The impact of maternal diet in pregnancy and lactation on allergy and atopy outcomes in offspring: A systematic review

By

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Abstract

Allergic disease and atopy create a substantial emotional and financial burden for affected individuals and their families. Significant healthcare costs are also incurred with New Zealand children showing consistently high rates of allergic disease when compared with global statistics. The potential to decrease the incidence of allergic disease and atopy through modification of maternal diet has been the subject of recent attention with the possibility for transgenerational impact being of considerable interest.

The objectives of this systematic review were firstly to investigate the relationship between maternal diet in pregnancy and lactation on allergic outcomes in the offspring, and to then relate these findings to the New Zealand context.

The following databases were accessed as part of this review: PubMed via helicon (advanced search), ProQuest (MEDLINE) via helicon, CINAHL Complete (EBSCO host via helicon). Limits were "humans". The key search terms were 'diet' or 'supplements', 'pregnancy' or 'lactation', 'allergy' or 'atopy' or 'asthma; NOT 'elimination' or 'avoidance'. The studies for inclusion in this review were restricted to studies written in the English language. The final search was undertaken 11/04/17 once data extraction completed and one new study found. Initial search was 14/07/16. Search period 14/04/16-11/04/17.

Randomised controlled trials and cohort studies that systematically recorded maternal intake of diet or supplements were included. The health-related outcomes assessed were asthma, wheeze, eczema and allergic rhinitis. Data was extracted for this review using the Cochrane Public Health Group's template. Risk of bias was assessed using the Cochrane risk of bias assessment tool for the randomised controlled trials and the Newcastle-Ottawa Scale for the cohort studies. Risk of bias was assessed again and presented using the Grade summary of findings tables.

Overall, 54 studies were included in this review, collectively involving more than 100,000 children and comprising of 16 randomised controlled trials and 38 cohort studies that were

selected based on predetermined inclusion and exclusion criteria. Data on vitamins, oligo-elements, food groups and dietary patterns during pregnancy and lactation were also collected. A meta-analysis was not performed due to the diversity in variables, multiple outcomes assessed, and the variety of measurements implemented within the studies.

This work presents a comprehensive summary and review of the identified studies that explored the impact of maternal diet in pregnancy and lactation on allergy and atopy outcomes. Although individual studies demonstrated various associations between maternal diet during pregnancy and lactation to impact on health outcomes for the offspring, overall, this work did not show any consistent findings collectively across the studies reviewed. This was due to the differing methods of measurement of association, intake and outcome assessment used in the reviewed studies which further complicated the ability to compare and contrast the findings of the studies with each other. Each study was assessed both for its individual findings and then collectively according to the variables assessed. The findings of this review lend support for the undertaking of additional trials and studies with more consistent and controlled measurements of interventions and outcomes to better facilitate comparisons between studies.

Key findings from the reviewed studies, which included only one New Zealand based study, were related to the New Zealand context. Additional New Zealand based information and related works highlighted a need for personally tailored maternal nutrition information to be delivered consistently by all health professionals interacting with pregnant women.

Key words: diet, supplements, pregnancy, lactation, allergy, atopy, asthma.

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List of Abbreviations

Abbreviation	In full
AHEIP	Alternative Healthy Eating Index (modified for Pregnancy)
ALSPAC	Avon Longitudinal Study of Parents and Children
CPHG	Cochrane Public Health Group
DNA	Deoxyribonucleic acid
DNBC	Danish National Birth Cohort
DOMInO	Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome
FFQ	Food frequency questionnaire
GRADE	Grades of recommendation, assessment, development and evaluation
HR	Hazards Ratio
IgE	Immunoglobulin E
INMA	INfancia y Medio Ambiente
ISAAC	International Study of Asthma and Allergies in Childhood
KOALA	in Dutch, the Child, Parent and Health: Lifestyle and Genetic Constitution study
KOMCHS	Kyushu Okinawa Maternal and Child Health Study
LCPUFA	Long chain polyunsaturated fatty acids
MOH	Ministry of Health
n-3 PUFA	Omega-3 polyunsaturated fatty acids
n-6 PUFA	Omega-6 polyunsaturated fatty acids
NOS	Newcastle-Ottawa Scale
NZ	New Zealand
OMCHS	Osaka Mother and Child Health Study
OR	Odds Ratio
PIAMA	The Prevention and Incidence of Asthma and Mite Allergy
PICO	Population Intervention Comparison Outcome

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
ROB	Risk of bias
RR	Risk ratio or Relative risk
SCFA	Short chain fatty acids
SOF	Summary of findings
Th1	T helper cell type 1
Th2	T helper cell type 2
Treg	Regulatory T cell
VDAART	Vitamin D Antenatal Asthma Reduction Trial
WHO	World Health Organization

Glossary

Allergic rhinitis: symptoms include sneezing and runny or blocked nose in the absence of a cold and with sensitization to at least one aeroallergen. (Best, 2016)

Allergy: a hypersensitivity reaction started by immunologic mechanisms linked to immunoglobulin E (IgE) (Bindslev-Jensen, 2004)

Alternative healthy eating index - modified for pregnancy - (AHEIP): A measure of diet quality based on modified recommendations from the US Department of Agriculture (Lange et al. 2010)

Asthma: A chronic complex disease characterised by airway oedema, remodelling and hyperresponsiveness. Symptoms include shortness of breath, cough, chest tightness and/or wheezing (Maslan & Mims, 2014).

Atopy: a personal and/or familial predisposition, usually occurring in childhood or adolescence, to develop abnormal IgE antibody responses to low doses of allergens, usually proteins. Affected people can develop asthma, rhinoconjunctivitis or eczema consequently. (Johansson et al., 2004)

Eczema: (Atopic eczema, atopic dermatitis). A chronic inflammatory itchy skin condition that is typically an episodic disease of exacerbations and remissions. There is often a genetic component and it is typified by a breakdown of the skin barrier increasing susceptibility to trigger factors in the environment (NICE, National Institute for Health Care and Excellence, 2007)

Hay fever: see **allergic rhinitis.**

Mediterranean diet: characterised by high intake of vegetables, legumes, fruits and nuts, cereals (unrefined), and olive oil, and moderately high intake of fish, low to moderate intake of dairy products and a low intake of meat and poultry. (Usual definitions also include a regular but moderate intake of alcohol that the studies in this work did not assess as it is recommended not to consume alcohol in pregnancy). The Mediterranean diet is also described as rich in carbohydrates, fibre and antioxidants. (Chatzi, 2013; Weichselbaum, 2013)

Microbiome: the composite of microorganisms and its genomes on the body (Pelzer, Gomez-Arango, Barrett, & Nitert, 2017). In this review, microbiome will be used when both the microbiota and its genomes are being discussed.

Microbiota: the microorganisms present on a certain body site (Pelzer et a., 2017).

Pakeha: The Māori word used to describe those of white European descent who colonised New Zealand. A white New Zealander.

Pasifika: Pacific peoples who are now living or were born in New Zealand

Prudent diet: characterised by high intakes of vegetables, fruit, legumes, fish and shellfish, poultry, eggs, and wholegrains (Lange, 2010, Weichselbaum, 2013)

Rhinoconjunctivitis: includes the same symptoms as allergic rhinitis but also includes itchy watery eyes. (Best et al., 2016). Rhinoconjunctivitis will be included in allergic rhinitis outcomes in this work.

Sensitisation: describes the innate tendency to produce immunoglobulin (Ig) E antibodies in response to allergens. Skin prick testing to common allergens is a common way to assess atopic sensitisation (Netting, Middleton & Makrides, 2014; Weiland et al., 2004)

Transgenerational: acting across multiple generations. In this work this term describes the effects of environmental factors today on this generation and multiple generations in the future (Vickers, 2014).

Western diet: characterized by high intakes of red and processed meats, French fries, sweets (including sugar-sweetened beverages) and desserts, high-fat dairy products, butter and refined grains (Lange, 2010; Weichselbaum, 2013).

Chapter 1:

General Introduction

Poipoia te kākano kia puawai (Māori proverb)
Nurture the seed and it will blossom.

Background

Maternal diet in the Western or developed world has changed over the past three decades and has been shown to affect both maternal and fetal health (Brantsæter et al., 2014). These changes in maternal dietary patterns can continue to have an impact on offspring health outcomes throughout their lifetime (Barker, 2002). This chapter presents health-related research that highlights the links between maternal diet and offspring health outcomes assessed within the studies comprising this review. The health-related outcomes of interest in this systematic review are asthma, wheeze, eczema and allergic rhinitis and these will be defined and further discussed. A description of the interventions undertaken to modify maternal diet and/or supplementation will be presented. Immunology, epigenetics and microbiome research elements that relate to how offspring outcomes can be affected by maternal diet will be discussed. The importance of this review for the individual, their affected family members and for further research will be explained. Finally, the relevance to the New Zealand context will be highlighted showing the importance of this review for those populations most affected by allergy and atopy and where further support and education could be helpful.

Description of the health outcomes included in this review

Atopy

The health outcomes explored in this systematic review include allergic diseases that are associated with atopy. Johansson et al. (2004) define atopy as a personal and/or inherited tendency that usually occurs in infancy or childhood causing sensitisation and production of IgE in response to exposures to allergens that do not affect most people. People with atopy are described by Johansson et al. (2014) as typically having one or more of the following allergic diseases; asthma, rhinoconjunctivitis or eczema. None of these allergic diseases have clearly defined or widely agreed upon diagnostic criteria and present a risk of both over- and under- diagnosis especially in the pre-school or younger child population groups (Asher et al., 1995, Bakirtas, 2016). The International Study of Asthma and Allergies in Childhood (ISAAC) is a large multinational study that was based on determining time trends and determinants of asthma and allergies in children and asthma severity. Over 105 countries and nearly two million children were included in this study which was established in 1991 and formally concluded in 2012 (ISAAC steering committee, n.d.). ISAAC researchers created a questionnaire used in over 100 different countries to determine the prevalence and severity of asthma (includes wheeze), rhinitis and eczema in children (Asher et al., 1995). This questionnaire has been validated in children aged 6-7 and 13-14 years of age and is used in many studies researching these outcomes. For the purpose of this systematic review the word atopy is used to describe the collection of allergic diseases typically associated with the term atopy and these diseases will now be described further.

Asthma

Asthma is a chronic inflammatory disorder which is characterised by airway obstruction and hyperresponsiveness. Symptoms arising from airway inflammation are defined as shortness of breath, cough, chest tightness and/or wheeze (Maslan & Mims, 2014). Maslan and Mims (2014) explain that asthma has multifactorial causes showing both genetic heritability and epigenetic environmental triggers. Asthma is also described as a global disease with

prevalence rates continuing to rise in developing countries (Nunes, Pereira, & Morais-Almeida, 2017). The New Zealand Ministry of Health (MOH) statistics show that rates of asthma in New Zealand children vary on a yearly basis but overall, have generally increased over the last ten years (MOH, 2017)

Asthma is difficult to diagnose in young children, particularly in those under five years of age and there are concerns regarding the potential for both under-and overdiagnosis (Bakirtas, 2017). Bakirtas asserts that the only diagnostic tool for asthma in children under five years old is the "treatment trial," where a child is given low dose inhaled corticosteroids for a six to twelve-week period and is followed up at the end of this trial period to assess effectiveness of the treatment. Due to the difficulty in diagnosing asthma many studies assessing allergic disease outcomes include wheezing as a health outcome with the ISAAC study questions including assessment of wheeze in the asthma questionnaire (Asher et al., 1995).

Wheeze

Many studies included in this systematic review assessed wheeze as an allergic disease outcome as described previously. There are concerns with this use of wheeze as a precursor to allergic disease as many infants have viral illnesses with associated wheeze. These infants often have multiple presentations of bronchiolitis or viral illness with wheeze and many go on to develop or be diagnosed with asthma, while at the same time many grow out of it (Bakirtas, 2017, Chipps, 2007). Wheeze is included in this review because many studies used an assessment of wheeze as part of the asthma assessment, especially when using the ISAAC study questionnaire.

Eczema

Eczema is a chronic condition affecting the barrier function of the skin causing itchiness and inflammatory responses that occur in an episodic pattern of exacerbation and remission (NICE, 2007). The financial and emotional burden of eczema is well researched in

developed countries with the costs of moisturisers and healthcare visits along with the attempts to avoid triggers by making household changes such as removing carpets, changing cleaning products and trialling special diets described (Filanovsky et al., 2016). These costs coupled with broken sleep, constant itchiness, and the social impact of looking and feeling different and being unable to undertake some activities making this disease one of high burden to both the sufferer and their families (Filanovsky et al., 2016). Eczema is often the first allergic disease to develop in children with atopy and New Zealand MOH (2017) statistics show that childhood eczema, in children 0-14 years of age, have significantly increased over the last ten years.

Allergic rhinitis

The prevalence of allergic rhinitis is high in both adults and children worldwide and has similar quality of life effects as those described in the previous section for eczema (Meltzer, 2016). It is characterised by a set of symptoms that include sneezing, an itchy nose, airflow obstruction and copious clear nasal secretions caused by IgE-mediated reactions to inhaled allergens (Solomon, Wheatley & Togias, 2015). Rhinoconjunctivitis includes the symptoms mentioned above but also involves watering and itchy eyes (Best et al., 2016).

The health outcomes measured as part of this review are consistent with the accepted allergic diseases associated with atopy. The following section will describe the interventions used in the included studies and how these interventions are thought to impact on the offspring health outcomes.

Description of the interventions included in this review

Maternal nutrition during pregnancy impacts fetal growth and the development of the physiological functions of all organ systems making nutrition one of the most influential environmental factors in the development of the fetus (Brantsaeter et al., 2014; Salisbury & Robertson, 2013). Maternal diet can be modified by using supplements to increase maternal intake of vitamins, fish oils and probiotics. The effects of increased intake of these

supplements on the developing fetus can then be assessed by measuring the health outcomes of the offspring. Similarly, maternal diet can be assessed for intake of certain vitamins, oligo-elements, food groups and dietary patterns and the effects of these on the developing fetus are assessed by measuring the offspring health outcomes of interest.

The link between maternal diet and health outcomes

The maternal diet in the Western or developed world can be described in many ways that include the following; Western diet, Western 'junk food' diet, Mediterranean diet, healthy and unhealthy, prudent or traditional (Bengmark, 2013; Lange et al., 2010; & Miyake et al., 2011). Changes in the maternal diet over the past three decades have been shown to have had significant effects on health outcomes for both mother and child (Brantsæter et al., 2014). The changes in dietary intake in developed countries will be discussed in relation to their effect on the microbiome (both the microorganisms and genomes) and allergy prevalence.

Black and Sharpe (1997) discuss the link between the public health campaign in developed countries to decrease heart disease where the increase in omega-6 polyunsaturated fatty acids (n-6 PUFA) contained in margarine and vegetable oils coincided with a decrease in the intake of omega-3 polyunsaturated fatty acids (n-3 PUFA) found in fish, especially oily fish. The increased intake of n-6 PUFA in these developed countries has been linked to the rise in allergic disease whereas the n-3 PUFA have been shown to have a protective effect on asthma and allergies (Sausenthaler et al. 2007). Another proposed explanation for the increased incidence of asthma and atopy in Western countries over the last three decades is the change of diet from one comprised of a plentiful intake of fruit and vegetables to a more processed and junk food diet (Palmer, Huang, Craig & Prescott, 2014; Peroni et al., 2012, Warner, 2004). Bengmark (2013) discusses the impact of the Western diet, given that most processed foods are absorbed in the upper part of the small intestine which leads to a reduction of metabolic fuels and a lack of proper nutrition to the microbiota (microorganisms present), as a potential contributing factor in the formation of a sub-optimal gut microbial

profile. This in turn leads to an imbalance of microbiomes (the composite of microorganisms and its genomes) and the likelihood of chronic elevated inflammation which is often linked to allergy and atopy. Providing proper nutrition to the microbiota as described above also means that the use of supplements to enhance diet is an area of controversy with studies highlighting the importance of a healthy intake of whole foods studied as a dietary pattern rather than a reliance on supplements or the study of one or two specific nutrients (Allan et al., 2015, Palmer, 2017).

Maternal diet in pregnancy and lactation has been shown to affect the developing fetus and newborn infant's immune system, to alter genetic expression through epigenetic mechanisms and to affect the fetal and infant microbiome. The areas of immune development, epigenetics and the microbiome will be briefly explored further with reference to the effect of maternal diet on allergic disease outcomes. Laitinen, Mokkala, & Kalliomaki (2017) report that the importance of maternal nutrition and its effect on gut development, the microbiome and immune system development, is a growing area of research significance.

Maternal nutrition and/or supplement intake during pregnancy and lactation may modulate the immune system of the developing fetus, neonate or infant. Dietary intake of a range of dietary factors, including long chain polyunsaturated fatty acids (LCPUFA) and antioxidants, have immunomodulatory and gene expression effects through their potential to change the local tissue environment due to the influence they exert, as metabolic components within the cells and tissues (Amarasekera et al., 2013). A recent study examining the effect of a high fibre diet in pregnant mice reported that increased fibre intake in pregnancy results in an inability for the adult offspring of these mice to develop allergic airways disease through priming of forkhead box protein (FOXP3)-mediated protection of development of asthma (Thorburn et al., 2015). FOXP3's role as a broad regulator of gene expression is vital to the identity and purpose of regulatory T (Treg) cells that are responsible for suppressing the activation and function of other leucocytes. This regulation occurs through the combined action of transcription and epigenetic factors (Lu, Barbi & Pan, 2017).

West, Jenmalm and Prescott (2015) report that it is likely that both pre- and postnatal microbial stimulation are important factors in optimal Th1 and Treg development. Th1 related cytokines tend to produce the inflammatory responses needed to kill intracellular parasites and for prolonging autoimmune responses whilst the Treg cells suppress this response (Berger, 2000; Lu et al., 2017). A component of allergic disease development is a persisting imbalance of Th1 and Treg cells post-delivery. Fetal T cells are important immune cells that are needed to fight pathogens and for proper immune development and function, they are also important to ensure that the maternal immune response is diverted away from damaging Th1 mediated immunity (Jenmalm, 2011). Fetal T cells develop during the second trimester of pregnancy making this gestational stage one of critical importance in the development of the immune system and one of high susceptibility to epigenetic changes due to environmental influences such as maternal diet (Jenmalm & Duchén, 2013). Potaczek et al. (2017) and Wallack and Thornburg (2016) describe epigenetic modifications as biochemical changes of the DNA or histones that do not affect the nucleotide sequence of the genome but are functionally relevant. The effects of epigenetic influences are often likened to 'on, off' switches in that they can activate or silence gene expression. Prescott and Clifton (2009) discuss the main epigenetic mechanisms of histone methylation and histone acetylation and describe how these interplay with various T cell populations, silencing some gene expression pathways and affecting Treg differentiation. Immune development may be both nutritionally and epigenetically regulated and there is great interest in the potential to restore and rebalance immune development to enhance favourable neonatal immune responses.

Both immune development and epigenetic changes can be affected by maternal diet as shown above. It has been reported that if the health and well-being of a pregnant woman is optimised throughout her pregnancy through measures such as diet, exercise, emotional support and decreased exposure to toxins, lifelong beneficial effects can be measured in the health and wellbeing of her offspring (Lillycrop, 2011). Vickers (2014) discusses the transgenerational programming that can occur around the time of conception and describes this as a form of epigenetic inheritance from either the maternal or paternal line. This study highlights the importance of improved nutrition prior to conception as well as during

gestation. Vickers (2014) illustrates the potential for maternal nutrition in pregnancy to have ongoing generational effects and highlights the need for further research to identify critical times of developmental plasticity to ensure the best health outcomes for offspring. Plasticity is a term used by Barker (2002) to describe periods where fetal and infant organ development has increased sensitivity and undergoes adaptation in response to environmental influences. This is further displayed in the frequently measured effects of environment and maternal stress on health outcomes of offspring; most notably by Barker et al. (1993) when describing the fetal origins of adult disease and by those researching the Dutch famine (Roseboom et al., 2001); it is also shown when studying the effects of both maternal malnutrition and obesity (Davies et al., 2016). These studies describe the effects of maternal malnutrition on the developing fetus and/or being born with low birthweight and the links to hypertension, diabetes, and coronary heart disease in adult life, but further research is showing that the maternal environment, including diet, has the potential to impact on other non-communicable diseases such as asthma, eczema and allergic rhinitis. The need to uncover and explain how these environmental effects could impact upon the developing fetus led researchers to further explore the microbiome. The microbiome describes the composite of microbial symbionts and their genomes that live both inside and on humans (Pelzer et al., 2017).

An area of research that has demonstrated the impact maternal diet can have on the development of allergic disease is that of the human microbiome. “Diet is the most powerful influence on gut microbial communities in healthy human subjects” (Bengmark, 2013, p. 93). Campbell, et al. (2015) highlight that epidemiological studies have shown that the microbial environment during pregnancy can infer greater protection from allergy than postnatal exposure alone. The human microbiome project aimed to identify and characterise the microorganisms that constitute the microbiome of around 300 people in multiple body sites of ‘healthy’ adults (Aagaard et al., 2014; The Human Microbiome Project Consortium 2012). The microbiome of the human placenta, amniotic fluid, colostrum and meconium were later distinguished to establish whether there is a link to perinatal gut colonisation and more specifically *in utero* gut colonisation (Aagaard, et al., 2014; Collado, Rautava, Aakko, Isolauri, & Salminen, 2016). A theory that has gained recent attention, is that of the

developing gut being directly affected by the maternal microbiome (Neu, 2015). The notion that an infant is born with a sterile gut (one that harbours no evidence of bacteria) has now been challenged by research into the microbiome and has been shown as being too simplistic a concept (Neu, 2015, Nuriel-Ohayon, Neuman, & Koren, 2016). The presence of microbes in the amniotic sac has led to the hypothesis that the fetal immune system is developing within the womb and that the swallowing of amniotic fluid is one of the initial mechanisms by which the gut is prepared and colonised to promote establishment of a healthy microbiome (Campbell, Boyle, Thornton, & Prescott, 2015; Neu, 2015; Thum et al., 2012). An earlier study that set about to identify whether gut colonisation began prior to birth was conducted by Jiménez et al. (2008), this study showed that pregnant mice inoculated with genetically labelled *Enterococcus faecium*, then delivered of their pups via caesarean section had pups with the same labelled bacteria retrieved from internal meconium. This study provided evidence that maternal nutrition could alter the microbiome of the developing fetus. Campbell, et al. (2015) point out that epidemiological studies have shown that the microbial environment during pregnancy can infer greater protection from allergy than postnatal exposure alone.

