2; 2–4 times a week = 3; and ≥ 4 times in weeks = 4. Afterward, the scores of the frequency of	<u>Outcomes studied:</u> Asthma by ISAAC questionnaire 10.6% From this analysis, 2 components (patterns) were extracted that accounted for 45.7% of the total variance. The eating patterns that were extracted were named as Western and Prudent. The first component was positively correlated with the intake of sugars, typical Brazilian dishes, pastries, fast food, oils, milk, cereals, cakes, and sauces. The second component was positively correlated with roots, legumes, fruits, and leafy vegetables. The indices relating to internal consistency (a > 0.60) ensured an acceptable	<u>Confounders taken into account:</u> BMI, physical activity, pubertal development, gender (male, female reference category), age (< 10 years, ≥ 10 years reference category), education of caregiver (£ 4th grade, 5th grade ± reference category), household location (urban, rural reference category), per capita income [as minimum salary (MS); £ 1 MS, > 1 MS reference category], number of people living in the household (> 3, £ 3 reference category), and

<u>Atopic Disease Risk Status:</u>	consumption were calculated as weighed proportion consumption where the numerator is the sum of the categories of all food items into in food cluster multiplied by 4 and the denominator the number of food items into food cluster multiplied by 4. This score or weighed proportion consumption represents a summary measure of the food consumption	level of accuracy of measurement for the 2 patterns, ensuring internal consistency for the dimensions of the questionnaire. Certain foods and food groups were not considered in the analysis due to the low communality presented ($h^2 < 0.30$): soft drinks, beef, chicken, fish, eggs, processed meat products, bread, baked beans, and artificial sweeteners. We found a positive statistically significant association of the Western pattern with wheeze (odds ratio = 1.77, 95% confidence interval: 1.10–2.84) after adjustment for total energy intake and controlling for potential confounders	presence of smokers in the house (no reference category, Yes) <u>Limitations:</u>
Lee et al. 2012 ¹⁰⁰ Cross-sectional study Taiwan <u>Sample Size:</u> Baseline N: 2,419 schoolchildren Analytic N: 2082 Response rate: 78.8%. Sample Size Calculation: NR <u>Sex:</u> m 1111, f 971 <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Parental asthma: 3,7%	<u>Intervention/Exposure:</u> Dietary pattern identified by reduced rank regression (RRR) <u>Assessment Methods of DP:</u> FFQ with 21 food groups to assess dietary intake (at home) Average intake in days/wk in the past month Food groups included vegetables, fruits, milk, yogurt, Yakult (lactic acid beverages with low dairy protein and high sugar), cheese, meat, fish, shellfish, organ meat (e.g. heart, liver, kidney and stomach of poultry and livestock), soybean milk, soy products, eggs, fast foods (e.g. hamburgers, pizza, French fries, fried chicken, and fried Asian delicacies), high-fat snacks (e.g. potato chips, flour based and rice flour-based crisps), sweet drinks (e.g. cola and soda), candy (e.g. chocolate and candy), desserts (e.g. cakes, cookies and sweet pastries), instant noodles, rice and flour.	<u>Outcomes studied:</u> Asthma assessed by ISAAC questionnaire by face-to-face interviews Asthma ever 5.4% Current asthma 3.5% Current severe asthma 2.3% Exercise-induced wheeze 3.1% Nocturnal cough 6.9% More prevalent in boys The RRR derived dietary pattern was characterized by high consumption of fast foods, high-fat snacks, candy, and cheese; and low consumption of fruit, vegetables and rice. The RRR-derived dietary pattern was associated with an increased risk of current asthma (OR [95% CI]) (2.42 [1.19-4.93] for Q4/Q1, p-for-trend=0.01), current severe asthma (3.21 [1.11-9.25] for Q3/Q1, 4.45 [1.59-12.5] for Q4/Q1; p-for-trend=0.003), and nocturnal cough (1.79 [1.06-3.05] for Q2/Q1, 1.74 [1.02-2.97] for Q3/Q1, 1.82 [1.07-3.11] for Q4/Q1; p-for-trend=0.049).	<u>Confounders taken into account:</u> Age, sex, BMI z-score, older sibling number (0, 1 and 2+), parental education level (<high school, high school, and college+), parental asthma status (yes and no), ambient NOx concentration and Seasonal effect (spring and summer versus fall and winter) <u>Limitations:</u> Cross-sectional design -> no causal relationship
Jonsson et al. 2016 ¹⁰¹ Birth cohort	<u>Intervention/Exposure:</u> Dietary differences in relation to allergy	<u>Outcomes studied:</u> AR, asthma, FA, AD (pediatrician diagnosed	<u>Confounders taken into account:</u>