Palmer et al. (2014) describe the role of nutrition in epigenetics and links nutrition, epigenetics, the immune system and the microbiome. Diet derived methyl donors are of interest because of their role in DNA methylation. Other dietary influences described by Palmer et al. (2014) include antioxidants, LCPUFAs and short chain fatty acids (SCFAs) which have the potential to modulate gene expression through epigenetic influences (see Figure 1).

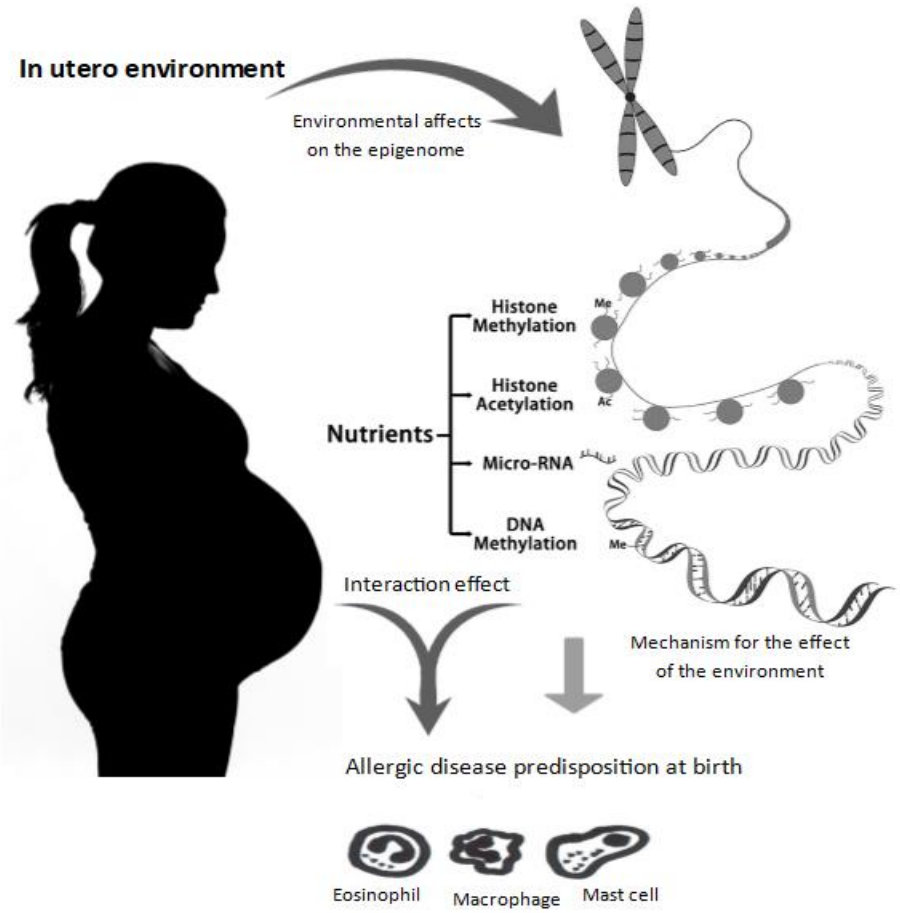


Figure 1 The *in-utero* environment can interact with or alter the epigenome and influence the predisposition to develop allergic disease. The different areas of interaction between nutrition and the epigenome are shown. The mechanisms for the effect of the environment then interplay with the development of the immune system. Adapted from Lockett, Huoman, & Holloway (2015) and Ji et al. (2016).

The importance of this review

The health outcomes assessed in this review are significant in terms of the physical, emotional, psychosocial and economic impacts they have on an individual, their family and on society (Filanovsky et al., 2016; Pawankar, 2014). The effects these studies describe are the physical burden of the condition and its effects on the quality of life through, for example, lack of sleep and the inability to participate in activities such as sports. The financial burden to the affected child and their family in terms of the cost of prescriptions and healthcare costs

but also missed days of school and the caregiver burden of missed days of work is substantial. There are also the financial costs to the health system for appointments and prescriptions and specialist hours to be considered. The emotional and psychological burden of looking or feeling different due to their illness and the mental fatigue of dealing with a chronic illness for both the sufferer and their caregivers are also described by Filanovsky et al. (2016) and Pawankar (2014).

Maternal diet has been described by several authors mentioned previously in this work as the most important factor in influencing these outcomes (Bengmark, 2013, Brantsaeter et al., 2014 & Laitinen et al., 2017). The potential for maternal dietary changes to affect offspring health outcomes for more than one generation, as highlighted by Vickers (2014), emphasises the significance this systematic review has in terms of drawing attention to the potential health improvement in a transgenerational context. The effect that improvement of maternal diet in pregnancy could have globally is also substantial and in terms of the potential for impact within New Zealand, these changes could significantly support improved health of Māori and Pasifika populations. These populations are consistently shown to have poorer health related outcomes when compared to the non-Pacific and non-Māori populations in New Zealand and will be discussed further in the upcoming section.

Relevance to the New Zealand context

Within New Zealand there is a greater prevalence of asthma, wheeze, severe eczema and allergic rhinitis for Māori and Pasifika children. Pattemore et al. (2004) reported on the ISAAC study findings in New Zealand and showed that Māori children aged 6-7 and 13-14 years had the highest prevalence of asthma symptoms, Pasifika children had the lowest rates the other identified ethnicity group (European) was represented between the Maori and Pasifika outcomes. Pattemore et al. (2004) also identified that Māori and Pasifika children, aged 6-7 and 13-14 years, had a higher prevalence of severe asthma symptoms and morbidity. Further research that repeated the questionnaire in the same geographical areas 8-10 years later showed that asthma prevalence and severity were decreasing in New Zealand, but this study did not present data on prevalence in different ethnic groups (Asher

et al., 2008). Pattemore et al. (2004) showed that the prevalence of wheeze symptoms was highest in Māori children in New Zealand and lowest in Pasifika children, the other specified ethnic group was European children.

New Zealand based research from the ISAAC study (Clayton et al. 2013) shows that there is a higher prevalence of 'eczema ever' (an outcome describing whether the participant had ever experienced the symptoms of eczema or had a doctor diagnosis of eczema in their lifetime) in Pakeha children, but that Māori and Pasifika children have higher rates of current and severe eczema. Although the higher prevalence of eczema ever in Pakeha children is mentioned by the authors, reasons for this trend are not discussed. This may reflect a higher utilisation of health resources by Pakeha and the likelihood to attend a general practitioner and receive a diagnosis rather than actual increased prevalence of eczema among Pakeha.

Moyes et al. (2012) reported that symptoms of rhinoconjunctivitis are common in New Zealand children particularly amongst Māori and Pasifika children. Moyes et al. (2012) goes on to discuss that the severity of symptoms is reported as being higher in Māori and Pasifika children but that 'hay fever ever' (a term used in this study and others to describe either present hay fever or a history of hay fever) was reported as higher in Europeans, Moyes et al. (2012) discuss the possibility of greater use of medical services or cultural bias in interpretation of symptoms as potential reasons for these findings.

The New Zealand MOH website has resources available for pregnant women to access regarding a healthy diet and lifestyle during pregnancy, these are also available as an information pamphlet from the lead maternity provider. Salisbury and Robertson (2013) report that women are often aware of the need for good nutrition in pregnancy but don't make changes because they believe their diet to be healthy. The women in this study were found to either lack the time, or finances to make the necessary dietary changes (Salisbury and Robertson, 2013). Watson and McDonald (2009) reviewed the major influences on nutrient intake for pregnant women in New Zealand. This cohort study showed that almost all subjects had intakes of Vitamin D, folate, iron and selenium below the estimated average requirement. This finding is especially significant since the risk of developing asthma and

allergy is associated with a lack of Vitamin D, and selenium (Peroni et al., 2012). Nutrient intake was found to be further decreased for pregnant women in New Zealand with limited education, welfare dependence and smoking. These factors showed an increased lack of fibre, pantothenate, biotin, vitamin B6 and magnesium in these women's diets (Watson & McDonald, 2009). The ability to tailor information for the individual was suggested as a potential intervention for changing dietary habits (Watson & McDonald, 2009). Recent New Zealand based studies researching nutrition attitudes and the impact of tailored advice will now be discussed further.

The Growing up in New Zealand birth cohort study, Morton et al. (2014) looked at maternal adherence to nutritional guidelines and showed that only 3% of pregnant women in New Zealand met the recommended daily intake for all four food groups. A study of Australian women found similar results regarding adherence to dietary guidelines with none of the women in the study adhering to the recommendations for all five food groups (Malek, Umberger, Makrides, & Zhou, 2015).

A study based in the South Auckland region of New Zealand surveyed pregnant women on their knowledge and beliefs about nutrition and physical activity during pregnancy (Okesene-Gafa, Chelimo, Chua, Henning, & McGowan, 2016a). Although this study was focused on the effects of obesity the findings are relevant to this review as the participants were asked about the volume of intake of food throughout pregnancy and the intake of take-away foods, in addition to information about nutrition sources during pregnancy. Over 90% of the mothers reported that they knew about or had received healthy eating information and that most of this information had been delivered by health professionals. Okenese-Gafa et al. (2016a) found that although the women included in their study had received or knew about the importance of healthy eating in pregnancy many of them reported eating more and the reasons given were 'cravings' and 'eating for two'. Most women (411/422) consumed takeaways more than once a week and reported recognising their diet was not healthy. Over 80% of the women surveyed indicated a willingness to participate in a nutritional intervention trial, signalling recognition of the need for change and some motivation to do so (Okesene-Gafa et al, 2016a). A randomised controlled trial is currently underway in New

Zealand focussing on comparing culturally tailored nutritional interventions versus routine dietary advice for obese pregnant women with a secondary intervention being included in the study involving the use of probiotic capsules from recruitment to delivery (Okesene-Gafa et al., 2016b).

Wall et al. (2016) discuss the dietary patterns of pregnant women in New Zealand and the impact of socio-economic factors on the health and lifestyle of these women. Unhealthy dietary patterns were found to be associated with lower age and educational levels, Pasifika or Māori ethnicity and smoking. Except for the ethnicity data, these findings were similar for studies undertaken in other countries (Malek, Umberger, Makrides, & Zhou, 2015; O'Keeffe et al., 2016; Wennberg et al., 2013)

Maternal nutrition education

The ability to deliver the appropriate education about diet to pregnant women is crucial. Elias and Green (2007) reported that midwives in New Zealand delivered a high standard of nutrition information and self-reported high confidence in this area. In Western society maternal dietary advice has tended to centre around 'safe' and 'unsafe' foods during pregnancy and less around the improved health outcomes for mum and baby of eating a nutritional diet (Morton, 2014; Gardner, 2012). The UpToDate Nutrition in Pregnancy literature review (2015) is a typical example of the focus on the foods to avoid in pregnancy with little information on how to access help or information for changing dietary patterns to a more healthful diet. Many studies agree that pregnancy is a time where women are most receptive to information about making healthy dietary and lifestyle changes (Davies et al., 2016; Hillier, & Olander, 2017; Malek, Umberger, Makrides, & Zhou, 2015; O'Keeffe et al., 2016; Wennberg et al., 2013). These previous studies note the lack of adherence to nutrition guidelines and the difficulty women face in making dietary changes during pregnancy despite more healthy intentions and, in some cases, changes to the usual diet.

Gravida New Zealand (http://www.gravida.org.nz) is part of the Liggins Institute's LiFePaTH (Liggins Fetal, Perinatal and Maternal Translational Research for Lifelong

Health) group research programme and is currently implementing a nutrition education programme –Healthy Start - for midwives and other health professionals involved in the care of pregnant women. The aim of this programme is that women will receive high quality nutrition education in a more consistent manner across health disciplines than is currently available. Most commonly, the main source of nutrition information provided by lead maternity carers (midwives, specialists and General Practitioners) in New Zealand consists of the 'Eating for Healthy Pregnant Women' brochure a document that is well supported by an exhaustive background paper prepared by the Ministry of Health called the Food and Nutrition guidelines for Healthy Pregnant and Breastfeeding Women (MOH, 2006).

This chapter has described the health-related outcomes being explored in this review and the interventions used to determine the effects of maternal diet on these outcomes. The influences of these interventions on immune development, epigenetics and the microbiome were highlighted. The impact of these influences on offspring health outcomes was then explored. The New Zealand context was then described, showing that increased maternal adherence to nutritional guidelines could have transgenerational health benefits. Finally, methods for achieving increased maternal adherence were highlighted.

Thesis outline

This thesis is presented in four chapters and follows the template set out in the Cochrane handbook for systematic reviews. Chapter one provides the introduction to the review, highlighting how the question arose and then introduces the review itself giving the background, context and objectives of this review. Chapter two describes the methodology used and addresses the criteria for considering and including studies. The search methods used to identify these studies are shown and the tools used to assess risk of bias are introduced. This is followed by the presentation of the results in the third chapter.
Chapter three provides a description of the studies. The risk of bias is presented as identified in the studies as a whole and then individually in the study characteristics tables. The effects of the interventions are described narratively and then shown in the summary of findings tables. Chapter four provides a summary of the main results and then determines the overall

completeness and applicability of the evidence. These findings are then discussed in the New Zealand context. The quality of the evidence is then described as are the potential limitations in the review process. Other reviews are discussed and finally the author's conclusions are given with implications for practice and further research

Objectives

The objectives of this systematic review were firstly to investigate the relationship between maternal diet in pregnancy and lactation on allergic outcomes in the offspring, and to then relate these findings to the New Zealand context.

Summary

This chapter has given the context and background for this review highlighting key literature for both the review and for the New Zealand context. The objectives of the review were identified.

Chapter 2:

Methods

This chapter will describe the methods undertaken in developing this systematic review. A description of the search method and the inclusion and exclusion criteria will be given. The approach used for data extraction and analysis is then given with an explanation of how risk of bias was assessed in both randomised controlled trials (RCT) and cohort studies. The use of summary of findings tables is then described.

Criteria for considering studies in this review

Types of studies

This review included RCTs and cohort studies that investigated the effect of maternal diet (food based and supplementation) in pregnancy and during lactation on the allergy and/or atopy outcomes of the offspring. Studies needed to be in the English language and abstracts were not included. This review excluded studies with a focus on participants with a genetic predisposition for conditions that may affect the generalisability of this review. Studies that focused on food allergen avoidance diets were also excluded.

Types of participants

Pregnant and/or breastfeeding women with or without a history of atopy themselves were included. Offspring were then assessed as a mother infant/child pair

Types of interventions

This review considered all studies that reported systematically recorded maternal intake of food and/or supplements. This included assessment of both macro and micronutrients.

Types of outcome measures

The defined primary outcomes for this review included infant or child offspring with asthma, wheeze, eczema and allergic rhinitis.

Primary outcomes

1. Physician or research nurse diagnosed
2. National registry/database
3. Parental report of medical diagnosis
4. Parental report based on questionnaire responses

Search methods for identification of studies

Electronic searches

The databases utilised for this systematic review included PubMed via helicon (advanced search), ProQuest (MEDLINE) via helicon, CINAHL Complete (EBSCO host via helicon). Limits were “humans”. The key search terms were ‘diet’ or ‘supplements’, ‘pregnancy’ or ‘lactation’, ‘allergy’ or ‘atopy’ or ‘asthma; NOT ‘elimination’ or ‘avoidance’. The studies were restricted to English only studies. The final search was undertaken 11/04/17 once data extraction completed and one new study was identified. The initial search was 14/07/16. Search period 14/04/16-11/04/17.

The Cochrane Library, The Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar. Other databases and sources searched were The Liggins Institute’s research themes and recent publications, World Health Organisation (WHO’s) website, clinical trials databases.

Searching other resources

Handsearching was undertaken through the reference lists of the studies and reviews already identified. New Zealand paediatric conference 2015 proceedings were hand searched. The writer attended the early life nutrition symposium in 2015 and the New Zealand lactation consultant's association conferences in 2014-2016 and relevant studies and information were sourced for this review.

Data collection and analysis

Selection of studies

Ideally the eligibility assessment of studies being reviewed should be undertaken by two or more individuals. In keeping with the process outlined by the Cochrane handbook (Higgins & Deeks, 2011) the study selection at title and abstract screening was carried out by the writer while the full text selection was carried out by both the writer and supervisor to ensure that Cochrane guidelines were followed. Any disagreements were further discussed, and a mutual decision formulated, there was no need to involve a third party to settle disagreements. The template used for the RCT studies and adapted for the cohort studies also contained a preliminary assessment to determine whether the study met the criteria determined and should be included in the review. This was useful for the full text assessment.

Data extraction and management

This review used an author modified template developed by the Cochrane Public Health Group (CPHG) (see Appendix 1, p. 186). This method is best suited as this review includes both RCT and cohort studies but is not suitable for entering data into the Cochrane systematic review management software. Data extraction was carried out independently by the writer.

Assessment of risk of bias in included studies

A Risk of Bias (ROB) tool developed by the CPHG and based on the older version of the Cochrane risk of bias tool was used for the RCT studies and the cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) (see Appendix 1, p. 207). These methods for assessing risk of bias are further described in the following sections. The method of

assessment presented is based on the criteria for judging risk of bias in the assessment tool used in the Cochrane handbook (Higgins, Altman & Sterne, 2011). The risk of bias assessment was carried out solely by the writer.

RCT study risk of bias

The tool developed by the CPHG assesses for risk of bias as follows:

(1) Random sequence generation (checking for possible selection bias)

The method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups was described for each included RCT study.

The method was assessed as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

The method used to conceal allocation to interventions prior to assignment was described for each included RCT study and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

The methods were assessed as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding

(3.1) Blinding of participants and personnel (checking for possible performance bias)

The methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received were described for each included study. Studies were considered at low risk of bias if they were blinded, or if it was judged that the lack of blinding was unlikely to affect results. Blinding was assessed separately for different outcomes or classes of outcomes.

Methods were assessed as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

The methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received were described for each included study. Blinding was assessed separately for different outcomes or classes of outcomes.

Methods used to blind outcome assessment were assessed as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

The completeness of data including attrition and exclusions from the analysis were described for each included study, and for each outcome or class of outcomes. It was stated whether attrition and exclusions were reported, and the numbers included in the analysis at each stage (compared with the total randomised participants). Reasons for attrition or exclusion were reported, and whether missing data were balanced across groups or were related to outcomes.

Methods were assessed as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

The possibility of selective outcome reporting bias was investigated, and the findings were described for each included study.

The methods were assessed as:

- low risk of bias (where it was clear that all the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);
- high risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (6) above)

Any important concerns about other possible sources of bias were described for each included study.

Cohort study risk of bias

The Newcastle-Ottawa Scale (NOS) was used to assess ROB in the cohort studies. This tool assesses for areas of bias that are specific to cohort studies and awards a star when criteria for reduction of the ROB are met. There are eight criteria described within three categories and a star is awarded if the criteria are met. The comparability category can be awarded a potential of two stars. The most stars a study can achieve is nine. These categories and items are described as follows:

Selection

(1) Representativeness of the exposed cohort

Each cohort study included in this review was assessed as to whether the exposed individuals were representative of the community the study was based in. If representative of the study community then a star was awarded.

(2) Selection of the non-exposed cohort

This describes whether the non-exposed participants in the cohort were drawn from the same community as the exposed participants or a different source. Each study in this review was assessed and if the non-exposed participants were drawn from the same community then the study was awarded a star.

(3) Ascertainment of exposure

Assessment of measurement of exposure was conducted for each study in the review with a star being given for ascertainment through secure records or a structured review.

(4) Demonstration that outcome of interest was not present at start of study

Each study in this review received a star for this item as the unborn fetus may have the genetic predisposition for any of these allergic diseases but they are not present during fetal development or at birth.

Comparability

(1) Comparability of cohorts on the basis of the design or analysis

Each study in this review was assessed for whether adjustments were made for the confounders of maternal history of allergy or atopy, and maternal smoking during pregnancy as both factors are well recognised as having a significant effect on the allergy-based health outcomes of offspring. This item can be awarded two stars, one for each of the confounding variables identified and adjusted for.

Outcome

(1) Assessment of outcome

The method of assessment of outcome for each study in this review was assessed. Those studies that used independent blinded assessments or record linkage received a star.

(2) Was follow-up long enough for outcomes to occur

Asthma as an outcome is difficult to accurately diagnose before three years of age, while the other outcomes can present and be diagnosed according to symptoms very early in infancy. The criteria for length of follow up for asthma was predefined by the author and each study was assessed as to whether there was an acceptable length of time before the outcomes were assessed. A star was awarded if the outcomes were assessed at an acceptable age. If a study assessed more than one outcome and the criteria were met for one and not the other, a 'half star' was awarded.

(3) Adequacy of follow-up of cohorts

Each study was assessed to ensure that losses to follow-up of both the exposed and non-exposed cohort were not related to the outcome of the exposure. Acceptable follow-up rates were specified as >80% follow up after reviewing literature regarding acceptable attrition rates in cohort studies (Fewtrell et al., 2008; Kristman, Manno & Côte, 2004). A secondary measure of this assessment was the description of those lost to follow-up. If a study had <80% follow up but provided an adequate description of those lost to follow-up, a star could still be awarded.

Measures of treatment effect

Dichotomous data

Results are presented in this work as they are reported in each study. Most RCT studies presented as relative risk (RR), but there were others that presented odds ratios (OR) or hazards ratios (HR), one presented as incidence rate ratio (IRR) and another as prevalence rates with a *p* value (see Summary of Findings Tables 3-6). Most cohort studies used OR to present findings for ease of translation only the *p* values are given as the cohort studies often presented multiple presentations of outcome reporting, adjustments and association measures usually in quartiles or quintiles. Where *p* values are not given the results are presented in adjusted OR or RR using the highest level of intake reported. One cohort study presented findings as prevalence rates and was reported in this work as such.