Sweden <u>Sample Size:</u> Baseline N: 65 children, 28 living on a farm, 37 controls from a rural area but not farm (10-14 months of age) <u>Sex:</u> farm: m 36%, f 64% Control: m 62%, f 38% <u>Atopic Disease Risk Status:</u> Farm: mother 25%, father 4% Controls mother 30%, father 32%	outcomes <u>Assessment Methods of MD:</u> 24-h dietary recall by pre-decided interview protocol + 24-h food diary at 1 year of age	at year 1.5 and 3): 1 farm child with eczema (4%), 10 controll children (32%): 6 AD, 4 A, 2 FA, 1 AR Farm children had a higher intake of farm milk (comment: median intake was 0g), whole cream (comment: median intake was 1g, energy-adjusted 0g), cholesterol, saturated fat, and fat in total and tended to eat more butter, while controls consumed more carbohydrates and poultry (comment: median intake was 0g) and tended to eat more margarine (comment: median intake was 2g, energy-adjusted 0g). Farm children also had higher intakes of homemade porridge/gruel (comment: median intake was 0g), oily fish (comment: median intake was 0g), and iodine. A weak negative association was found between seafood intake and allergy development, while allergy was positively associated with the intake of pork as well as zinc in the control group; these intakes also correlated with each other.	<u>Limitations:</u> Numbers too small for statistical analysis
Loo et al. 2017 ¹⁰² cohort study (GUSTO study) Singapore <u>Sample Size:</u> Baseline N: 486 infants Analytic N: Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> Chinese, Malays and Indians <u>Atopic Disease Risk Status:</u>	<u>Intervention/Exposure:</u> Influence of infant dietary pattern on allergic outcomes until 5 yr of age <u>Assessment Methods of DP:</u> Analysis of dietary data from 6-12 months revealed 4 patterns: <i><u>Predominantly breastmilk</u></i>—mainly breastmilk and less formula milk; <i><u>according to Guidelines</u></i>—rice porridge, vegetables, fruits and low-fat fish and meat; <i><u>Easy-to-prepare foods</u></i>—infant cereals, juices, cake and biscuits; <i><u>Noodles (in soup) and seafood</u></i>—rice and wheat noodles and common accompaniments such as fish and shellfish. A fifth pattern emerged at age 12 months: <i><u>Pulses and grains</u></i>—characterized by high intake of nuts and seeds, grains, legumes and lentils	<u>Outcomes studied:</u> Allergic outcomes (sensitization, eczema, rhinitis, wheeze with use of nebulizer) by modified ISAAC questionnaire at 3,6,9,12,18,24,36,48,60 months <i>“Noodles and seafood”</i> dietary pattern at month 12 which consists of consumption of rice and wheat noodles, prawn, scallop and cuttlefish was associated with reduced odds of developing allergen sensitization at ages 18 months [adjusted OR (95% CI): 0.5 (0.3-0.98)] and at 60 months [adjusted OR (95% CI): 0.7 (0.4-0.98)] Further analysis showed that a <i>“Noodles and seafood”</i> dietary pattern at month 12 was also associated with reduced odds of developing house dust mite allergen sensitization at ages 18 months [adjusted OR (95% CI): 0.4 (0.2-0.9)] and 60 months [adjusted OR (95% CI): 0.7 (0.4-0.99)]. There were no associations between a <i>“Noodles and seafood”</i> dietary pattern at month 12 and development of food	<u>Confounders taken into account:</u> Sex, ethnicity, maternal education level, FA, eczema <u>Limitations:</u> Regular collection of information at multiple time points. The collection of infant dietary patterns also reduces recall and response bias as this information is collected prior to the assessment of infant allergic outcomes. To further reduce misrepresentation of day-to- day variation of infant diet, a high correlation of dietary pattern scores across the 3 days of the food diaries was observed, signifying good reproducibility of 1-day dietary records

	and high energy-dense confectionaries	allergen sensitization at 18, 36 and 60 months. In addition, no associations were observed between a “ <i>Noodles and seafood</i> ” dietary pattern at month 12 and eczema, rhinitis and wheeze with use of nebulizer. “Predominantly Breastmilk” dietary pattern at months 6 and 9 was associated with increased odds of developing allergen sensitization at 18 months [adjusted OR (95% CI): 1.6 (1.01-2.5) and adjusted OR (95% CI): 1.5 (1.01-2.1) after adjusting for sex, ethnicity, maternal education levels, family history of allergy and eczema. There were no changes in trend upon performing sensitivity analysis.	
Nguyen et al. 2017¹⁰³ Population-based cohort (Generation R) see also Tromp 2012¹⁰⁴ Netherlands <u>Sample Size:</u> Baseline N: 5225 Analytic N: 2796 at infancy, 4066 at childhood for diet assessment <u>Sex:</u> m 49.2%, f 50.8% <u>Race/Ethnicity:</u> 63.7% Dutch background <u>Atopic Disease Risk Status:</u> Maternal history of atopic disease 40.5%	<u>Intervention/Exposure:</u> Impact of diet quality on allergic outcomes <u>Assessment Methods of DP:</u> Diet assessed during (pregnancy)*, infancy (mean age 12.9 months), childhood (mean age 8.1 yr) by validated semi-quantitative FFQ filled out by parents *not relevant in this table Food-based diet quality scores reflecting adherence to guidelines with 10 components representing a healthy diet	<u>Outcomes studied:</u> Sensitization with 10 years of age by SPT 26% Information on physician-diagnosed inhalant (10.6%) and food allergies (1.9%), eczema 20%, asthma (8.3%) by questionnaires Max diet quality score not reached by any participant diet quality in infancy (mean 4.3 of 10) or childhood (4.5 of 10) were not associated with atopic outcomes in childhood in any of the models. The findings did not support the hypothesis that a healthy dietary pattern in early life is associated with a lower risk of allergic sensitization or atopic diseases in childhood	<u>Confounders taken into account:</u> All associations were analyzed in three models with stepwise adjustment for potential confounders based on previous evidence. 1. Model: adjusted for child’s ethnic background, sex, age at outcome assessment, and total energy intake. 2. Model: additionally, adjusted for several socioeconomic and lifestyle factors, including maternal BMI at enrolment, maternal educational level, household income, parity, prenatal pet exposure, alcohol intake during pregnancy, smoking during pregnancy, folic acid supplements during pregnancy, and maternal history of atopic disease. 3. Model: associations of diet quality in pregnancy, infancy, or childhood with allergic sensitization and atopic diseases were independent of diet at the other two time points by additionally adjusting them for each other. Breastfeeding, child’s sex, child’s ethnic background, and maternal history

			of atopic diseases were separately examined as potential effect modifiers by including interaction terms in the models <u>Limitations:</u>
Grimshaw et al. 2015¹⁰⁵ nested, case-control within a cohort study (PIFA) UK <u>Sample Size:</u> Baseline N: 41 food-allergic infants (DBPCFC+), 82 controls <u>Sex:</u> FA: male 58.5% Control: male 52.4% <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Maternal asthma 26.8% (FA), 13.4 % (controls), maternal allergy 53.7% (FA), 37.8% (controls)	<u>Intervention/Exposure:</u> Characterization of a DP related with diagnosed FA <u>Assessment Methods of DP:</u> Food diary sets of 4weekly sheets about infant nutrition without amounts were sent out every 2 months for the 1st year of life (prospectively collected) The first PCA looked at characteristics of the early infant diet, such as duration and exclusivity of breast-feeding, infant formula use, and timing and types of solid food introduced into the infant diet. The second PCA looked at the diet from solid introduction to 1 year of life and was termed the ongoing infant diet (not including foods, the child was allergic to).	<u>Outcomes studied:</u> No difference between the study groups for the early infant diet pattern, but significant difference for the ongoing diet pattern (P = .001). PCA for ongoing infant diet finally produced a pattern in which the first 3 components accounted for 50% of the variance, with the first component accounting for 32% of the variance. Component 1 depicted a dietary pattern, with high positive values associated with fruit, vegetable, fish, and poultry consumption, “predominantly home cooked”. Highly processed adult foods and commercial baby foods were not important in the component. It was named “healthy infant diet”. Component 2 was a pattern defined by finger foods. The highest positive values were allocated to healthy finger foods, and the low/negative values were allocated to pureed baby foods and unhealthy finger foods. The third component had high values allocated to highly processed adult foods. The PCA assigned a score to each infant in the analysis according to how his or her diet corresponded to each of the dietary components. These scores were significantly different between the symptomatic and control infants (P = .002) for component 1 but not for components 2 or 3. Control infants having a significantly higher healthy infant diet dietary pattern score than	<u>Confounders taken into account:</u> Infant guidance score from PCA analysis, age at solid introduction, maternal asthma, maternal allergy, maternal smoking, maternal education, maternal age, pet ownership, female sex, any siblings <u>Limitations:</u>

		children who had a food allergy.	