Unit of analysis issues

Both the RCT and cohort studies published trials with multiple follow up periods and/or follow-up periods that varied from 3-4 months to 10 years. The Cochrane Handbook gives options for how to collate data for a meta-analysis when this issue occurs. This issue was one of the many reasons a meta-analysis was not performed as the available options could not adequately address the issues concerning the combination of studies for analysis the given the diversity of the outcomes and appropriate follow-up periods encountered. The option chosen was to select the longest follow-up from each study (Deeks, Higgins, & Altman, 2011). Trials using one or more intervention groups were combined to create a single pair-wise comparison.

Dealing with missing data

There were levels of attrition noted in most of the studies assessed in this review. The included studies addressed attrition using various methods with some using intention to treat data. The complete case results from these studies have been presented in this review. A meta-analysis was not performed. This review assessed ROB according to how each study addressed missing data and there has been no imputation of missing data.

Assessment of heterogeneity

Heterogeneity was assessed at a basic level using the Cochrane Handbook (Higgins & Green, 2011) as a guide. The studies in this review had significant levels of clinical, methodological, and statistical heterogeneity; therefore, a narrative synthesis of the findings was deemed a more appropriate method for this work.

Assessment of reporting biases

Assessment of reporting bias was completed by the author on the individual studies. It is noted that studies with negative findings are well represented in this review. Reporting bias issues noted within this review are predominantly shown as outcome reporting bias where multiple outcomes are specified but only those showing potentially significant outcomes are reported (Sterne, Egger, & Moher, 2011).

Data synthesis

Grades of recommendation, assessment, development and evaluation (GRADE) summary of findings (SOF) tables and a narrative synthesis were used to present the findings of the studies.

Summary of findings tables

SOF tables were created using the tables provided on the GRADE website and following the GRADE (Schünemann, Brożek, Guyatt, & Oxman, 2013) and Cochrane (Higgins & Green, 2011) handbook recommendations. Due to the diverse associations explored within the cohort studies criteria was set to determine whether a SOF table would be produced or whether a short narrative would be presented following the presentation of the SOF tables. Accordingly, associations for which there are three or more studies will be presented in a SOF table. SOF tables include a quality assessment and the summary of findings itself. The quality assessment determines the level of quality assigned to the studies reviewed for each outcome. Finally, a rating of the importance of the outcome is given. This importance is generally determined by the review author/s and reflects the importance of the outcome for decision making. The scale is given as a one being least important and a nine as critical or most important. For this review the outcomes have been determined according to frequency of hospitalisation and impact on quality of life. Asthma is rated as a seven (critical), wheeze as a five (important), eczema as a six (important) and allergic rhinitis as a four (important).

Chapter Summary

This chapter has presented the methods used to search for the studies included in this review. The tools used to extract data, assess risk of bias and present the findings were then discussed. The results will be described in the following chapter.

Chapter 3:

Results

This chapter will present the findings of the search method used and describe the included and excluded studies. The risk of bias assessments for the RCT and cohort studies are presented. Tables presenting the characteristics of included studies and the GRADE SOF tables are included as is a narrative summary of the findings.

Description of studies

For this section, please refer to the "Characteristics of included studies tables" (p 54-101) and the "Characteristics of excluded studies" (Table 1).

Results of the search

The total number of studies identified through database and hand searching was 1330. Duplicate studies were removed, and the studies screened using the inclusion and exclusion criteria already described when reading the abstracts. The number of studies remaining after initial screening and the removal of duplicates was 103. The full-text of these studies was then assessed for eligibility leaving 54 studies to be included in the systematic review. This data is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2) on the following page. RCTs accounted for 16 of these studies and 38 were cohort studies.

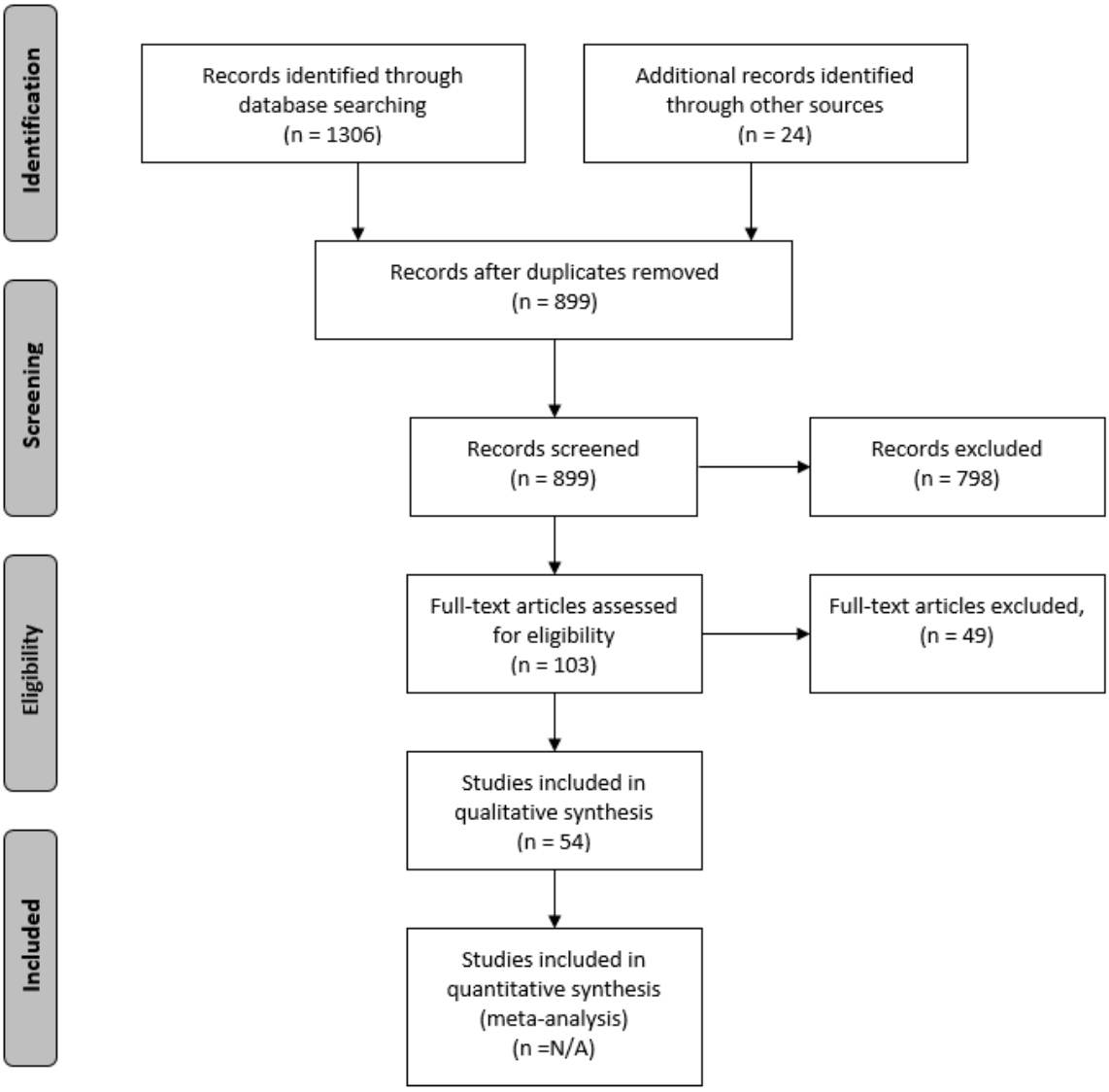


Figure 2 *Prisma flow diagram adapted from:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal. pmed1000097).

Included studies

Collectively this review comprised of 54 studies involving 142,487 mother infant pairs. Women were either given supplements or had their dietary intake assessed during pregnancy, lactation or both pregnancy and lactation and the included studies assessed the specified allergic outcomes of asthma, wheeze, eczema and allergic rhinitis in their offspring. Full details are provided in the Characteristics of included studies tables (p 54-101).

Design of included studies

There were sixteen RCT and 38 cohort studies all published in English. Full details of the included studies are provided in the characteristics of included studies tables (p 54-101).

Participants

Pregnant women were recruited during pregnancy in all the studies included in this review apart from Manley et al. (2011). In the Manley et al. (2011) RCT study 657 mothers of preterm infants, <33 weeks gestation, were given fish oil supplements and the infants were breastfed. This supplementation continued until the infant was considered term by corrected gestational age.

Participants in the RCT studies account for 5194 of the total participants. The study undertaken by Noakes et al. (2012) included 123 women and was the only RCT study assessing increased dietary intake of food (not supplements) and increased the salmon intake of the women in the intervention group. Supplements were given, and diet assessed in pregnancy and lactation for one trial with three publications (Furuhjelm et al., 2009; Furuhjelm et al., 2011; Warstedt, Furuhjelm, Falth-Magnusson, Fageras & Duchen, 2016) and consisted of 145 participants with Warstedt et al. (2016) including 95 of the original 145 participants. Four RCT studies (two studies from one trial) reported supplementing mothers in both pregnancy and postpartum. Chawes et al. (2016) continued supplementation until one week post-delivery and included 623 women. Rautava et al. (2012) continued supplements for 241 mothers until two months post-delivery and the Dotterud et al. (2010) and Simpson et al. (2015) studies are based on the same trial and supplemented 415 mothers until three months post-delivery. The remaining seven RCT studies assessed supplementation only and only during pregnancy and accounted for 2,990 participants (Best et al., 2016; Escamilla-Nuñez et al., 2014; Goldring et al., 2013; Greenough et al., 2010; Litonjua et al., 2016; Palmer et al., 2012, 2013).

There were some RCT studies that only included women with a family history of atopy (usually defined as the woman herself and/or the father of the baby, or an older sibling). These studies are described in detail in the Characteristics of included studies tables and included the Warstedt et al. (2016) study and related studies, the DOMInO trial including the Best et al., 2016, study, the Rautava et al. (2012) study and the VDAART study

reported by Litonjua et al. (2016). The remaining included RCT studies had a mix of both mothers with a family history of atopy and those without.

Participants in the collective cohort studies reviewed included 137,293 mother-infant pairs with mothers recruited in pregnancy in all but two studies. These two studies included the study undertaken by Romieu et al. (2007), where an interviewer asked 458 mothers about their diet in pregnancy three months post-delivery. The second study was reported by von Ehrenstein, Aralis, Flores, and Ritz (2015), where 2,543 mothers reported dietary intakes during pregnancy at 3-6 months post-delivery using a questionnaire.

All the included cohort studies identified the women studied as a mix of both those with a family history of atopy and those with no history.

Sample sizes

The sample size of the included RCT studies ranged from 95 (Warstedt et al., 2016) to 1,094 (Escamilla-Nuñez et al., 2014); while the sample sizes of the cohort studies ranged from 458 (Romieu et al., 2007) to 61,909 (Maslova, Halldorsson, Strøm, & Olsen, 2012).

Study location

The 16 RCT studies were set in Australia (n=4), Sweden (n=3), UK (n=3), Norway (n=2), Mexico (n=1), Finland (n=1) Denmark (n=1) and USA (n=1) (Figure 3A). Two cohort groups made up eight studies that were set in Japan and another cohort based in Denmark had six studies looking at various food and nutrient intakes. The remaining studies were set in the UK (n=6), USA (n=5), Netherlands (n=4), Australia (n=2), France (n=1), Germany (n=1), Ireland (n=1), New Zealand (n=1), Spain (n=1) and a study that combined results from studies in both Spain and Greece, (Figure 3B).

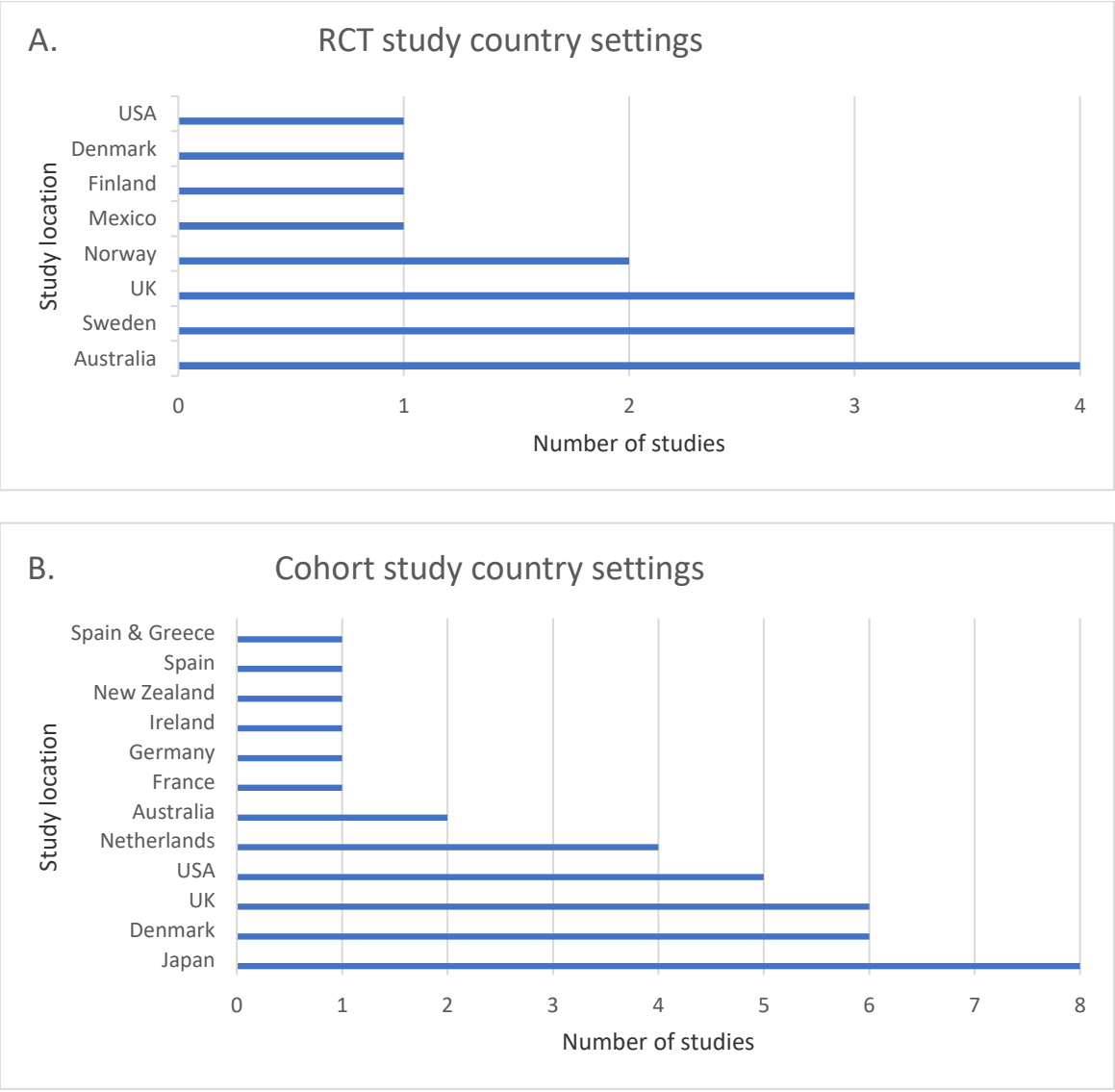
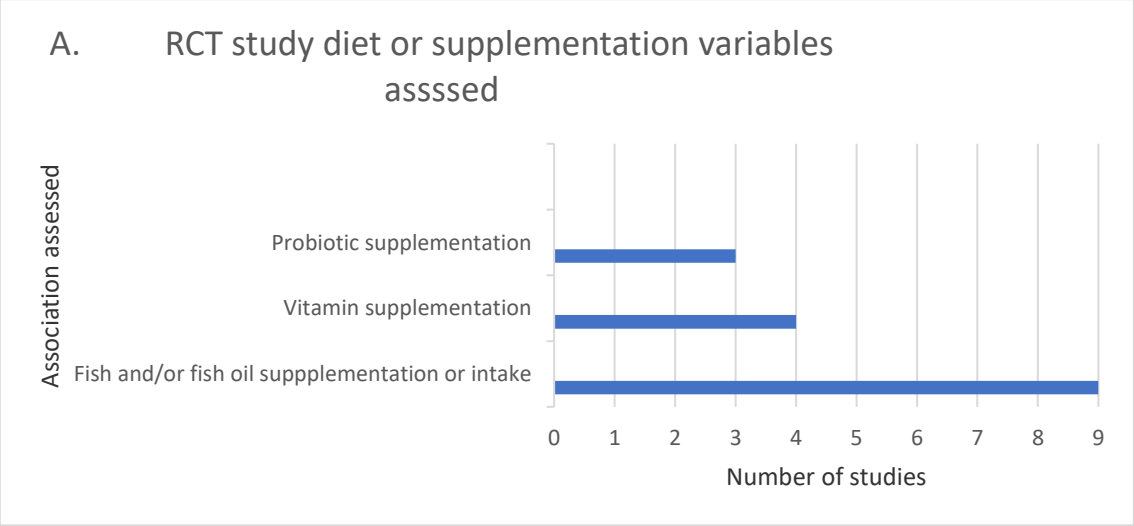


Figure 3 Country settings and numbers of studies included in this review. Bar graphs show numbers of studies based in each country for (A) RCTs and (B) cohort studies.

Intervention

The RCT studies can be categorised into three groups defined by the diet or supplement variables they studied and are shown in Figure 4A. These groupings are fish and/or fish oil supplementation or intake (n=9), vitamin supplementation (n=4), and lastly probiotic supplementation (n=3). Most of the RCT studies assessed supplement intake by returned packaging of the supplement provided. Three studies also used 24-hour food diaries for three consecutive days to measure dietary intake as well as the supplement (Furuhjelm et al., 2009, Furuhjelm et al., 2011; Warstedt et al., 2016. Escamilla-Nunez et al., 2014) used both supplementation and a food frequency questionnaire to assess intake.

The cohort studies assessed a larger variety of diet and supplement variables and may be included in more than one grouping according to the association studied these are shown in Figure 4B. The cohort studies are grouped as fish and/or fish oil supplements and/or diet (n=10), fruit and vegetable (n=5), meat and oils/fats (n=5), dairy (n=4), nut (n= 3), fast-food/soft drink (n=2) vitamin D supplements and/or diet (n =7), folic acid supplements and/or diet (n=9), other vitamin and mineral supplements and/or diet (n=7), dietary patterns (n=4) and other (n=5). Most cohort studies used a Food Frequency Questionnaire (FFQ) to assess diet and/or supplement intake, 22 used a FFQ once in pregnancy and four of those used a FFQ twice in pregnancy to measure two different time points (usually first and second trimester). Diet history questionnaires were used in eight studies and the remaining eight studies used various questionnaires or a mixture of 24-hr dietary recall and 3-day food records with two of these studies assessing diet twice during pregnancy.



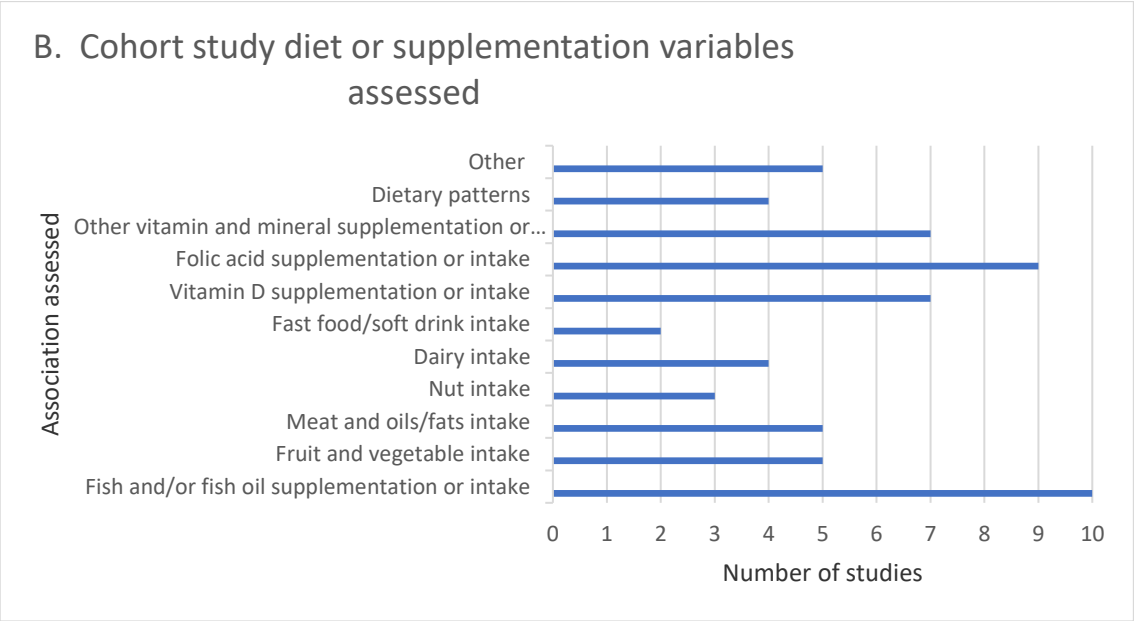
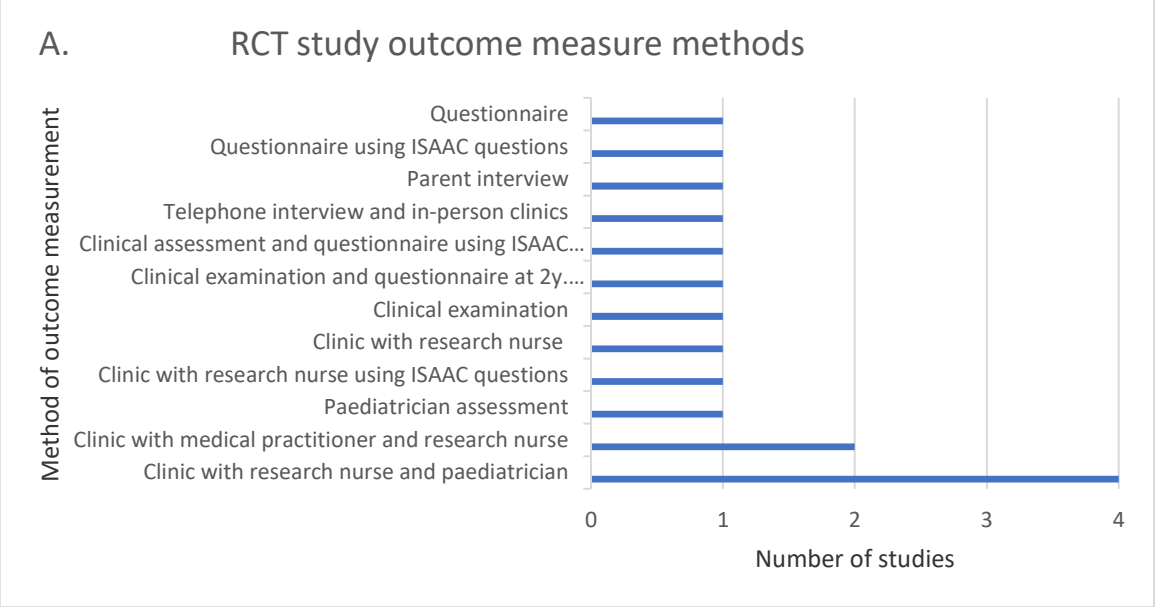


Figure 4 Categorisation of studies according to diet or supplementation variables. Bar graphs show numbers of studies categorised according to the diet or supplementation variables assessed for (A) RCTs and (B) cohort studies in this review.