Grimshaw et al. 2014 ¹⁰⁶ Nested, case-control within a cohort study (PIFA) UK <u>Sample Size:</u> Baseline N: 41 food-allergic infants (DBPCFC+), 82 controls <u>Sex:</u> FA: male 58.5% Control: male 52.4% <u>Race/Ethnicity:</u> NR <u>Atopic Disease Risk Status:</u> Maternal asthma 26.8% (FA), 13.4 % (controls), maternal allergy 53.7% (FA), 37.8% (controls)	<u>Intervention/Exposure:</u> Timing of solid food introduction <u>Assessment Methods of DP:</u> Food diary sets of 4weekly sheets about infant nutrition without amounts were sent out every 2 months for the 1st year of life Descriptive analysis of baseline characteristics	<u>Outcomes studied:</u> Infants who were diagnosed with food allergy by the time they were 2 years of age were introduced to solids earlier (≥ 16 weeks of age) and were less likely to be receiving breast milk when cow's milk protein was first introduced into their diet	<u>Confounders taken into account:</u> <u>Limitations:</u>
Tromp et al. 2012 ¹⁰⁴ Prospective cohort study (Generation R) Netherlands <u>Sample Size:</u> Baseline N: 5088 mothers received FFQ Analytic N: 2173 preschool children (≤ 4 years of age) Attrition: Sample Size Calculation: NR <u>Sex:</u> NR <u>Race/Ethnicity:</u> only children of Dutch origin were included in the analyses (n=2443). Siblings within the Generation R cohort were randomly selected and excluded	<u>Intervention/Exposure:</u> Dietary patterns related to asthma-related symptoms <u>Assessment Methods of DP:</u> Validated quantitative FFQs at 14 months of age The frequency of consumption of a food item was to be recorded per day, per week, or per month over the past 4 weeks. Prinzipal component analysis (PCA)	<u>Outcomes studied:</u> Asthma-related symptoms by ISAAC questionnaire at age 2,3 and 4 Questionnaire regarding respiratory tract infections at age 2,3 and 4 2 dietary patterns (DP) identified: DP 1 was associated with starchy foods, fruit, vegetables, potatoes, vegetable oils, fish, legumes and meat. This pattern is referred to here as the "Health conscious" DP. Comment: very similar to MD DP 2 was associated with refined grains, soups and sauces, savoury and snacks, other fats, sugar containing beverages and meat. This pattern will be referred to as the "Western" dietary pattern. high adherence to the "Western" dietary pattern was significantly associated with frequent wheeze at 3 years of age (RR: 1.39; 95% CI: 1.02-1.89) and frequent shortness of breath (RR: 1.44; 95% CI: 1.03-2.01) and respiratory tract infections (RR: 1.54; 95% CI:	<u>Confounders taken into account:</u> Gender, gestational age and birth weight, maternal age, maternal socioeconomic status (SES), maternal smoking during pregnancy, Multiple parities and parental history of atopy <u>Limitations:</u> Several arbitrary decisions are involved in identifying dietary patterns by PCA. Decisions on combining food items into food groups, the number of factors to extract, the method of rotation, and the labelling of the components may influence the reproducibility of the findings. [Although we adjusted for potential confounders residual confounding cannot be fully excluded thereby precluding final

(n =270) <u>Atopic Disease Risk Status:</u>		1.08-2.19) at 4 years of age. However, this association was partially explained by energy intake After adjustment for total energy intake, high adherence to the “Western” dietary pattern remained significantly associated with frequent wheeze (≥ 4) (aRR: 1.47, 95% CI: 1.04-2.07) at 3 years of age and frequent respiratory tract infections (≥ 3) (aRR: 1.46, 95% CI: 1.00-2.13) at 4 years of age, but no longer significantly associated with shortness of breath up to 4 years of age. Adherence to the “Western” dietary pattern remained not significantly associated with any respiratory symptom at age 2 years or short-term respiratory symptom up to 4 years of age. Adherence to the “Health conscious” diet was not significantly associated with respiratory symptoms up to 4 years of age, even after adjustment for total energy intake. Therefore, it does not support a protective effect of a “Health conscious” diet on respiratory outcomes in children younger than 4 years of age.	conclusions regarding the causality of the study results.
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