Outcome measures

Many studies used the validated ISAAC questionnaire questions to assess outcomes (Asher et al., 1995). This questionnaire is validated for use in 6-7-year olds and in 12-13-year olds. Other outcome measures are also shown in Figure 5 were parental report, parental report of doctor diagnosis, national health registers and General Practitioner records.



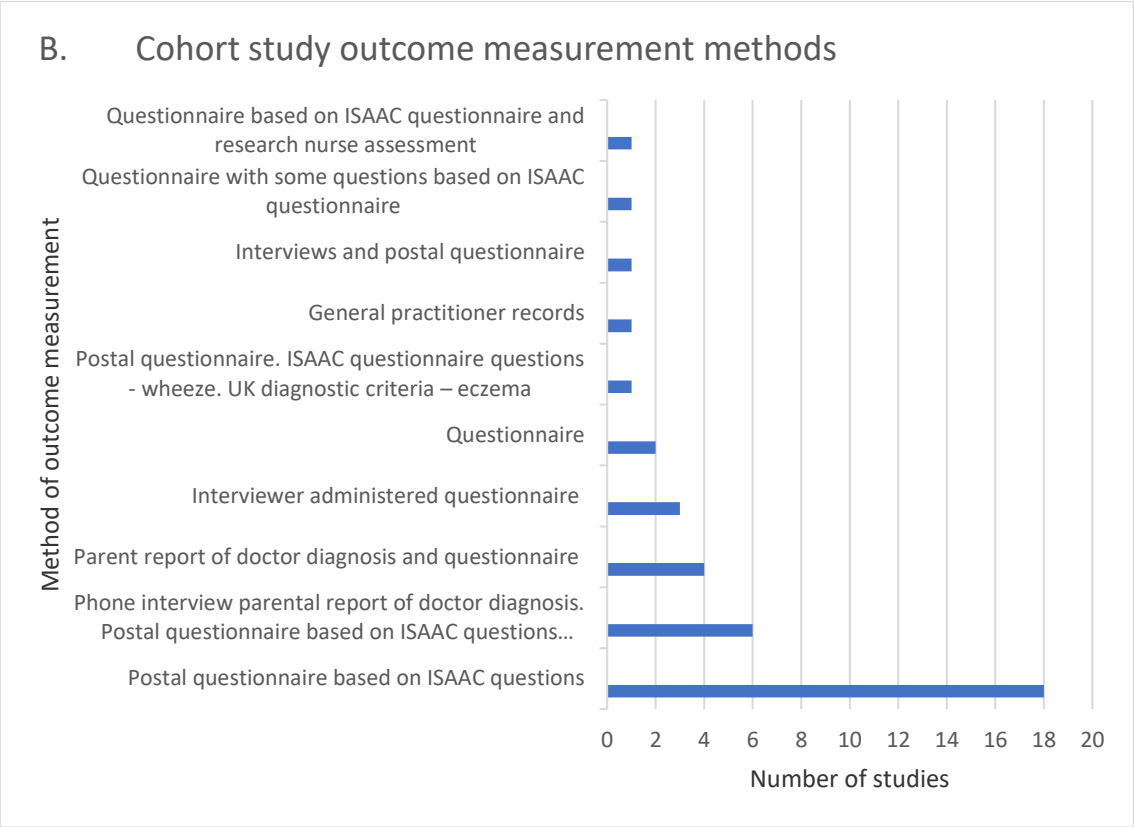


Figure 5 Categorisation of studies according to method used to measure health outcomes. Bar graphs show numbers of studies included in this review categorised according to the method used to measure health outcomes for (A) RCTs and (B) cohort studies**.**

The age of offspring assessments for measured health outcomes with reported findings varied from as young 3-4 months in Saito et al. (2010) and up to 10 years of age in Allan et al. (2015). Many studies had multiple assessments at various ages. These are described in the characteristics of included studies tables (p 54-101).

Excluded studies

For excluded studies please refer to "Characteristics of excluded studies" (Table 1). There were 49 studies excluded from this review. The reasons for exclusion were that studies did not assess the specified outcomes (n = 9), included a genetic predisposition for conditions that might affect the generalisability of the review (n=10), included infant or child's diet or supplement intake in reported associations (n=16), maternal intake was not systematically recorded (n=9) and lastly did not fulfil the quality assessment criteria (n=5).

Table 1 Excluded studies

Study	Reason for exclusion
Anderson et al. (2015)	Infant/child supplementation
Bertelsen et al. (2014)	Infant/child supplementation
Calvani et al. (2006)	Not the specified outcomes
Castro-Rodriguez et al. (2010)	No systematic recording of diet/supplements in pregnancy
Castro-Rodriguez et al. (2016)	No systematic recording of diet/supplements in pregnancy
Chatzi et al. (2008)	Infant/child diet
Checkley et al. (2011)	Infant/child supplementation
DeBatlle, Garcia-Aymerich, Barraza-Villarreal, Antó, & Romieu (2008)	Infant/child diet
Dotterud, Storrø, Simpson, Johnsen, & Øien (2013)	Infant/child diet
Dunstan et al. (2003)	Study reports but was not designed for clinical outcomes
Dunstan et al. (2012)	Study design issues
Erkkola et al. (2009)	Genetic predisposition
Erkkola et al. (2012)	Genetic predisposition
Furuhjelm, Jenmalm, Fälth-Magnusson, & Duchén (2011)	Not the specified outcomes
Gale et al. (2007)	No systematic recording of diet/supplements in pregnancy
Granell et al. (2008)	Genetic predisposition
Hansen et al. (2015)	No systematic recording of diet/supplements in pregnancy
Hansen et al. (2016)	Study design issues
Hoppu et al. (2005)	No systematic recording of diet/supplements in pregnancy
Huurre, Laitinen, Rautava, Korkeamäki, & Isolauri (2008)	Not the specified outcomes
Jedrychowski et al. (2011)	Mixed associations (diet and fine air pollutants)
Jonsson (2016)	Not the specified outcomes
Kalliomaki et al. (2001)	Infant/child supplementation
Kiefte-de Jong et al. (2012)	Genetic predisposition
Kim et al. (2010)	Infant/child supplementation
Lee et al. (2013)	Not the specified outcomes
Linnamaa et al. (2010)	Infant/child supplementation
Lumia et al. (2011)	Genetic predisposition
Lumia et al. (2012)	Genetic predisposition
Marks et al. (2006)	Infant/child supplementation
Mihrshahi et al. (2003)	Infant/child supplementation
Morales et al. (2012)	No systematic recording of diet/supplements in pregnancy
Notenboom, Mommers, Jansen, Penders, & Thijs (2011)	No systematic recording of diet/supplements in pregnancy
Nwaru et al. (2010)	Genetic predisposition
Nwaru, et al. (2011, May)	Genetic predisposition
Nwaru et al. (2011, December))	Genetic predisposition
Nwaru et al. (2012)	Genetic predisposition
Øien, Storrø, & Johnsen (2010)	Infant/child diet

Olsen et al. (2008)	Study design issues
Papadopolou et al. (2015)	Infant/child diet
Peat et al. (2004)	Infant/child supplementation
Prescott et al. (2008)	Infant/child supplementation & not the specified outcomes
Thijs et al. (2011)	No systematic recording of diet/supplements in pregnancy
Veeranki et al. (2015)	No systematic recording of diet/supplements in pregnancy
Wagner, Hulsey, Fanning, Ebeling, & Hollis (2006)	Not the specified outcomes
West et al. (1999)	Not the specified outcomes
West et al. (2012)	Infant/child supplementation
Wickens et al. (2012)	Infant/child supplementation
Yang et al. (2015)	Study design issues

Risk of bias in included studies

Risk of bias was assessed using different tools appropriate for each of the two methodologies according to the Cochrane Handbook for Systematic Reviews of interventions (2011). A detailed risk of bias assessment is given in the Characteristics of included studies tables (p 54-101). Most information in this review is from studies at low to unclear risk of bias except the von Ehrenstein et al. (2015) cohort study which had a high ROB due to a high attrition rate of participants.

Risk of bias – RCTs

Allocation

All 16 RCT studies were assessed as having a low risk of bias for sequence generation. Fifteen trials reported adequate allocation concealment methods. Noakes et al. (2012) did not describe allocation concealment.

Blinding

Blinding of participants and healthcare providers was assessed for the RCT studies. There were issues highlighted in the Furuhjelm et al. (2009, 2011) studies and the follow-on study by Warstedt et al. (2016); these studies assessed fish oil supplementation and had problems with women belching and being able to tell if they were on the fish-oil supplement. Simpson et al. (2015) is a follow-on study from Dotterud et al. (2010) and

the participants were unblinded after publication of the results from the two years of age follow up by Dotterud et al. Participants were not blinded in the trial reported by Goldring et al. (2013).

Incomplete outcome data

All the assessed RCT studies reported withdrawals and losses to follow-up. It was determined that Warstedt et al. (2016) and Chawes et al. (2016) made little or no attempt to account for incomplete data while some attempt or adequate description of withdrawals or losses to follow-up were made by Manley et al. (2011) and Noakes et al. (2012). The remaining studies showed adequate follow-up rates and/or descriptions of withdrawals and those lost to follow-up.

Selective reporting

There was one RCT study assessed as having a high risk of selective reporting bias. Greenough et al. (2010) did not describe the outcomes of interest but rather the questionnaire used and the questions it asked.

Other potential sources of bias

Six of the 16 RCT studies had other potential risks for bias identified and are now described. Best et al. (2016) is the latest follow up of participants from the Palmer et al. (2012, 2013) studies. These studies included a subset of those enrolled in the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial specified as having a family history (mother, father, sibling) of allergic disease and only included Adelaide based families (DOMInO included participants from New South Wales, Queensland and Victoria).

Greenough et al. (2010) is a follow-up of a trial that had different primary outcomes and part of their inclusion criteria was that mothers were identified as being at heightened risk for pre-eclampsia**.** This study is very brief on specific study details making assessment for bias difficult.

Chawes et al. (2016) excluded offspring with chronic disease post-delivery and included outcomes for both children of twin births in the study data.

Manley et al. (2011) reported secondary outcomes for a study designed to assess the effect of fish oil supplement on neurodevelopment.

Risk of bias – cohort studies

Representativeness

Fitzsimon et al. (2007) did not provide enough information about the exposed cohort to allow for rigorous assessment and while there is a mention of earlier studies no reference is provided.

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) studies (Bekkers et al., 2012; Willers et al., 2008) used a screening questionnaire prior to 'selecting' women to participate. The description of the study design referred to in these included studies (Brunekreef et al., 2002) does not elaborate on the screening questionnaire and this prevents an accurate assessment of the potential for selection bias.

Shaheen et al. (2009) reported findings from the Avon Longitudinal Study of Parents and Children (ALSPAC), this study retrospectively defined the cohort dependent on many factors described in the cohort profile, which also states that the cohort may not be generalisable to the population (Boyd et al., 2012).

The Osaka Mother and Child Health Study (OMCHS) studies reported some evidence of 'snow balling' by enrolling women from outside of the defined cohort area to increase study population size Miyake et al., 2009, 2010a, 2010b; Miyake, Okubo, et al., 2011; Miyake, Sasaki, et al., 2011; Saito et al., 2010). There was also no record kept of the number of women invited to participate so there was no information available to assess participation bias.

The remaining studies based in Japan, the Kyushu Okinawa Maternal and Child Health Study (KOMCHS) cohort, also reported issues with a lack of record kept of the number of women approached and declining to participate (Miyake et al., 2013, 2014).

Magdelijns et al. (2011) describes recruitment through an existing cohort study in the Netherlands, the KOALA birth cohort (in Dutch, the Child, Parent and Health: Lifestyle and Genetic Constitution study). The Magdelijns et al. (2011) study enrolled 2343 women from this cohort and they comprised the conventional recruitment group while other 491 women were recruited through posters at 'alternative' medical practitioners and organic health food shops and they comprised the alternative recruitment group. Participation bias is likely to be high in both groups and the sample is likely to have issues with generalisability.

Dunstan et al. (2012) included only healthy non-smokers with uncomplicated term pregnancies.

Selection of non-exposed cohort

The non-exposed cohort was drawn from the same community as the exposed cohort in all studies.

Ascertainment of exposure

Most of the studies assessed exposure using self/parent-reported FFQ (see Figure 5). Chatzi et al. (2013) reported on the findings of two cohort studies, the INMA (INfanciay Medio Ambiente Cohort) trained interviewers who administered the FFQ, but the Rhea cohort method of administration is not described in the same detail and is likely to have been self-administered.

Watson et al. (2014) used an interviewer-administered 24-hour dietary recall and a 3-day food record. The von Ehrenstein et al. (2015) study doesn't clearly state whether diet was assessed in an interview situation or self-administered.

Demonstration that outcome of interest not present at start of the study

There were studies that did not address this issue directly as the outcomes assessed were not present during fetal development or birth. It is assumed that the inherited predisposition is present but the outcome itself is not and therefore all studies were awarded a star.

Comparability of cohorts on the basis of design or analysis

It was determined by the study author that maternal or familial history of allergy (father or sibling) and maternal cigarette smoking during pregnancy were important confounders that should have been adjusted for.

Saito et al. (2010) adjusted for maternal and paternal history of allergy but did not adjust for maternal smoking in pregnancy. Dunstan et al. (2012) excluded smokers from their study. Pele et al. (2013) considered prenatal smoke exposure as a confounder but results were adjusted for postnatal smoke exposure. Watson et al. (2014) did not discuss or adjust for maternal smoking in pregnancy. Von Ehrenstein et al. (2015) considered maternal smoking but did not retain it as a confounder in the final models as it didn't change the estimates of interest by >10%.

Assessment of outcome

Most studies used parental report of outcomes via self-administered questionnaires (see Figure 5). Fitzsimon et al. (2007) assessed GP records. The Danish National Birth Cohort (DNBC) studies reported by Maslova, Granström, et al. (2012); Maslova, Halldorsson, et al. (2012); Maslova, Hansen, et al. (2013); Maslova, Strøm, Oken, et al. (2013); Maslova, Strøm, Olsen, et al. (2013); and Maslova, Hansen, Strøm, Halldorsson, and Olsen (2014), used both parental report and national registry data.

Follow up long enough for outcomes to occur

It was decided by the author that a diagnosis of asthma at <3 years was prone to misdiagnosis as described by Bakirtas (2017). The DNBC studies reported by Maslova, Granström, et al. (2012); Maslova, Halldorsson, et al. (2012); Maslova, Hansen, et al. (2013); Maslova, Strøm, Oken, et al. (2013); Maslova, Strøm, Olsen, et al. (2013); and Maslova, Hansen, Strøm, Halldorsson, and Olsen (2014), assessed asthma at both 18 months and 7 years of age so a half star was awarded to these studies.

Adequacy of follow up

Guyatt et al. (2011) discuss loss to follow up and emphasise the need to interpret the data before accepting the arbitrary thresholds suggested by methodologists in the past. The Newcastle-Ottawa Scale requires a percentage determined by the review author to be

acceptable but also gives opportunity for the losses to follow up to be described. For this work, the given suggestion in Guyatt et al. (2011) of 80% follow up has been adopted. If studies within this work have greater than 20% loss to follow up and do not describe those losses, then they are graded down in the GRADE SOF tables. Von Ehrenstein et al. (2015) reported issues with high attrition due to a very transient population in Los Angeles. They reported a 49.3% response rate to follow-up at 3 years of age and then only had sufficient data to present findings for 49% and there was no description of those losses given.

Characteristics of included studies tables ordered alphabetically by study design

Randomised Controlled Trials

Best et al. (2016)

Methods	Randomised controlled trial. Best et al. (2016) was the last published follow up of the three DOMInO trial studies included in this review (see Related studies).
Participants	Setting: Australia. 706 women <21 weeks' gestation with a singleton pregnancy were enrolled during their antenatal clinic visit. Women were eligible to enrol in a nested childhood allergy follow-up if their unborn child had a family history of allergic disease (mother, father, or sibling with a history of medically diagnosed eczema, asthma, or hay fever).
Interventions	Intervention: 500 mg of fish oil concentrate, providing ~800mg/day DHA and 100 mg/day EPA Control: 500 mg vegetable oil capsules Duration of intervention: from 21 weeks' gestation until delivery.
Outcomes	Palmer et al. (2012) assessed eczema at 1y of age. D. Palmer et al. (2013) assessed asthma, eczema and hayfever at 1 and 3y of age. Best et al. (2016) assessed asthma, wheeze, eczema and hayfever at 6y of age.
Notes	Funding: Dr Best was supported by a MS McLeod Pediatric and Child Health Nursing PhD scholarship; Dr Makrides was supported by Australian National Health and Medical Research Council senior research fellowship 1061704. This 6-year follow-up study was supported by Australian National Health and Medical Research Council grant 1027710.
Related studies	Palmer et al. (2012) Palmer et al. (2013)
Risk of bias	
Bias	**Author's Judgement** **Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "computer-driven telephone randomization service, stratified by center and parity (first birth versus subsequent births)."
Allocation concealment (selection bias)	Low risk	Quote: ". . . and neither the women nor research staff was aware of the treatment allocated."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All capsules were similar in size, shape, and color, and neither the women nor research staff was aware of the treatment allocated." Unblinding was performed by an independent data management center to ensure all research staff remained blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised: trial entry n= 706 (Intervention 368, control 338) Palmer et al. (2012) 96.5% follow-up at 1 year Palmer et al. (2013) 90.4% follow up at 3 years Best et al. (2016) 90.2% follow up at 6 years. Reasons given for losses to follow up. All analyses were performed according to the intention to treat principle. Multiple imputation, implemented under a missing-at-random assumption and performed separately by randomized group using chained equations, was used to address missing outcome data.
Selective reporting (reporting bias	Low risk	Trial registered at ClinicalTrials.gov Identifier: NCT00159523. Prespecified outcomes relating to this review all reported on.
Other bias	Unclear risk	Of the original DOMInO trial (n = 2399), a subset of mothers whose unborn child had a family history of allergies were included in these studies (706).

Chawes et al. (2016)

Methods	Randomised Controlled Trial. Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) 2010 cohort.
Participants	Setting: Denmark Enrolment began March 2009 with a goal of 708 participants, but due to delayed ethical approval, only 623 women were recruited at 24 weeks of pregnancy. Exclusion criteria were gestational age above week 26; any endocrine, cardiovascular, or nephrological disorders; or vitamin D3 (cholecalciferol) intake more than 600 IU/d.
Interventions	Intervention: daily dose of 2400 IU vitamin D3 supplementation Control: matching placebo tablets Duration of intervention: from pregnancy week 24 to 1 week postpartum. All women were instructed to continue supplementation of 400 IU of vitamin D3 during pregnancy as recommended by the Danish National Board of Health; thus, the study is a dose comparison of 2800 IU/d vs 400 IU/d of vitamin D3 supplementation.
Outcomes	Asthma, wheeze and eczema at 3y of age.
Notes	The Lundbeck Foundation, Danish State Budget, Danish Council for Strategic Research, Danish Council for Independent Research, and the

	Capital Region Research Foundation have provided core support for COPSAC.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Women were randomized using a computer-generated list of random numbers . . ."
Allocation concealment (selection bias)	Low risk	Quote: "Women were randomized using a computer-generated list of random numbers, supplied by an external investigator who had no further involvement in the RCT." "Matching placebo tablets".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The intervention code was unblinded when the youngest child reached age 3 years or in case of a medical emergency."
Incomplete outcome data (attrition bias) All outcomes	Low risk	623 women randomised (intervention 315, control 308) At 3 years of age: 581 (intervention 295, control 286) 93% follow-up.
Selective reporting (reporting bias)	Low risk	Trial registered at ClinicalTrials.gov identifier: NCT00856947. Prespecified outcomes relating to this review all reported on.
Other bias	Unclear risk	Study included twin pregnancies. All the women also participated in a concomitant factorial designed, double-blind RCT of 2.4 g per day of long-chain n-3 polyunsaturated fatty acids. (PUFAs) during pregnancy (ClinicalTrials.gov: NCT00798226).

Escamilla-Nuñez et al. (2014)

Methods	Randomised Controlled Trial.
Participants	Setting: Mexico 1094 pregnant women were recruited during routine prenatal care visits between February 2005 and February 2007. These pregnant women were between the ages of 18-35 years and were 18-22 weeks pregnant. All expressed willingness to breastfeed exclusively or predominantly during the first three months of life. Exclusions: women with high-risk pregnancies (pregnancy complications, including premature placental abruption, preeclampsia, pregnancy-induced hypertension, severe bleeding episode in pregnancy) or lipid absorption disorders, or who regularly consumed fish oil or DHA supplements or chronically used certain medications (eg, drugs for epilepsy).
Interventions	Intervention: two capsules per day of 200 mg of DHA derived from an algal source. Control: placebo capsules which contained a mixture of corn and soy oil and were similar in appearance and taste to DHA capsules Duration of intervention: week 18-22 of pregnancy until delivery
Outcomes	Wheeze.

Notes	This study was supported by the National Council of Sciences and Technology CONACYT [Grant 87121] and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development [Award R01HD058818]	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We used block randomization to randomly create balanced replication of four treatments (two colors for DHA and two for control subjects) using a block size of eight."
Allocation concealment (selection bias)	Unclear risk	Not discussed in detail in study report. Quote: "The assignment codes were placed in sealed envelopes at the beginning of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study participants and members of the study team remained blinded to the treatment scheme throughout the intervention period of the study. Since the study is ongoing for follow-up of children, the participants and fieldworkers remain blinded to the treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised n = 1094 (547 intervention, 547 control). 53 randomised but did not begin treatment 67 did not complete treatment (lack of family support, moved from area, disliked flavour, heartburn, nausea). Outcomes were reported on 869 infants whose information was complete – 82% follow-up rate, similar between intervention (80%) and control (78%).
Selective reporting (reporting bias)	Low risk	ClinicalTrials.gov Identifier: NCT00646360. Most of the prespecified outcomes were reported in this trial according to their protocol.
Other bias	Low risk	No obvious risk of other bias.

Goldring et al. (2013)

Methods	Randomised Controlled Trial.
Participants	Setting: United Kingdom 180 women presenting at 27 weeks gestation for routine glucose challenge test from the following ethnic groups: Asian, Middle Eastern, Black and White were randomised. Exclusions: known sarcoidosis, osteomalacia, renal dysfunction or tuberculosis**.**
Interventions	Intervention: 1) 800 IU ergocalciferol until delivery (daily) Or 2) single oral dose of 200,000 IU cholecalciferol (bolus). Control: no treatment Duration of intervention: 1) From 27 weeks gestation until delivery. 2) One off dose at 27 weeks gestation
Outcomes	Wheeze (ever, recurrent, in the last year, with a positive asthma predictive index), eczema (ever, in the last year) and allergic rhinitis at 3 years of age.
Notes	Supported by Grant number 09/36 from Asthma UK

Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: ". . .computer generated random number lists in blocks of 15, stratified by 4 ethnic groups in a 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation sequence was generated by an independent researcher . . ."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised 180 (60 intervention 1, 60 intervention 2, 60 control). 158 (88%) of offspring attended the 3 year follow up (56 intervention 1, 52 intervention 2, 50 control).
Selective reporting (reporting bias)	Low risk	Trial registered at Controlled-Trials.com ISRCTN68645785. All outcomes relevant to this review and specified in the study protocol were reported on.
Other bias	Low risk	No obvious risk of other bias.

Greenough et al. (2010)

Methods	Randomised Controlled Trial. Vitamins in Pre-eclampsia (VIP) trial. (See related studies for original VIP trial article).
Participants	Setting: UK and Holland 752 women were included in this study which utilised data and participants from the VIP study (27% of those in original VIP study). GPs for these infants were contacted to find out if the infant was still alive and if they were then the mother was contacted to take part in this study. This study included 330 who had taken vitamins in pregnancy and 313 control (placebo). Exclusion criteria: women who were taking vitamin supplements if they contained doses of vitamin C of 200 mg or more or of vitamin E of 40 IU or more daily. (Poston et al., 2006).
Interventions	Intervention: 1000 mg vitamin C and 400 IU RRR a-tocopherol daily Control: Placebo Duration of intervention: from second trimester (14^{+0}-21^{+6} weeks) until delivery.
Outcomes	Asthma, wheeze and eczema at 2y of age.
Notes	This study was supported by Asthma UK. Support was also given by the Wellcome Trust and Tommy's, the baby charity, to the Vitamins In Pre-eclampsia trial.
Related studies	Original VIP article used for supplementary information. Poston, L., Briley, A.L., Seed., P.T., Kelly. F.J., and Shennan, A.H. (2006).

Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation sequence was blocked—i.e., balanced—by centre in groups of two to ten individuals (mean size 6.7)."

Allocation concealment (selection bias)	Low risk	Quote: "The trial statistician (PTS) wrote the computer program that generated the sequence and a statistician not involved with the trial ran it with a new random number sequence. We gave copies of the sequence to MedSciNet and DHP."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study participants were unblinded after original study. Quote: "Researchers assessing the respiratory outcome of the infants were blind to the maternal allocation of treatment." Assessed using a posted respiratory questionnaire. If not returned the research nurse contacted the family and completed during a telephone interview if possible.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up for the outcomes assessed in this review.
Selective reporting (reporting bias)	High risk	VIP study was registered as an International Standard Randomised Controlled Trial, number ISRCTN 62368611. No registration for the Greenough trial. Predefined outcomes for assessment and outcome definitions are poorly described.
Other bias	Unclear risk	Characteristics of the participants who were included in this study compared to those who refused to participate have significant differences.

Litonjua et al. (2016)

Methods	Randomised Controlled Trial. Vitamin D Antenatal Asthma Reduction Trial (VDAART).
Participants	Setting: United States of America. Women between the ages of 18 and 39 years, who presented between the estimated gestational ages of 10 and 18 weeks; who had a history of asthma, eczema, or allergic rhinitis, or whose partner (biologic father of the child) had a history of asthma, eczema, or allergic rhinitis; who was a non-smoker; and who was English or Spanish speaking, with intent to participate for 4 years (up to the third birthday of the child). Exclusion criteria: Gestational age >18 weeks, presence of chronic medical conditions: (i) hypertension on medications, (ii) diabetes mellitus, (iii) parathyroid disease, (iv) uncontrolled thyroid disease, v) kidney stones, and (vi) sarcoidosis, intake of vitamin D supplements containing > 2,000 IU/day of vitamin D3, multiple gestation pregnancy, pregnancy achieved by assisted reproduction techniques (e.g. IUI, IVF), current use of illicit drugs (defined as any use in the past 6 months prior to enrolment), previously enrolled in VDAART for a prior pregnancy, any major fetal anomalies detected prior to delivery, patient Health Questionnaire depression scale ≥ 15, any condition, in the opinion of the Clinical Center Principal Investigator, that would inhibit compliance with the study medications or prohibit long-term participation in the trial

	881 women were randomised but 5 were found to be ineligible so study started with 876 women.	
Interventions	Intervention: 440 women were randomized to receive daily 4000 IU vitamin D plus a prenatal vitamin containing 400 IU vitamin D Control: 436 women were randomized to receive a placebo plus a prenatal vitamin containing 400 IU vitamin D Duration of intervention: Intervention commenced, on average, at gestational week 14 and continued until delivery.	
Outcomes	Parental report of physician diagnosis of asthma or occurrence of recurrent wheeze in the child's first 3 years of life, parental report of physician diagnosis of eczema 3y of age.	
Notes	VDAART was supported by grant U01HL091528 from the NHLBI. Additional support was provided by grant U54TR001012 from the National Centers for Advancing Translational Sciences (NCATS) for participant visits at the Boston Medical Center.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was performed using a system that automates the random assignment of treatment groups to study identification numbers. The randomization scheme used stratified permuted blocks with randomly varied block sizes of 4 and 6, and 1 block allocation list per stratum (study site and racial/ethnic group).
Allocation concealment (selection bias)	Low risk	All medications (including placebo) were manufactured by one company. These were then sent to the data control centre for packaging. Quote: "The vitamin D bottles and the placebo pill bottles were given a letter label from A to F, with 3 letters corresponding to the vitamin D pills and 3 letters corresponding to the placebo. Clinical Center investigators and staff were blinded to the treatment code. Once packaged and labelled, the pill bottles were shipped to the respective Clinical Centers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Until the end of the trial, all investigators, clinical staff and participants are masked to trial outcome data, with the exception of the trial statisticians, the data manager, and the Data, Safety and Monitoring Committee."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised: 881 with 5 found to be ineligible after randomisation = 876 At 3 years of age follow-up 806 participants (intervention 405 and control 401). 92% follow-up.
Selective reporting (reporting bias)	Low risk	Trial registered at ClinicalTrials.gov identifier: NCT00920621 Prespecified outcomes relating to this review all reported.
Other bias	Low risk	No obvious risk of other bias.

Manley et al. (2011)

Methods	Randomised Controlled Trial.

	Docosahexaenoic Acid (DHA) for the Improvement of Neurodevelopmental Outcome in Preterm Infants (DINO) trial.
Participants	Setting: Australia. Infants born before 33 weeks' gestation were eligible, and families were approached within 5 days of the infant commencing any enteral feedings. Exclusion: major congenital or chromosomal abnormalities, multiple birth in which not all live-born infants were eligible, or enrolled in other trials of fatty acid supplementation. Lactating mothers in whom tuna oil was contraindicated were also excluded.
Interventions	Intervention: lactating women whose infants were randomly assigned to the high-DHA group consumed 6 x 500 mg DHA-rich tuna oil capsules per day which provided 900 mg DHA and 195 mg EPA. The intent was to achieve a breast milk DHA concentration that was∼1% of total fatty acids without altering the naturally occurring concentration of AA in breast milk. If supplementary formula was required, infants were given a high-DHA preterm formula (1% DHA and 0.6% AA). Control: lactating women with infants allocated to the standard-DHA group consumed 6 500 mg placebo soy oil capsules with no n-3 LCPUFA. If supplementary formula was required in this group, a standard preterm infant formula was used (0.35% DHA and 0.6% AA). Duration of intervention: within 5 days from the infant receiving any enteral feeds until infants reached their expected date of delivery.
Outcomes	Parent reported asthma, eczema and allergic rhinitis at 18 months corrected age.
Notes	The DINO trial was supported by a grant from the National Health and Medical Research Council of Australia (ID 250322). Treatment and placebo capsules were donated by Clover Corporation, and infant formula was donated by Mead Johnson Nutritionals and Nutricia Australia.

Risk of bias

Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Mother-infant pairs were randomly assigned a unique study number through a computer-driven telephone randomisation service according to an independently generated randomisation schedule. Stratification was by centre, birth weight (≤1250 grams vs ≥1250 grams), and infant sex. Multiple births were considered a single randomisation unit and randomisation of twins or triplets was according to the sex and birth weight of the first-born infant".
Allocation concealment (selection bias)	Low risk	Quote: ". . . computer-driven telephone randomisation service. "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "Parents, clinicians, and all research personnel were blinded to participant study group".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A total of 657 infants were enrolled (high-DHA diet: 322; standard-DHA diet: 335), and 614 infants (93.5%) completed the 18-month follow-

		up. Although there was a high retention rate in the trial, allergy data were incomplete at 12- and 18-month corrected age, largely because the families who participated in the pilot phase of the trial did not complete the allergy questionnaires.
Selective reporting (reporting bias)	Low risk	Trial registered at anzctr.org.au Identifier: ACTRN12606000327583. All outcomes of interest for this review described for assessment were reported in results.
Other bias	Unclear risk	Reliance on parental report of medical attention for or treatment of the outcomes pertaining to this review.

Noakes et al. (2012)

Methods	Randomised controlled trial. Salmon in Pregnancy Study (SiPS).	
Participants	Setting: United Kingdom. 123 pregnant women aged between 18-40 years, <19 weeks gestation, with a healthy uncomplicated singleton pregnancy and an infant at risk of atopy (one or more first degree relatives affected) were recruited. These women had to consume <2 portions oily fish per month and not be using or have used fish oil supplements in the last 3 months. Exclusions: women participating in another research study, known diabetes, autoimmune disease, learning disability, terminal illness or mental health problems.	
Interventions	Intervention: Intake of two 150g portions of farmed salmon per week into their diet. Control: continue habitual diet. Duration: from 20 weeks gestation until delivery.	
Outcomes	Wheeze at 6 months of age – assessed by parental report to research nurse who obtained detailed information to determine if "noisy breathing" was wheeze. Eczema at 6 months of age – assessed by research nurse using the SCORAD index.	
Notes	Supported by the European Commission under Framework 6: Sustainable aqua feeds to maximize the health benefits of farmed fish for consumers (Aquamax; FOOD-CT-2006-16249). 2 researchers were supported by the Southampton NIHR Biomedical Research Unit in Nutrition, Diet & Lifestyle. Salmon was donated by the University of Bergen, Norway.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The women were allocated to one of two groups according to a previously generated random number table".
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were not blinded. Quote: "Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded to the groups."

Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled 123 (62 salmon, 61 control). At delivery: 107 (87%): 53 (85%) salmon, 54 (89%) control. 6-month clinic visit: 86 (70%): 48 (77%) salmon, 38 (62%) control.
Selective reporting (reporting bias	High risk	Trial registered at clinicaltrials.gov as NCT00801502. Multiple non-specific outcomes given. Limited data reported on the prespecified review outcomes.
Other bias	Low risk	No obvious risk of other bias.

Rautava et al. (2012)

Methods	Randomised Controlled Trial.	
Participants	Setting: Finland 241 pregnant women with atopic sensitization and either a history of or active allergic disease and the intention to breast feed for a minimum of 2 months were recruited between August 2005 and April 2009. Exclusions: Women with immune-mediated disease other than atopic or allergic disease were excluded from the study. Infants born of multiple pregnancies were excluded from the analyses to ensure independence of the study subjects.	
Interventions	Intervention: Dietary food supplement that contained minerals, including calcium, vitamins, including vitamins B12, A, and D, folic acid and other micronutrients, including iron, zinc, and iodine, with composition and dosage in compliance with recommended daily allowances supplemented with either the combination LPR and BL999 (LPR1BL999) consisting of Lactobacillus rhamnosus LPR (CGMCC 1.3724) and Bifidobacterium longum BL999 (ATCC: BAA-999) or the combination ST11 and BL999 (ST111BL999) consisting of L paracasei ST11 (CNCM 1-2116) and B longum BL999. Daily dose for each probiotic was $13x10^9$ cfu provided in 1 sachet of 7 g/d (powder form) which was diluted in a glass of water. Control: the same dietary supplement without probiotics served as placebo Duration of intervention: 2 months before the expected day of delivery and continued during breast-feeding until the child was 2 months of age.	
Outcomes	Eczema and chronically persistent eczema until 24 months.	
Notes	Supported by a research grant from the Sigrid Jusélius Foundation and Turku University Hospital EVO research funding.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The random allocation was computer-generated . . ."
Allocation concealment (selection bias)	Low risk	Quote: ". . . computer-generated independently from the investigators by the manufacturer of the study products."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study preparations were provided by Nestlé S.A. and were similar in appearance."

All outcomes		"All investigations were performed double-blind . . . "
Incomplete outcome data (attrition bias)	Low risk	241 women randomised (81 LPR + BL999, 82 ST11 + BL999, 78 placebo).
All outcomes		205 (85%) mother-infant pairs completed follow-up at 24 months (73 LPR + BL999, 70 ST11 + BL999, 62 placebo).
Selective reporting (reporting bias)	Low risk	Trial registered at ClinicalTrials.gov identifier: NCT00167700. All outcomes described for assessment and outcomes of interest to this review are reported.
Other bias	Low risk	No obvious risk of other bias.

Simpson et al. 2015

Methods	Randomised controlled trial. Simpson et al. (2015) was the last published follow-up of the two Pro-PACT trial studies included in this review (see Related studies).
Participants	Setting: Norway. 415 pregnant women were recruited through all seven midwives in Trondheim during pregnancy check-ups. All pregnant women were eligible for inclusion if they understood Norwegian, signed the written consent form, were planning to breastfeed during the first three postnatal months, were in week ≤ 36 of pregnancy, liked and tolerated fermented milk and were not at risk of developing pregnancy complications such as pre-eclampsia.
Interventions	Intervention: Probiotic supplementation consisted of 250 mL of low-fat fermented milk containing 5×10^{10} colony-forming units (CFUs) of Lactobacillus rhamnosus GG (LGG) and Bifidobacterium animalis subsp. lactis Bb-12 (Bb-12) and 5×10^{9} CFU of L. Acidophilus La-5 (La-5). Control: Equivalently tasting placebo milk that was sterile and contained no probiotic bacteria. Duration of intervention: 36 weeks gestation until 3 months postpartum.
Outcomes	Children who attended the clinical examination(s) were assessed for eczema using the UK Working Party (UKWP) diagnostic criteria. The cumulative incidence of ARC was defined by a positive answer to the question "Has your child ever had hay fever or allergic rhinoconjunctivitis?" in the 1, 2 or 6-year questionnaire. Current asthma was defined as a positive answer to both questions "Has your child ever been diagnosed with asthma by a doctor?" and "In the past 12 months, has your child been treated with tablets, inhalers or other medications for wheezing, chest tightness or asthma. Simpson et al 2015 also state that "Prompted by the findings of other probiotic trials, we include here the cumulative incidence of wheeze defined by a positive answer to both questions "Has your child ever had whistling in the chest?" and "Has your child ever had episodes of wheezing or tightness in the chest?" these questions were not used in the earlier Dotterud et al. (2010) study.
Notes	This study was funded by the Norwegian University of Science and Technology, the Norwegian Research Council, Nidarosfondet and Siemens

	Medical Solutions Diagnostics AS. Tine BA sponsored the study through supply of study milk and logistics of its distribution.	
Related studies	(Dotterud et al. 2010).	

Risk of bias

Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote. . . "treatment allocation which was conducted by the Department of Applied Clinical Research at the Norwegian University of Science and Technology through a computer-generated randomisation list without restrictions."
Allocation concealment (selection bias)	Low risk	Quote. "Prior to this, the participants and investigators were blinded to treatment allocation . . ."
Blinding of participants and personnel (performance bias)	Dotterud et al. (2010)	Quote "Participants were unblinded after the publication of the 2-year follow-up results. Prior to this, the participants and investigators were blinded to treatment allocation."
All outcomes	Low risk Simpson et al. 2015)	"UKWP diagnosis was based on assessment by research nurses who were unaware of treatment allocation."
	Unclear risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote. "The 6-year child health questionnaire was completed by 281 (67.7 %) families and 163 (39.3 %) attended the clinical interview." "Due to the presence of missing data, the intention to treat (ITT) analysis strategy [29] included a main analysis using multiple imputations by chained equations (MICE) under the assumption that the data is missing at random (MAR) and a pattern mixture model (PMM) analysis to assess the sensitivity of the conclusions to this assumption." Dotterud et al. (2010) 67% follow up at 2 years.
Selective reporting (reporting bias	Low risk	The trial protocol is registered in ClinicalTrials. gov Identifier NCT00159523. Most of the prespecified review outcomes were reported in this trial.
Other bias	Unclear risk	Quote. "The PMM sensitivity analysis is particularly pertinent in this case because atopic sensitisation and or a diagnosis of AD at 2 years are associated with both attendance at the 6-year clinical examination and a diagnosis of AD at 6 years. This raises suspicions that the data is partially MNAR which would lead to biased estimates under both the complete case and multiple imputations analysis models".

Warstedt et al. (2016)

Methods	Randomised controlled trial. Warstedt et al. (2016) was the last published follow up of the three Swedish-based trials included in this review (see Related studies).
Participants	Setting: Sweden.

	Furuhjelm et al. (2009, & 2011) included 145 pregnant women in families with a history of allergic disease were recruited through antenatal clinics during a two-year period in 2003-2005. Warstedt et al. (2016) included 95 of these women for whom there were colostrum samples available.	
Interventions	**Intervention:** Women took nine 500 mg capsules a day containing 35% EPA, and 25% DHA, to provide 1.6 g of EPA and 1.1 g of DHA, n = 70. **Control:** 9 soy oil capsules a day, containing 58% LA to provide 2.5 g LA/day and 6% ALA to provide 0.28 g ALA/day, (n.=.75). **Duration of intervention:** 25th week of gestation to an average of 3 to 4 months breastfeeding.	
Outcomes	Furuhjelm et al. (2009) reported - Medically diagnosed allergy outcomes at 3, 6 and 12 months of age including: IgE antibody analysis, food allergy and eczema. Furuhjelm et al. (2011) and Warstedt et al. (2016) reported - Medically diagnosed allergy outcomes at 2 years of age including: food allergy, eczema, allergic rhinitis, asthma and any allergies with or without IgE associated.	
Notes	Funding: The study was supported by grants from The Ekhaga Foundation, The Swedish Research Council Formas, The Research Council for the South-East of Sweden, The Östergötland County Council and The Swedish Asthma and Allergy Research Foundation, The Swedish Research Council and Trygg Hansa Research Foundation.	
Related studies	Furuhjelm et al. (2009) Furuhjelm et al. (2011)	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The mothers were randomly allocated to dietary supplementation either with ω-3 fatty acids (ω-3 group) or placebo."
Allocation concealment (selection bias)	Low risk	Quote: "The producer performed the block randomization. "
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ". . . active and placebo capsules could not be distinguished from each other." Furuhjelm et al. (2009) Quote: "After about 4 weeks of supplementation, 11/80 (14%) mothers reported belching. Ten of them were supplemented with ω-3 fatty acids (p = 0.001)."
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomised n = 145 (70 intervention, 75 control). Furuhjelm et al. (2009), 25 did not complete the requested 15-week intervention period (16, 23% treatment and 9, 12% placebo) and were excluded from the analysis, 1 withdrew post-delivery, 2 not followed as moved before 6/12 follow up (group not stated). Total 28 (19%) not included in analysis, 117 included (81%). SPT 117 (81%) at 6 months, 115 (79%) at 12 months. Furuhjelm et al. (2009). Medically diagnosed allergy outcomes were reported on n = 117 (81%)

		(fish oil group n = 52 (74%) and control group n = 65 (87%), at 6 months and at 1 year of age. Furuhjelm et al. (2011), The mothers who were unable to complete the intervention (n – 25) were invited to a clinical examination of their infants comprising skin prick test (SPTs) but no blood sampling at 6 and 24 months. Thus, a follow-up at 2yr was accomplished for 143/145 families. Furuhjelm et al. (2011). Medically diagnosed allergy outcomes were reported on n = 119 (82%) (fish oil group n = 54 (77%) and control group n = 65 (87%), at 2 years of age. Warstedt et al. (2016). Medically diagnosed allergy outcomes were reported on n = 94 (99%). Numbers reported in this study do not align with numbers given, for example study gives 53 women in non-supplemented group but reports for 55 women. Study states that 84 women were included for analysis after exclusion of 11 women as they did not meet study definition of atopy but study reports analysis for up to 95 women.
Selective reporting (reporting bias	Low risk	Trial registered at ClinicalTrials.gov identifier: NCT00892684. Prespecified outcomes were reported in this trial according to their protocol. Outcomes of interest to the review are reported.
Other bias	Low risk	No obvious risk of other bias.

Cohort studies

The following tables present the characteristics of the included cohort studies. The Newcastle-Ottawa Scale was used to assess the risk of bias. In this system a star is awarded if the criteria are met. For ease of reading the stars are presented beside the Newcastle-Ottawa scale's criteria in the authors' judgment column. If a full star is presented the criteria was fully met a half star means some of the criteria were met and no star means that the author's judgement is that the criteria were not met. A study can receive a total of nine stars as described in the methods section.

Allan et al. (2015)

Methods	Cohort study. Allan et al. (2015) is the last published study of the Aberdeen cohort studies included in this review. There were five publications at different times assessing different associations included in this review (see related studies).
Participants	Setting: Scotland. 2000 healthy unselected pregnant women attending an antenatal clinic, at median 12 weeks gestation, were recruited between 1997

	and 1999. 1924 singleton children were born to the women in the cohort. Participant numbers varied for each publication due to losses to follow up and missing data.	
Interventions	At 32 weeks gestation, dietary intake over the preceding 3 months was assessed using version 5.4 of the Scottish Collaborative Group Food Frequency Questionnaire (FFQ). Martindale et al. (2005) assessed antioxidant intake. Devereux et al. (2006) assessed vitamin E intake. Devereux et al. (2007) assessed vitamin D intake. Willers et al. (2007) assessed food consumption (food groups of interest were fruit, vegetables, fruit juice, whole grain products, fish, dairy products, and fat spreads). Allan et al. (2015) assessed vitamin D and E intake.	
Outcomes	Martindale et al. (2005) assessed for wheeze and eczema outcomes at 2 years of age. Devereux et al. (2006) assessed for asthma, wheeze and eczema outcomes at 5 years of age. Devereux et al. (2007) assessed for wheeze outcomes at 5 years of age. Willers et al. (2007) assessed for asthma, wheeze, eczema and hayfever outcomes at 5 years of age. Allan et al. (2015) assessed for asthma, wheeze, eczema and hayfever outcomes at 10 years of age (and longitudinally).	
Notes	Funding: UK medical research council.	
Related studies	Martindale et al. (2005), Devereux et al. (2006), Devereux et al. (2007), Willers et al. (2007).	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Scottish women in the community	Quote: "the mothers of children actively participating in the questionnaire and clinical phases were less likely to smoke, were older, of higher SES, less likely to have wheezed, and had higher plasma ascorbate and β-carotene, whereas participating children were more likely to be girls and of higher birth weight."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort ★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	At 32 weeks gestation, dietary intake over the preceding 3 months was assessed.
Demonstration that outcome of interest was not present at start of study	yes ★	Developing fetus, outcomes of interest not present at birth.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal smoking during pregnancy. ★	Quote: "adjusted for maternal smoking during pregnancy, maternal atopy, . . ."

	study controls for maternal atopy ★	
Outcome		
Assessment of outcome	self-report	Quote: "In the month of the child's 10th birthday, an ISAAC (International Study of Asthma and Allergies in Childhood) based questionnaire was mailed to all participating families, with a single reminder if necessary."
Was follow up long enough for outcomes to occur	yes ★	Each study assessed outcomes at ages where diagnosis is generally accepted.
Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias > 80% follow up, OR description provided of those lost ★	Martindale et al. (2005) >70% follow-up at 2 years. Devereux et al. (2006) >65% follow-up at 5y. Devereux et al. (2007) >65% follow-up at 5y. Willers et al. (2007) >65% follow-up at 5y. Allan et al. (2015) 49% follow up at 10y. Descriptions of losses to follow up provided in all the studies.

Bekkers 2012

Methods	Cohort study. Bekkers et al. 2012 was the last published cohort study in this review from The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study. There were two publications at different times assessing different associations included in this review (see related studies).
Participants	Setting: Netherlands. 4,146 pregnant women were recruited for this cohort, but 183 women were lost to follow up before any data on the child had been obtained. The studies, therefore, started with 3963 women and child pairs. Participant numbers varied for each publication due to losses to follow up and missing data.
Interventions/association measures	Questionnaire administered during pregnancy at a median of 33 weeks gestation with diet and supplement questions included. Frequency of intake was assessed. No discussion around validation of questionnaire. Bekkers et al. (2012) assessed folic acid supplementation. Willers et al. (2008) assessed multiple food associations which included both food groups and specific foods.
Outcomes	Willers et al. (2008) assessed asthma symptoms yearly from age 3-8y of age and wheeze yearly from 1-8y of age. Bekkers et al. (2012) assessed asthma symptoms yearly from age 3-8y of age and wheeze and eczema yearly from 1-8y of age Asthma symptoms: at least one attack of wheeze, and/or at least one attack of dyspnoea, and/ or prescription of inhalation steroids for respiratory or lung problems by a medical doctor (at 3–8 yrs.). Wheeze: at least one attack of wheeze. Eczema: an itchy rash that came and went on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles).

Notes	Supported by the Netherlands Organization for Health Research and Development; the Netherlands Organization for Scientific Research; the Netherlands Asthma Fund; the Netherlands Ministry of Spatial Planning, Housing, and the Environment; and the Netherlands Ministry of Health, Welfare and Sport.	
Related studies	Willers et al. (2008)	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	Somewhat representative	Quote: "A cohort of ~4,000 newborns was enrolled, who have now been followed up for ~4 years. Loss to follow-up has, to date, been small. Response rates in the initial phase have been slightly below (intervention study) or above (natural history study) 50%. There is the potential therefore that the study population is not representative of the population of newborns in the study areas, in general".
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort ★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	Written self-report (parental)	Quote: Bekkers et al. (2012) "In the questionnaire administered during pregnancy, expectant mothers were asked whether or not they used specific vitamin or mineral supplements during pregnancy, including folic acid, pre-natal vitamins (multivitamin supplements especially for pregnant females), multivitamins and vitamin B complex supplements. Quote Willers et al. (2008) "The pregnancy questionnaire contained questions about diet. Expectant mothers were asked ''How often did you consume vegetables, fresh fruit, fish, egg, milk, milk products, nuts, and nut products such as peanut butter during the last month?'' Answer options were (1) never, (2) one to three times a month, (3) once a week, (4) two to four times a week, (5) more than four times a week, (6) once a day, or (7) several times per day. These frequency values were combined into three categories: rarely (value 1 and 2), regularly (value 3, 4, and 5), and daily (value 6 and 7).
Demonstration that outcome of interest was not present at start of study	Yes ★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	Study controls for maternal history of asthma/allergy ★	Quote: "Of these variables, the following were considered potential confounders: . . . maternal allergy (allergy to house dust mite or pets, hay fever or asthma ever, reported during pregnancy or not), . . . maternal smoking during pregnancy

	Study controls for maternal smoking during pregnancy ★	(any smoking during the first 4 weeks of pregnancy)."
Outcome		
Assessment of outcome	Self-report (parental report)	Quote: "The annual parental questionnaires contained questions on the child's asthma symptoms and eczema, based on the International Study of Asthma and Allergies in Childhood, as well as on respiratory infections."
Was follow up long enough for outcomes to occur	Yes ★	Quote: "The study was designed to follow-up the study children for 8 years to allow sufficient time for allergic sensitization and clinical manifestations to develop."
Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias > 80% follow up, OR description provided of those lost ★	Bekkers 2012 reported: "After exclusion of children with missing data on exposures (n=91) and on all health outcomes at every age (n=86), the study population for analysis consisted of 3,786 (95.5%) out of 3,963 children." Willers 2008 reported. "After 8 years of follow-up, around 80% of the population initially recruited was still participating."

Chatzi et al. (2013)

Methods	Cohort study. This report assessed two cohort studies the INfancia y Medio Ambiente Cohort (INMA) and the RHEA cohort.
Participants	Setting: INMA – Spain. RHEA – Greece INMA 1771 children included in the final analysis of this report. Women were recruited at their first routine antenatal care visit. RHEA 745 women were included in the final analysis of this report. Women were recruited at the time of the first major ultrasound examination.
Interventions	INMA – FFQ administered by trained interviewers. RHEA – FFQ questionnaire completed by mothers.
Outcomes	Wheeze and eczema in the first year of life.
Notes	The INMA study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176, CB06/02/0041, FIS-FEDER 03/ 1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314 and 09/02647, FISS-PI042018, FISS-PI09/02311, FIS-PI06/0867, FIS-PS09/00090, FIS-PI041436, FIS-PI081151), the Conselleria de Sanitat Generalitat Valenciana, Generalitat de Catalunya-CIRIT 1999SGR 00241, Obra social Cajastur, Universidad de Oviedo, Department of Health of the Basque Government (2005111093 and 2009111069) and the Provincial Government of Gipuzkoa (DFG06/004 and DFG08/001). The RHEA study was partly supported by the European Union (EU) Integrated Projects (EU FP6-2003-Food-3-A NewGeneris, EU FP6; STREP Hiwate, EU FP7 ENV.2007.1.2.2.2; Project no. 211250 Escape, EU FP7-2008-ENV-1.2.1.4 Envirogenomarkers, EU FP7-HEALTH-2009-single-stage CHICOS, EU FP7 ENV.2008.1.2.1.6. Proposal no. 226285 ENRIECO) and the Greek Ministry of Health (Program of Prevention of obesity and neurodevelopmental disorders in preschool children, in Heraklion district, Crete, Greece: 2011–2014).
Risk of bias	

Bias	Author's Judgement	Support for judgement
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Spanish and Greek (Mediterranean) women in the community	Quote: "In the RHEA cohort, there were no significant differences regarding sociodemographic characteristics between the mother–child pairs who participated in the study and those who were excluded. The children lost to follow-up in the INMA cohort were from a lower social class, had a poorer paternal education and had a higher frequency of being preterm and having a low birth weight, but showed much less difference in terms of respiratory outcomes.
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort studies with those who didn't develop allergy used as internal control.
Ascertainment of exposure	INMA - structured interview★ RHEA - written self-report	INMA Quote: "a FFQ was administered by trained interviewers, with 100 food items to assess usual food and nutrient intakes during the first trimester of pregnancy." RHEA Quote: "The RHEA FFQ was administered in mid-pregnancy (14th–18th weeks of gestation, mean 14·6 (SD 3·2)) assessing dietary habits over pregnancy. This is a semi-quantitative questionnaire, containing 250 food items. "
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal history of asthma/eczema ★ study controls for maternal smoking during pregnancy★	Quote: "Potential confounders included: . . . maternal smoking during pregnancy (yes/no); . . maternal and paternal history of asthma (yes/no); maternal and paternal history of eczema (yes/ no) . . ."
Outcome		
Assessment of outcome	Self-report	INMA- Interviewer administered questionnaires. RHEA – Structured telephone interviews. Both based on ISAAC phase-1 questionnaire.
Was follow up long enough for outcomes to occur	yes★	Outcomes assessed at ages generally accepted as appropriate for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias >80% follow up (INMA) but only 46% RHEA OR description provided of those lost) ★	INMA – 2150 women were recruited at their first routine specialised antenatal care visit. "The present analysis included only those women who had completed a FFQ in the first trimester and their infants had available data on respiratory outcomes (n 1784, 83 %). Due to implausible values for total energy intake (outside the range of 4184–16 736 kJ/d), thirteen additional women were excluded from the analysis. Thus, the final analysis was based on 1771 children."

	RHEA – "A total of 798 (67 %) participants provided complete questionnaire data on diet during pregnancy and health outcomes. Due to implausible values for total energy intake (outside the range of 4184–16 736 kJ/d), fifty-three women were excluded from the analysis. Hence, a cohort of 745 women was available for this analysis."

Dunstan et al. (2012)

Methods	Cohort study.	
Participants	Setting: Australia 628 pregnant women were recruited in the last trimester of pregnancy. Only healthy non-smokers with uncomplicated term pregnancies were included.	
Interventions	Semi-quantitative food frequency questionnaire collected in the third trimester (after 28 weeks gestation). The SQFFQ (CSIRO, Adelaide, Australia) reported the frequency of consumption of 212 individual foods, mixed foods and beverages over the preceding month. Reported supplement intake (brand, dose, and frequency) was converted into daily folic acid intake (microgram/day) using dosage information provided on the packaging.	
Outcomes	Eczema and recurrent wheeze (defined as asthma in study but assessed and presented as recurrent wheeze) at 1y of age.	
Notes	This project was supported by funds from the National Health and Medical Research Council (NHMRC) of Australia.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Australian women in the community	Quote: "The population is over represented with allergic women and women with a tertiary education."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	SQFFQ. Study does not define how this was carried out whether posted, given at clinic and returned, or interview situation. Assume not interview situation as study states "Four hundred and seventy women completed the SQFFQ and supplied data on vitamin supplements taken in the third trimester." Serum folate levels also taken in third trimester.
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		

Comparability of cohorts on the basis of the design or analysis	study controls for maternal allergy ★ study controls for maternal smoking during pregnancy★	Quote: "We collected detailed information about maternal factors that may influence folate status or risk of infant allergic disease, including maternal age, maternal allergic disease (and sensitization), . ." Study excluded smoking mothers.
Outcome		
Assessment of outcome	independent blind assessment☆ Self-report	Not well described in study report, appears to be a mixture of independent blind assessment, parent-reported physician diagnosis, symptoms and medication use. Quote: "At 12 months of age, the main clinical outcome measures were eczema, food allergy, and allergic sensitization. A child was classified as having 'allergic disease' if he/she had a physician diagnosis of IgE-mediated food allergy, eczema, or asthma. A diagnosis of eczema was made in infants with typical skin lesions. A diagnosis of asthma was based on a history of recurrent wheeze (>2 episodes of wheezing) that was demonstrated to be responsive to bronchodilator medications, but the limitations are recognized at this age."
Was follow up long enough for outcomes to occur	yes☆	Not for asthma. Recurrent wheeze would be difficult to ascertain at 1y of age also. Eczema outcomes = adequate latency.
Adequacy of follow up of cohorts	follow up rate <80% and no description of those lost	Of the 628 women recruited, 594 had at least one measure of folate status (questionnaire or serum level) in pregnancy and 484 infants were assessed at 1 year of age (77%). No description of losses to follow up provided.

Fitzsimon et al. (2007)

Methods	Cohort study. Life-ways Cross-Generation Cohort Study.
Participants	Setting: Ireland It was planned to recruit at least 1000 families over a one-year period, that is the expectant mother at first maternity hospital booking visit, with a special focus on those general medical services eligible (medical card holders), her infant at birth (the proband), her partner if agreeable, and at least one living grandparent. (O'Mahony et al., 2007). 1001 mother-singleton baby pairs included in this study recruited at 14-16 weeks gestation.
Interventions	A 149-item food frequency questionnaire administered during pregnancy (time of completion not specified but given to mothers to complete and send back when recruited at 14-16 weeks gestation).
Outcomes	GP diagnosed asthma at 3 years of age.
Notes	This study has been funded by the Health Research Board and the Department of Health and Children's Health Promotion Policy Unit (HPPU). (O'Mahony et al., 2007).
Related studies	This study report relies heavily on The Lifeways Cross-Generation Study: Design, Recruitment and Data Management Considerations (O'Mahony et al., 2007) article in the same issue of the journal.

Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Irish woman in the community	Quote: "The cohort was never necessarily intended to be representative of the general obstetric population in Ireland at the time, since the focus was on longitudinal follow-up and within-cohort comparison and the commitment anticipated for the project was high given the number of family members involved." (O'Mahony et al, 2007).
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Quote: "The food frequency part of the questionnaire was designed to cover the whole of the Irish diet and included 149 food items, arranged by food group. Each food item was assigned a standard portion size. Mothers were asked to indicate their average use of each food item during pregnancy."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study did not control for maternal asthma study controls for smoke exposure★	Quote: "To assess the effect of potentially confounding covariates we examined the association of dietary factors with asthma before and after including the covariates in the model. These were . . . maternal smoking during pregnancy . . . "
Outcome		
Assessment of outcome	record linkage★	Quote: "All general practitioners were contacted, with prior consent of the mother, during summer 2005, when the children were on average three years old, and asked to review their clinical records for the proband child."
Was follow up long enough for outcomes to occur	yes★	Outcome assessed at an age generally regarded as appropriate although pre-school diagnosis of asthma is known to be difficult.
Adequacy of follow up of cohorts	follow up rate <80% and no description of those lost	Quote: "General Practice follow-up records were available for 631 of 1001 singleton children, twins having been excluded (63% follow-up rate)." No description of losses to follow up given.

Håberg et al. (2009)

Methods	Cohort study. Norwegian Mother and Child Cohort Study (MoBa).
Participants	Setting: Norway The target population of the MoBa study is all women who give birth in Norway. There are no exclusion criteria.

	The study population for the current analyses included all children born between the beginning of 2000 and June 2005 who had reached 18 months of age, and for whom the 17-week and the 30-week questionnaires in pregnancy, and the 6-month and the18-month questionnaires had been processed as of April 2007. Data from the first 32 077 children in MoBa was used.	
Interventions	The main exposure was maternal intake of folic acid supplements in pregnancy, assessed from week 0 to 30 in pregnancy. The pregnant women recorded in which 4-week period they used different supplements, according to the label on their supplement container. Exposure to folic acid in any 4-weekperiod during weeks 0–12 in pregnancy was defined as exposure in the first trimester, and any use after week 12 as exposure after the first trimester.	
Outcomes	Wheeze up to 18 months of age.	
Notes	The study was supported by the Norwegian Association of Heart and Lung patients with EXTRA funds from the Norwegian Foundation for Health and Rehabilitation. The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health, NIH/NIEHS (grant no. N01-ES-85433), NIH/NINDS (grant no. 1 UO1 NS 047537-01) and the Norwegian Research Council/FUGE (grant no. 151918/S10).	
Related studies	Poston, Briley, Seed, Kelly, and Shennan. (2006).	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	truly representative of the average pregnant Norwegian woman in the community★	Quote (from supporting material): "there are minor differences between the MoBa births and the total number of births in the same period."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Questionnaire. Quote: "The pregnant women recorded in which 4-week period they used different supplements, according to the label on their supplement container."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present at delivery.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal atopy★ study controls for maternal smoking in pregnancy★	Quote: "Other covariates included were sex, birth weight, month of birth, and maternal atopy, maternal educational level, parity, maternal smoking in pregnancy. . "
Outcome		
Assessment of outcome	self-report	Parental questionnaire.
Was follow up long enough for outcomes to occur	yes★	Wheeze outcome assessed at an age where diagnosis is generally accepted.

Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - - > 60% follow up, or description provided of those lost★	Only used participants with data available as described in participants. Minimal loss to follow-up due to lack of information. Quote: "Children without information on respiratory outcomes were not included in analyses (2.1% for wheeze . . . "

Lange et al. 2010

Methods	Cohort. Lange et al. (2010) was the last published follow up of three cohort studies from Project Viva included in this review (see Related studies).
Participants	Setting: Massachusetts, U.S.A. Participant numbers varied in the three studies due to loss to follow-up and because recruitment was over 3 years and some children had not reached the age the follow-up was directed at. Litonjua et al. (2006) reported on 1290 participants. Camargo et al. (2007) reported on 1194 participants and Lange et al. (2010) reported on 1376 participants. Women with a singleton pregnancy were eligible if their first prenatal visit occurred before 22 weeks of gestation, they planned to continue care at Harvard Vanguard Medical Associates, and they were able to answer questionnaires in English.
Interventions	Maternal diet assessments at both visits were based on a validated 166-item semiquantitative food-frequency questionnaire (FFQ). Modifications for use in pregnancy included changing the time referent, beverage section, and vitamin and supplement assessment. The FFQ was administered twice in pregnancy to assess first and second trimester intakes. The first assessment included a separate interview to assess vitamin and supplement intake as it was not included in the FFQ. The second FFQ included vitamin and supplement assessment. Litonjua et al. (2006) assessed antioxidant intake. Camargo et al. (2007) assessed vitamin D intake. Lange et al. (2010) assessed dietary patterns.
Outcomes	Litonjua et al. (2006) assessed wheeze and eczema outcomes using a parental questionnaire (wheeze) and parental report of doctor diagnosis (eczema) (only wheeze outcomes reported) at 3y of age. Camargo et al. (2007) assessed wheeze and eczema outcomes as described above at 2y of age. Lange et al. (2010) assessed asthma, wheeze and eczema outcomes. Wheeze and eczema were assessed in the same way as Litonjua et al. (2006) asthma was assessed using parental report of doctor diagnosis at 3y of age.
Notes	Funding: Supported by NIH HL61907, HL64925, HD34568, AI35786, HL68041, and HL007427.

Related studies	Litonjua et al. (2006) Camargo et al. (2007)	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Massachusetts women in the community	Litonjua et al. (2006) participant characteristics of included and excluded participants presented in a table but representativeness not discussed. Camargo et al. (2007) report "This sample appears representative of the overall study population. Lange et al. (2010) highlight higher proportion of maternal white race (73% vs 55%), college or graduate education (72% vs 51%) in included vs excluded participants.
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	". . . administered a brief interview and provided a take-home self-administered questionnaire." No specific mention of whether the FFQ was included in the interview but due to excluded participants due to missing diet data presume FFQ was self-administered.
Demonstration that outcome of interest was not present at start of study	yes ★	Developing fetus, outcomes of interest not present at delivery.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal history of asthma/allergy★ study controls for maternal smoking during pregnancy★	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 prepregnancy BMI, breast-feeding duration, and passive smoke exposure.
Outcome		
Assessment of outcome	Self-report	Yearly questionnaires, method not described but presume mailed to parents for completion as earlier questionnaires were given to parents after in-person interviews (during pregnancy and within 72 hours of delivery) to complete and return by mail.
Was follow up long enough for outcomes to occur	yes ★	Litonjua et al. (2006) assessed children aged 2 years for wheeze and eczema. Camargo et al. (2007) assessed children at age 3 years for wheeze and eczema. Lange et al. (2010) assessed children at age 3 years for asthma (difficult to diagnose in preschool children – but doctor diagnosis as assessment of outcome), wheeze and eczema.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias -	Follow up numbers ranged from 56-65% of total recruited cohort in these studies but an adequate description of exclusions and losses to follow up are given.

	small number lost - >80% follow up, OR description provided of those lost★	

Leermakers et al. (2013)

Methods	Cohort study. This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards in Rotterdam.	
Participants	Setting: Netherlands. Dutch mothers were included during pregnancy, before a gestational age of 25 weeks (n=3361) and fully participated in the postnatal phase of the study. Information about fish consumption during pregnancy was available in 2969 (88%) of these mothers. Exclusions: twin pregnancies (n=42) to prevent bias due to correlation. Of the remaining 2927 children, we excluded 131 (4%) children of whom we had no information on wheezing and eczema available, leading to a population for analysis of 2796 mothers and children.	
Interventions	A validated SQFFQ was administered at enrolment.	
Outcomes	Outcomes of interest for this review assessed in this study: wheeze and eczema.	
Notes	The general design of the Generation R Study was made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development. The research leading to these results has received funding from the European Respiratory Society and the European Community's Seventh Framework Program FP7/2007-2013—Marie Curie Actions under grant agreement RESPIRE, PCOFUND-GA-2008-229571 and from the seventh framework program, project CHICOS (HEALTH-F2-2009-241504).	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Dutch women in the community.	Not addressed in study report.
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Quote: "The FFQ was administered at enrolment in the study (median gestational age 13.4 weeks, 95% range 10.1–21.8), as main interest was in the long-term effects of maternal diet during early pregnancy, which might be a critical period for the fetal lung development. The FFQ considered food intake over the prior 3 months, thereby

		covering dietary intake within the first trimester of pregnancy. The FFQ consists of 293 items structured to meal patterns. Questions include consumption frequency, portion size, preparation method and additions."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present at delivery.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal history of asthma or atopy★ study controls for maternal smoking during pregnancy★	All models were adjusted for maternal . . history of asthma or atopy, . . . smoking and alcohol use during pregnancy, . . "
Outcome		
Assessment of outcome	self-report	Quote: "We obtained information on wheezing (no, yes) and doctor-attended eczema (no, yes) in the last year by questionnaires, adapted from the International Study on Asthma and Allergy in Childhood at the ages of 1, 2, 3 and 4 years."
Was follow up long enough for outcomes to occur	yes★	Outcomes assessed at ages generally accepted for diagnoses.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias >80% follow-up, and description provided of those lost★	Quote: ". . with a loss to follow up percentage of <10% during the first 4 years."

Magdelijns et al. (2011)

Methods	Cohort study. KOALA Birth Cohort Study (in Dutch, the Child, Parent and Health: Lifestyle and, Genetic Constitution study).
Participants	Setting: Netherlands From October 2000, healthy pregnant women were recruited in week 10 to 14 of their pregnancy from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain (N = 7020); these individuals comprised the conventional recruitment group (n = 2343). In addition, pregnant women were recruited through posters in organic food shops, anthroposophical physician offices, and midwives at 10 to 14 weeks of pregnancy; these individuals comprised the alternative recruitment group (n = 491). Exclusion criteria were: multiple pregnancies, birth at <37 weeks of gestation, perinatal death, congenital abnormalities related to immunity (Down syndrome), and no response to any of the questionnaires in the first year of life. Ultimately, 2640 children were included in the study.
Interventions	To assess folic acid supplement use during pregnancy, the following question was included in the questionnaire completed in weeks 14 and 34 of pregnancy: "Did you take folic acid, either as a stand-alone

	supplement or as part of a multivitamin supplement, before or during your pregnancy?" Women were also asked when they had started taking supplements: before or after conception and in which trimester (first, second, and/or third).	
Outcomes	Asthma (until 6-7 years), wheeze (until 6-7 years), eczema (until 6-7 years) and atopic dermatitis (until 2 years).	
Notes	This study was financially supported by grants from the Netherlands Asthma Foundation (grants 3.2.07.022 and 3.2.03.48), the Netherlands Organization for Health Research and Development (ZonMw prevention program number 1.210-00-090), Royal Friesland Foods, Triodos Foundation, Phoenix Foundation, Raphaël Foundation, Iona Foundation, Foundation for the Advancement of Heilpedagogie, the Netherlands Brain Foundation, and the Netherlands Ministry of Public Health, Welfare and Sport.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant Dutch women in the community	Quote: "the distribution of population characteristics is fairly similar over the categories of folic acid use."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Quote: "To assess folic acid supplement use during pregnancy, the following question was included in the questionnaire completed in weeks 14 and 34 of pregnancy."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present at delivery.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal atopic disease★ study controls for maternal smoking during pregnancy★	Quote: "All analyses were adjusted for potential confounders: . . maternal antibiotic, smoking and alcohol use during pregnancy, . . . family history of atopy, . . . "
Outcome		
Assessment of outcome	Independent blind assessment★ Self-report	Quote: "A trained nurse examined the child for manifestations of AD during the home visit at the child's age of 2 years using the UK Working Party criteria" Eczema, wheeze and asthma symptoms assessed using ISAAC questions. Quote: "Asthma was defined as ever physician diagnosed asthma with clinical symptoms and/or the use of asthma medication in the last 12 months".

Was follow up long enough for outcomes to occur	yes★	All outcomes assessed at ages where diagnosis is generally accepted although asthma diagnosis in pre-school aged children is difficult.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - > 80% follow up, OR description provided of those lost.★	Quote: "Follow-up rates were high, and study populations' characteristics at 6 to 7 years of age were similar to those at birth, making bias as result of differential follow-up unlikely."

Martinussen et al. (2012)

Methods	Cohort study. Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM). A subset of the Asthma in Pregnancy Study (AIP).	
Participants	Setting: U.S.A Between April 1997 and June 2000, a total of 3413 women were invited from 56 private obstetric practices and 15 community-based clinics in Massachusetts and Connecticut to participate in the prospective Asthma in Pregnancy (AIP) study. Later, from September 2003 through January 2007 a subgroup of these subjects took part in a follow-up study, the Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM). In that study, women with a history of an asthma diagnosis (n = 872) or women who had symptoms or took asthma medications during pregnancy (n = 449) and a simple random sample of pregnant women without asthma or asthma symptoms (n 550) were included. Non–English-speaking participants were excluded, as were 3 infant deaths, which left 1807 subjects eligible for interview.	
Interventions	Information on folic acid, iron, and vitamin use was obtained before 24 weeks of gestation from the following questions in the prenatal exposure questionnaire: "Have you used any of the following vitamin or mineral supplements: prenatal supplement vitamins, multivitamin, vitamin A, vitamin C, vitamin E, iron/ferrous sulphate, folic acid/folate, calcium, or other; specify." If a respondent answered yes, she was specifically asked how often each item had been used (not at all, once a month, 2-3 times a month, twice a week, 3-4 times a week, 5-6 times a week, once a day, or 2 or more times a day). This information was collected for the month before conception through the third month of pregnancy.	
Outcomes	Asthma at six years of age.	
Notes	Funding: This work was supported in part by Grants AI41040 and DA05484 from the National Institutes of Health.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		

Representativeness of the exposed cohort	somewhat representative of the average pregnant American women in the community.	Not clearly discussed. By study design, there was an oversampling of women who had been diagnosed with asthma. Non-English-speaking women were excluded. This may affect representation of the cohort by further reducing the numbers in the lower SES group.
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Information on folic acid, iron, and vitamin use was obtained before 24 weeks of gestation from the prenatal exposure questionnaire.
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present at delivery.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal asthma★ study controls for maternal smoking during pregnancy★?	Quote: "Information on potential confounding variables was obtained from the interviews conducted during early pregnancy and at 6 years (± 3 months) of age. They included maternal parity, ethnicity, marital status, household income, maternal asthma, smoking during pregnancy. . . ."
Outcome		
Assessment of outcome	Interview - parental report.	Quote: "Asthma in the 6-year-old children was assessed by asking the mother the following questions: . . ."
Was follow up long enough for outcomes to occur	yes★	Age of assessment generally considered appropriate for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - > 80% follow up, OR description provided of those lost★	Quote: Of these, 302 mothers were excluded because of refusal, inability to locate, and missed interviews. Thus, 1505 women (83.3% of the 1807 eligible ones) were interviewed when the child was 6 years old (± 3 months) and included in our primary analyses. We excluded 6 individuals for whom information on confounding factors (marital status, family income, and maternal asthma) was missing, leaving 1499 participants in the final analyses."

Maslova 2014

Methods	Cohort study. Maslova et al. 2014 was the last published cohort study in this review from the Danish National Birth Cohort (DNBC). There were 6 publications at different times assessing different associations included in this review (see related studies).
Participants	Setting: Denmark. Pregnant women recruited for the DNBC. Limited to first DNBC pregnancies and singleton births the baseline participant number was 87,090. Each study then included only those women who had completed the dietary information for the specific association studied.

	This study had data for 44,594 mother infant pairs. Both 2012 studies had 61,909 mother infant pairs, Maslova, Strøm, Olsen, 2013 had data for 60,466 mother infant pairs, Maslova, Hansen, et al., 2013 had data for 44,825 mother infant pairs and Maslova, Strøm, Oken, et al., 2013 had data for 28,936 mother infant pairs.	
Interventions/association measures	A 360-item FFQ was administered at around 25 weeks gestation covering the previous four weeks intake. Each of the 6 studies assessed different dietary intakes. Maslova, Halldorsson, et al. (2012) assessed maternal dairy product consumption. Maslova, Granström, et al. (2012) assessed maternal peanut and nut intake. Maslova, Strøm, Olsen, et al. (2013) assessed maternal soft-drink intake. Maslova, Hansen, et al. (2013) assessed maternal Vitamin D intake. Maslova, Strøm, Oken, et al. (2013) assessed maternal fish intake. Maslova (2014) assessed maternal intake of vitamins A, E and K.	
Outcomes	Maslova 2014 reported. 'Asthma at 18 months' was defined from phone interviews as parent-reported doctor diagnosis. 'Current asthma at 7 years' was defined using standardised core questions from the International Study of Asthma and Allergies in Childhood (ISAAC). To increase the specificity of the 'current asthma at 7 years' outcome, we combined the parental-reported doctor diagnosis and wheezing symptoms in the past 12 months. In addition to the questionnaire information, data from two registries on hospital contacts and medication use were used to define asthma diagnoses in the first 7 years of life. Finally, allergic rhinitis cases were defined as a parental report of a doctor diagnosis of hay fever from the 7-year questionnaire.	
Notes	These studies were supported by the Danish Council for Strategic Research (09-067124); the Danish Council for Independent Research/Medical Sciences, Danish Agency for Science, Technology and Innovation (09-063410); the Lundbeck foundation (R13-A907); and the European Union Integrated Research Project EARNEST (FOOD-CT-2005- 007036). The European Union project EARNEST (http:// www.metabolic-programming.org) received financial support from the Commission of the European Communities under the FP 6 priority 5: food quality and safety. The Danish National Birth Cohort was financed by the March of Dimes Birth Defects Foundation, the Danish Heart Association, the Danish Medical Research Council, the Sygekassernes Helsefond, the Danish National Research Foundation, the Danish Pharmaceutical Association, the Ministry of Health, the National Board of Health and Statens Serum Institut.	
Related studies	Maslova, Halldorsson, et al., 2012; Maslova, Granström, et al., 2012; Maslova, Hansen, et al., 2013; Maslova, Strøm, Oken, et al., 2013; Maslova, Strøm, Olsen, et al., 2013.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	Truly representative of the average	Large study with few exclusion criteria.

	pregnant Danish woman in the community★	
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort ★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	Written self-report (parental)	Quote: "A 360-item FFQ was administered at around 25 weeks gestation covering the previous four weeks intake." Each of the 6 studies assessed different dietary intakes".
Demonstration that outcome of interest was not present at start of study	Yes ★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	Study controls for maternal history of asthma/allergy ★ Study controls for maternal smoking during pregnancy ★	Quote: "These covariates included . . . maternal smoking during pregnancy, . . maternal and paternal history of asthma and allergies, . . ."
Outcome		
Assessment of outcome	Record linkage ★ Self-report (parental report)	Quote: "We assessed child asthma status at two different time points using parental reports at 18 months and 7 years and population- based registry data."
Was follow up long enough for outcomes to occur	Yes ★ (at seven years) No (at 18 months)	Asthma is difficult to correctly diagnose before school age leading to some over or under reporting of diagnosis, with many physicians not wanting to formally diagnose asthma before 2-3y of age.
Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias >80% follow up, OR description provided of those lost ★	Quote: "Sample size varied depending on missing data for the individual outcomes (-26 to 36%)." "We also examined the distributions of sociodemographic and lifestyle covariates among participants and non-participants of the present study and found few differences, suggesting that any present selection bias would be limited."

Miyake 2014

Methods	Cohort study. Miyake et al. 2014 was the last published cohort study from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS) with 2 publications at different times assessing different associations included in this review (see related studies).
Participants	Setting: Japan Pregnant women recruited between 5-39 weeks gestation. Participant numbers were 1354 Japanese mother-child pairs.

Interventions/association measures	A 150-item diet history questionnaire administered at baseline from 5-39 weeks gestation assessing the previous four weeks intake. Each study assessed different associations. Miyake 2013 assessed maternal meat and fat intake. Miyake 2014 assessed maternal dairy product calcium and vitamin D intake.	
Outcomes	Wheeze and eczema between 23-29 months of age. Miyake 2014 reported. The questionnaire in the fifth survey included questions on allergic disorders. Symptoms of wheeze and eczema were defined as in the International Study of Asthma and Allergies in Childhood (ISAAC). In addition, physician-diagnosed asthma and atopic eczema were considered present if the child had been diagnosed by a physician as having asthma or atopic eczema, respectively, at any time since birth. (ISAAC questionnaire not validated for this age group).	
Notes	This study was supported by grants-in-aid for scientific research 19590606, 20791654, 21590673, 22592355, 22119507, 24390158, 25463275, and 25670305 from the Japan Society for the Promotion of Science; Health and Labour Sciences Research Grants for Research on Allergic Disease and Immunology and Health Research on Children, Youth, and Families from the Ministry of Health, Labour and Welfare; Meiji Co Ltd; and the Food Science Institute Foundation.	
Related studies	(Miyake et al., 2013)	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	Somewhat representative	Quote: "Our study participants were probably not representative of Japanese women in the general population" . . . "thus, our study participants were more educated and probably more aware of health topics than women in the general population."
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort ★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	Written self-report (parental)	Quote: "In the baseline survey, dietary habits during the preceding month were assessed using a self-administered diet history questionnaire (DHQ)."
Demonstration that outcome of interest was not present at start of study	Yes ★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	Study controls for maternal history of asthma/allergy ★ Study controls for maternal smoking during pregnancy ★	Quote: ". . . maternal and paternal history of asthma, atopic eczema, and allergic rhinitis; maternal smoking during pregnancy; . . . were selected a priori as potential confounding factors."

Outcome		
Assessment of outcome	Self-report (parental report)	Quote: "The questionnaire in the fifth survey included questions on allergic disorders."
Was follow up long enough for outcomes to occur	Yes ★	Age of assessment generally considered appropriate for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - small number lost - > 80% follow up, OR description provided of those lost	This study only included the participants that had full information available (1354). 1757 participants at baseline. Description given of those lost to follow up.

Miyake, Okubo, et al. 2011

Methods	Cohort study. Miyake, Okubo, et al. (2011) was the last published cohort study in this review from the Osaka Maternal and Child Health Study (OMCHS). There were 6 reports at different times assessing different associations included in this review (see Related studies).
Participants	Setting: Japan. Pregnant women recruited between 5-39 weeks gestation. Participant numbers given as 763 mother infant pairs in all but the Saito et al. 2010 study which had 771 mother infant pairs (earlier follow-up period).
Interventions/association measures	A 150-item diet history questionnaire administered at baseline from 5-39 weeks gestation. Each of the studies assessed different intakes except Saito et al. (2010) who assessed infants at 3-4mths for eczema and assessed maternal intake of meat and fats as did Miyake et al. (2009). Miyake et al. (2010a) assessed maternal vegetables fruit and antioxidants intake. Miyake et al. (2010b) assessed maternal dairy food calcium and vitamin D intake. Miyake, Sasaki, et al. (2011) assessed maternal vitamin B intake. Miyake, Okubo, et al. (2011) assessed maternal dietary patterns.
Outcomes	Wheeze and eczema between 16-24 months of age. Miyake, Okubo, et al. (2011) reported. A self-administered questionnaire in the third survey included questions on breastfeeding duration in months and symptoms of wheeze and eczema based on the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire. (ISAAC questionnaire not validated for this age group) Saito 2010 assessed eczema at 3-4 months of age and reported using a self-administered questionnaire in the second survey that inquired about doctor-diagnosed atopic eczema status.
Notes	This study was supported by KAKENHI (13770206, 16790351), Health and Labour Sciences Research Grants, Research on Allergic Disease and Immunology from the Ministry of Health, Labour, and Welfare, Japan, and Japan Dairy Association.

Related studies	(Miyake et al. 2009; Miyake et al. 2010a; Miyake et al. 2010b; Miyake, Sasaki, et al. 2011; Saito et al. 2010).	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	Somewhat representative	Quote: . . .Thus, the mother-child pairs in this study were probably not representative of Japanese mother-child pairs in the general population. In fact, educational levels were higher in the mothers in our study than in the general population." (Saito 2010 study followed up after second survey with the same issues).
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort ★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	Written self-report (parental)	Quote: "In the baseline survey, dietary habits during the preceding month were assessed using a self-administered diet history questionnaire (DHQ)."
Demonstration that outcome of interest was not present at start of study	Yes ★	Developing fetus – outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	Study controls for maternal history of asthma/allergy ★ Study controls for maternal smoking during pregnancy ★	Quote: "Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, allergic rhinitis, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration, and time of delivery before the third survey were a priori selected as potential confounding factors."
Outcome		
Assessment of outcome	Self-report	Quote "A self-administered questionnaire in the third survey included questions on . . . symptoms of wheeze and eczema based on the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire."
Was follow up long enough for outcomes to occur	Yes ★	Age of assessment generally considered appropriate for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - small number lost - >80 % follow up, OR description	Quote: "Of the 1002 pregnant women who participated in the baseline survey, 763 mother-child pairs participated in the third survey. There were no material differences between the 239 non-participants and the 763 participants in the third survey with regard to distribution of

	provided of those lost ★	maternal age, maternal and paternal history of asthma, atopic eczema, allergic rhinitis, maternal intake of total energy, and maternal dietary patterns. Compared with non-participants in the third survey, participants were less likely to report low family income and a low maternal and paternal education level."

Pele et al. (2013)

Methods	Cohort study. Assessment of the Impact of Exposure to Occupational and Environmental Chemicals During Pregnancy on Pregnancy Outcome and Child Development (PELAGIE).	
Participants	Setting: Brittany, France. The PELAGIE mother-child cohort study, enrolled 3421 pregnant women before 19 weeks of gestation in three districts of Brittany (France), from 2002 through 2006. They subsequently gave birth to 3323 liveborn singletons who were eligible for follow-up at two years of age. Around the children's second birthday, 2996 questionnaires were sent to families, excluding those whose child (n = 6) or mother (n = 1) had died in the meantime and the 320 children of the 2002 cohort who were already older than 2.5 years on the date follow-up began.	
Interventions	At inclusion, women were asked to fill out a food frequency questionnaire.	
Outcomes	Wheeze and eczema at 2years of age.	
Notes	The financial support from the National Institute for Public Health Surveillance (InVS), the Ministry of Labor, and the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) is acknowledged. Author contacted regarding FFQ which asked about prenatal exposure to fish and shellfish rather than in pregnancy. Response pointed out this was addressed in the report as follows: "Seafood consumption was evaluated before pregnancy, and women may have modified their habits at the beginning of pregnancy, especially for mollusk intake (because of the infectious risks). However, the biological half-life of both fatty acids and most of the contaminants in seafood is long, and reports of usual diet (i.e., before pregnancy) are likely to represent exposure during pregnancy."	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant French woman in Brittany in the community	Quote: "Shellfish consumption was four times higher in the PELAGIE population than at the national level. Moreover, this study of this highly educated population provided high quality questionnaire data."

Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Quote: "At inclusion, women were asked to fill out a food frequency questionnaire that inquired about their usual consumption, before pregnancy, of 18 specific categories of food, originally selected because of their contribution to intake of polychlorinated dibenzo-dioxins/furans in the French population. Seafood consumption was evaluated through 4 items: saltwater fish (including salmon), mollusks (oysters, mussels, etc.), large crustaceans (crabs, spider crabs, etc.), and small crustaceans (shrimp, etc.). For each of these 4 items, women reported their frequency of consumption on a five-point scale.
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal history of asthma/allergy★. study controls for maternal smoking during pregnancy★	Quote: "To estimate the adjusted effect of seafood consumption, the following known or suspected risk factors were considered for inclusion in the models: . . prenatal exposure to tobacco (0, 1 to 5 cigarettes/day, ≥5 cigarettes/ day), . . . family history of asthma/allergy (yes, no), . . ."
Outcome		
Assessment of outcome	Self-report	Quote: "At the 2-year follow-up, the child's principal caregiver, usually the mother (98%), completed a questionnaire aimed at evaluating the child's health since birth."
Was follow up long enough for outcomes to occur	yes★	Outcomes assessed at an age generally accepted for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - or description provided of those lost) ★	Quote: "Compared with the 1500 participants, non-respondents (n = 1496) were younger at the birth of the PELAGIE child ($p < 0.001$), less educated ($p < 0.001$), and more likely to smoke ($p < 0.001$). Shellfish consumption did not differ between respondents and non-respondents, but the latter were less likely to eat fish ($p = 0.001$)."

Romieu et al. (2007)

Methods	Cohort study.
Participants	Setting: Spain. Briefly, all women presenting for antenatal care in Menorca, Spain, over a 12-month period starting in mid-1997 were recruited (n = 507). Four hundred and eighty-two (95%) children were subsequently enrolled and from those 462 (97%) provided complete outcome data after 6.5 years of follow-up.
Interventions	Interviewer applied FFQ three months after delivery.
Outcomes	Eczema (assessed at 1 year of age), persistent wheeze (assessed at 6 years of age), atopic wheeze (assessed at 6 years).

Notes	Supported by the Instituto de Salud Carlos III red de Grupos Infancia y Media Ambiente (G03/176) and by the Fundacio 'La Caixa' (00/077-00) and the Instituto de Salud Carlos III, red de Centros de Investigacion en Epidemiologia y Salud Publica (C03/09).	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	truly representative of the average pregnant Spanish woman in the community★	95% enrolment into study allowing for a representative cohort.
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	structured interview★	Quote: "Three months after delivery a face to face food frequency questionnaire (FFQ) referred to the pregnancy period was applied by an interviewer."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal atopy and asthma★ study controls for maternal smoking during pregnancy★	Quote: "The following variables were considered as potential confounding factors: . . maternal and paternal atopy, maternal and paternal asthma, . maternal smoking during pregnancy, . . . "
Outcome		
Assessment of outcome	Self-report	Quote: "During the follow-up, parents answered a questionnaire on a yearly basis (with interviewer) and report all medical events over the preceding 12 months. One or more episodes of wheezing over 12 months constituted wheezing during a given year."
Was follow up long enough for outcomes to occur	yes★	Age outcomes were assessed are considered appropriate for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias >80% follow up and description provided of those lost★	Quote: ". . .462 (97%) provided complete outcome data after 6.5 years of follow-up."

Sausenthaler et al. (2007)

Methods	Cohort study. Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood (LISA) cohort.
Participants	Setting: Germany.

	3097 enrolled at birth. Follow up occurred at six-month intervals until 2 years of age. This study selected subjects who had participated in the follow-up at 2 y, excluding children with chronic diseases (eg, celiac disease and metabolic disorders; *n* = 9) and children for whom no information on their mothers' diet during the last 4 wk of pregnancy was available (*n*=14). Thus, the final study population consisted of 2641 children.	
Interventions	Semiquantitative FFQ administered shortly after birth assessing intake over previous four weeks.	
Outcomes	Doctor-diagnosed eczema at 2y of age.	
Notes	Supported by grants 01 EG 9732 and 01 EG 9705/2 from the Federal Ministry for Education, Science, Research, and Technology.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant German woman in the community.	Quote: "Subjects were excluded when their mothers had completed the FFQ on maternal diet during pregnancy but did not return the 2-y questionnaire (n = 427). Compared with those, children of respondent mothers more likely lived in Munich (50.0% compared with 31.9%; P < 0.001) and were born to older mothers (31.3 y compared with 28.9 y; P<0.001). They were less likely to have a smoking mother during pregnancy (10.1% compared with 24.2%; P < 0.001) and ≥2 older siblings (9.8% compared with 13.4%; P = 0.033), but were more likely to have parents with a very high level of education (54.6% compared with 31.8%; P < 0.001), at least one parent with atopic disease (52.7% compared with 43.0%; P < 0.001), and to have been breastfed for ≥4 mo (57.6% compared with 43.5%; P < 0.001)."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Quote: "We assessed maternal food intake during the last 4 wk of pregnancy by using a semiquantitative food-frequency questionnaire (FFQ) administered shortly after childbirth. For each food item, the mothers reported their average consumption frequency over the past 4 wk according to 5 categories ranging from "<2 times/mo or never" to "≥4 times/wk."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal history of atopic diseases★	Quote: "Then, we calculated an adjusted model that included . . maternal smoking during second or third trimester of pregnancy. . . parental history of atopic diseases (asthma, hay

	study controls for maternal smoking in pregnancy★	fever, or eczema; no parents atopic, one parent atopic, and both parents atopic) . . “
Outcome		
Assessment of outcome	Self-report	Quote: “Doctor-diagnosed eczema was based on a positive answer to the question, “Has a doctor diagnosed your child with allergic or atopic eczema in the past 6 mo?” Lifetime prevalence of doctor-diagnosed eczema was assumed if eczema has ever been diagnosed during the first 2 y of life.”
Was follow up long enough for outcomes to occur	yes★	Outcome assessed in this study at an age generally accepted as appropriate for diagnosis.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - >80% follow up, or description provided of those lost ★	Minimal loss to follow-up (<10%) due to the inclusion criteria for this study.

Shaheen et al. (2009)

Methods	Cohort study. Avon Longitudinal Study of Parents and Children (ALSPAC)	
Participants	Setting: UK ALSPAC is a population-based birth cohort established in the former county of Avon, UK by recruitment of 14 541 pregnant women who were resident in Avon and had expected dates of delivery between 1 April 1991 and 31 December 1992. There were 14,062 live-born children.	
Interventions	At 32 weeks of pregnancy, mothers completed a food-frequency questionnaire (FFQ) which comprised 110 questions. Mothers were asked about their current weekly frequency of consumption of 43 food groups and food items, and about daily consumption of a further eight basic foods. Five dietary patterns in pregnancy have been previously identified in this cohort using PCA (principal components analysis): ‘‘health conscious’’, ‘‘traditional’’, ‘‘processed’’, ‘‘vegetarian’’ and ‘‘confectionery’’. Dietary pattern scores were expressed in standard deviation units. Each mother was represented in each of these five mutually independent scores.	
Outcomes	Pertaining to this review: eczema (at 2.5 years of age), wheezing (at 3.5 and 7.5 years of age), hayfever (at 7.5 years of age), doctor-diagnosed asthma (at 7.5 years of age).	
Notes	The UK Medical Research Council, the Wellcome Trust and the University of Bristol provide core support for ALSPAC.	
Risk of bias		
Bias	**Author’s Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the	Quote: “As expected, attrition of the cohort during follow-up, as with other birth cohorts, was

	average UK based pregnant woman in the community	greatest among families of lower socioeconomic status." "Without outcome data for these individuals we cannot determine whether the associations measured in those with complete data are representative of those in the entire cohort."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	At 32 weeks of pregnancy, mothers completed a food-frequency questionnaire (FFQ) which comprised 110 questions.
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal atopy★ study controls for maternal smoking★	Quote: 'The confounders were: maternal factors during pregnancy . . . maximum smoked, . . history of asthma, eczema, rhinoconjunctivitis, . . ."
Outcome		
Assessment of outcome	Self-report	Parental questionnaire asking about symptoms and doctor diagnosis.
Was follow up long enough for outcomes to occur	yes★	Outcomes assessed at ages where diagnosis is generally accepted.
Adequacy of follow up of cohorts	follow up rate <80% and no description of those lost	Actual numbers of those assessed difficult to locate in this study. Supplementary material assists in interpreting participant numbers included for each outcome assessed. Study mentions losses to follow-up but does not adequately describe.

von Ehrenstein et al. (2015)

Methods	Cohort study. The UCLA Environment and Pregnancy Outcomes Study (originally designed to assess effects of air pollution on birth outcomes oversampling for preterm and low-birthweight births).	
Participants	Setting: USA. 6374 women of the original cohort were selected for this study (selected from birth records) and contact was made with 2543 women. 2438 women agreed to be contacted in the future.	
Interventions	Maternal questionnaire administered after birth and assessed dietary factors during pregnancy.	
Outcomes	Asthma, (current, severe and doctor's diagnosed asthma) and hay fever at 3.5 years of age.	
Notes	This work was supported by the National Institute of Environmental Health Sciences [NIEHS R01 ES010960-01] and the Southern California Environmental Health Sciences Center [NIEHS 5 P30 ES07048].	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		

Representativeness of the exposed cohort	somewhat representative of the average pregnant American women in the community	Quote: "Further, we had a relatively high rate of attrition between the first and second assessment; among responding women, more were highly educated, older, white non-Hispanic, and US-born."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	written self-report	Quote: "Dietary factors during pregnancy included the frequency of consumption of fast food on average (never, once a month, once a week, 3–4/week, daily), fish consumption (salmon, tuna, mackerel), and consumption of well-done meat or fish, and use of vitamins."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal history of asthma, hay fever eczema ★ study did not control for maternal smoking in pregnancy.	Quote: "The final models were adjusted for . . maternal/paternal history of atopy . . . Following variables were not retained in the final models because they did not further change the estimates of interest >10%: . . maternal smoking or alcohol consumption . . ."
Outcome		
Assessment of outcome	self-report ISAAC questionnaire not validated for this age group.	Follow-up survey. Quote: "Asthma and hay fever symptoms were assessed using the corresponding ISAAC core questions. We also recorded doctor's diagnosed asthma, pneumonia, and asked whether the child had bronchitis and has taken asthma medication in the past 12 months."
Was follow up long enough for outcomes to occur	yes★	Yes. Some difficulty noted in diagnosing asthma in pre-schoolers.
Adequacy of follow up of cohorts	follow up rate <80% and no description of those lost	Quote: "Of the 2438 women who agreed being recontacted, 1,201 could be located and participated in the follow-up survey (response 49.3%) in 2006–2007; a major reason for the attrition was the difficulty locating women after 3 years in Los Angeles, an area with high mobility."

Watson and MacDonald (2014)

Methods	Cohort study.
Participants	Setting: New Zealand 504 women were recruited around the 14th week of pregnancy.
Interventions	Dietary intake was assessed by two methods in both month 4 and month 7. The interviewer administered a 24- hour dietary recall, followed by a 3-day food record kept by the subject.
Outcomes	Wheeze at 18 months
Notes	New Zealand Ministry of Health and Health Research Council funding.

Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	somewhat representative of the average pregnant New Zealand women in the community	The funding body required 500 subjects with selection biased towards including a greater proportion of Polynesian women, and women of lower socioeconomic status, than in the general population.
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	structured interview★ written self-report	Quote: "The interviewer administered a 24- hour dietary recall, followed by a 3-day food record kept by the subject."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal allergy/atopy ★ study did not control for maternal smoking during pregnancy	Quote: "Variables considered as possible covariates included . . medical details including incidence of maternal or paternal asthma, eczema, rhinitis or allergy, . . " No mention of maternal smoking.
Outcome		
Assessment of outcome	self-report with interviewer ISAAC questionnaire not validated for this age.	Quote: "The same interviewer visited subjects at mean 18.1 months postpartum (SD=3.8), took anthropometric measurements of mother and child, and completed a questionnaire to determine details of infant feeding from birth, developmental milestones and symptoms of wheeze. Based on the ISAAC phase 1 questionnaire, . . ."
Was follow up long enough for outcomes to occur	yes★	Outcomes assessed at an age generally considered appropriate for diagnosis.
Adequacy of follow up of cohorts	follow up rate <80% and no description of those lost	Quote: "The present work is based on data from the 369 subjects who completed these questions."

Whitrow et al. (2009)

Methods	Cohort study. Generation 1 Cohort Study.
Participants	Setting: Australia. 605 women recruited, 557 (92%) completed the pregnancy phase of the study and had a live singleton baby. Women were recruited in the first 16 weeks of pregnancy in 1998–2000.
Interventions	Interview using a structured food frequency questionnaire and inventory of supplement use.

Outcomes	Asthma at 3.5 years of age, asthma at 5.5 years of age and 'persistent asthma' (asthma at both 3.5 and 5.5 years of age).	
Notes	No funding reported.	
Risk of bias		
Bias	**Author's Judgement**	**Support for judgement**
Selection		
Representativeness of the exposed cohort	truly representative of the average pregnant white Australian woman in the community★	Quote: "Participating women were similar to all women having children in South Australia in 1998–2000 for a range of social indicators."
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort★	Prospective single cohort study with those who didn't develop allergy used as internal control.
Ascertainment of exposure	structured interview★	Quote: "Mothers were interviewed by a research nurse in early (<16 weeks) and late (30–34 weeks) pregnancy on their personal circumstances and health, including diet, using a structured food frequency questionnaire and inventory of supplement use."
Demonstration that outcome of interest was not present at start of study	yes★	Developing fetus, outcomes of interest not present.
Comparability		
Comparability of cohorts on the basis of the design or analysis	study controls for maternal asthma ★ study controls for maternal smoking★	Quote: "The potential confounders considered were . . . maternal smoking. . . and maternal asthma . . ."
Outcome		
Assessment of outcome	structured interview★ written self-report	Quote: "Mothers and children had follow-up interviews with a structured protocol during the child's infancy (6, 9, 12 months), at 2 years, and at 3.5 years and by maternal-completed postal questionnaire at 5.5 years.
Was follow up long enough for outcomes to occur	yes★	Outcomes assessed at an age generally considered appropriate for diagnosis although there are known difficulties with diagnosing asthma in pre-school age children.
Adequacy of follow up of cohorts	subjects lost to follow up unlikely to introduce bias - >80% follow up, or description provided of those lost) ★	Quote: "Our study has the limitation that 76% of the original sample provided complete information at the 5.5-year assessment, . . ." Quote: "Mothers of children not participating at 3.5 years were younger and less likely to have breastfed for ≥3 months than those who completed the pregnancy phase of the study ($P < 0.05$). Mothers of children not participating at 5.5 years were younger, less likely to take a prepregnancy folic acid supplement, less educated, more likely to smoke during early and late pregnancy, and more likely to report a history of asthma than those who completed the pregnancy phase of the study ($P < 0.05$)."

Effects of interventions

Nine RCT studies (Table 3) assessed the effect of fish intake and/or fish oil supplementation and the outcomes of interest (Best et al., 2016; Escamilla-Nunez et al., 2014; Furuhjelm et al., 2009; Furuhjelm et al., 2011; Manley et al., 2011; Noakes et al., 2012; Palmer et al., 2012; Palmer et al. 2013; & Warstedt et al., 2016). Three assessed asthma (Best et al., 2016; Furuhjelm et al., 2011; & Manley et al., 2011), three wheeze (Best et al., 2016; Escamilla-Nunez et al., 2014; & Noakes et al., 2012), six eczema (Best et al., 2016; Escamilla-Nunez et al., 2014; Furuhjelm et al., 2011; Manley et al., 2011; Noakes et al., 2012; & Warstedt et al., 2016) and two allergic rhinitis (Best et al., 2016; & Manley et al., 2011). There were no significant findings shown for asthma, (RR range 0.95-1.05) wheeze (RR range 0.83-1.85) and eczema (RR range 0.41-1.29) outcomes. There were associations shown for intake of fish or fish oils and allergic rhinitis with increased intake decreasing the incidence of allergic rhinitis (RR range 0.41-0.77), but the optimal information size threshold was not reached for this outcome.

Three RCT studies (Table 4) assessed Vitamin D intake on the outcomes of interest (Chawes et al., 2016; Goldring et al., 2013; & Litonjua et al., 2016). Two assessed asthma (Chawes et al., 2016; & Litonjua et al., 2016), three wheeze (Chawes et al., 2016; Goldring et al., 2013; & Litonjua et al., 2016), three eczema (Chawes et al., 2016; Goldring et al., 2013; & Litonjua et al., 2016), and one allergic rhinitis (Goldring et al., 2013). There were no associations found for any of the included outcomes. Asthma, Chawes et al. (2016) adjusted OR 0.82 (95% CI 0.50-1.36) and Litonjua et al. (2016) adjusted HR 0.80 (95% CI 0.6-1.0), wheeze, Goldring et al. (2013) OR 1.14 (95% CI 0.42-3.13) Chawes et al. (2016) and Litonjua et al. (2016) presented as adjusted hazards ratios range 0.75-0.80, eczema, Goldring et al. (2013) OR 0.72 (95% CI 0.32-1.61). Chawes et al. (2016 and Litonjua et al. (2016) both present as adjusted hazards ratio of 0.90, allergic rhinitis, Goldring et al. (2016) adjusted OR 0.69 (95% CI 0.22-2.13).

One RCT study (Table 5) assessed vitamins C and E intake and asthma adjusted OR 0.94 (0.42-2.11), wheeze adjusted OR 0.81 (0.32-2.06) and eczema adjusted OR 1.10 (0.70-1.74) (Greenough et al., 2010).

Three RCT studies (Table 6) assessed probiotic intake and the outcomes of interest (Dotterud et al., 2010; Rautava et al., 2012; & Simpson et al., 2015). One assessed asthma (Simpson et al., 2015), adjusted OR 3.25 (0.33-31.60), one wheeze (Simpson et al., 2015), adjusted OR 0.85 (0.52-1.38) two eczema (Rautava et a., 2012; & Simpson et al., 2015), adjusted OR range 0.16-0.48, and one allergic rhinitis (Simpson et al., 2015), adjusted OR 1.22 (0.64-2.37). The two studies that assessed eczema showed increased intake of probiotics decreased the incidence of eczema, but the optimal information size threshold was not reached.

There were 10 cohort studies (Table 7) assessing fish intake and the outcomes of interest (Leermakers et al., 2013; Maslova et al., 2013; Miyake et al., 2009; Miyake et al., 2013; Pele et al., 2013; Romieu et al., 2007; Saito et al., 2010; Sausenthaler et al., 2007; Willers et al., 2007; & Willers et al., 2008). Two assessed asthma (Maslova et al., 2013; & Willers et al., 2008), eight wheeze (Leermakers et al., 2013; Maslova et al., 2013; Miyake et al., 2009; Miyake et al., 2013; Pele et al., 2013; Romieu et al., 2007; Willers et al., 2007; & Willers et al., 2008), seven eczema (Leermakers et al., 2013; Miyake et al., 2009; Miyake et al., 2013; Pele et al., 2013; Romieu et al., 2007; Sausenthaler et al., 2007; & Willers et al., 2007) and two allergic rhinitis (Maslova et al., 2013; & Willers et al., 2007). One of the two studies assessing asthma (Maslova et al., 2013) showed increased fish intake decreased asthma outcomes, this study used high frequency intake as reference and showed adjusted zero intake as OR 1.30 (1.05-1.63) adjusted *p* value for trend 0.001. Wheeze outcomes were shown to be reduced in one study, (Romieu et al., 2007) this study assessed atopic wheeze and persistent wheeze; atopic wheeze outcomes were reduced when fish intake was high, adjusted OR 0.55 (0.31-0.96) adjusted *p* value 0.034. Two of the eight studies assessing eczema showed that increased fish intake decreased eczema incidence. Romieu et al. (2007) adjusted OR 0.73 (0.55-0.98). Willers et al. (2007) assessed Doctor confirmed eczema adjusted OR 0.57 (0.35-0.92) adjusted *p* value 0.008 and ever eczema adjusted OR 0.68 (0.43-1.10) adjusted *p* value for trend 0.050. Willers

et al. (2007) also found an association between increased fish intake and decreased Doctor confirmed hayfever adjusted OR 0.28 (0.06-1.19) adjusted *p* value for trend 0.043.

Four cohort studies (Table 8) assessed vegetable intake and the outcomes of interest (Fitzsimon et al., 2007; Miyake et al., 2010; Sausenthaler et al., 2007; & Willers et al., 2008). Two assessed asthma (Fitzsimon et al., 2007; & Willers et al., 2008), two wheeze (Miyake et al., 2010; Willers et al., 2008), and two eczema (Miyake et al., 2010; & Sausenthaler et al., 2007). One study assessed fruit and vegetables together (Fitzsimon et al., 2007) and showed that increased fruit and vegetable intake decreased the incidence of asthma dependent on the confounders adjusted for and showed a range of adjusted *p* values for trend 0.04-0.09. Eczema incidence was shown to decrease with increased green and yellow vegetable intake in one study (Miyake et al., 2010) adjusted OR 0.53 (0.30-0.93), adjusted *p* value for trend 0.03.

Five cohort studies (Table 9) assessed fruit intake and the outcomes of interest (Fitzsimon et al., 2007; Miyake et al., 2010; Sausenthaler et al., 2007; Willers et al., 2007; & Willers et al., 2008). Three assessed asthma (Fitzsimon et al., 2007; Willers et al., 2007; & Willers et al., 2008), three wheeze (Miyake et al., 2010; Willers et al., 2007; & Willers et al., 2008), and two eczema (Miyake et a., 2010 & Sausenthaler et al., 2007). Two studies showed an effect of increased fruit intake on asthma outcomes one being the study described above that assessed fruit and vegetables together (Fitzsimon et al., 2007). Willers et al. (2007) assessed apple intake and found a decreased incidence of doctor-diagnosed asthma with increased apple intake adjusted OR 0.47 (0.27-0.82), adjusted *p* value for trend 0.008 and ever asthma adjusted OR 0.54 (0.32-0.92) adjusted *p* value for trend 0.026. This study also found an association between increased apple intake and decreased ever wheeze adjusted OR0.63 (0.42-0.95), adjusted *p* value for trend 0.029. The Miyake et al. (2010a) study did not show the same association with apple intake and wheeze outcomes adjusted OR 1.16 (CI) 0.69-1.95) adjusted *p* value for trend 0.51. Willers measured apple intake in tertiles with the highest tertile being intake frequency of ≥4/wk while Miyake et al measured quartiles of intake as grams per day adjusted energy intake with the highest measurement being 45g/day. Willers assessed outcomes at five years of age and Miyake assessed at 16-24 months. Miyake et al. (2010a) did show

that increased citrus fruit intake decreased the incidence of eczema adjusted OR 0.53 (0.30-0.93) adjusted *p* value for trend 0.03.

Four cohort studies (Table 10) assessed dairy intake and the outcomes of interest (Maslova et al., 2012; Miyake et al., 2010; Miyake et al., 2014; & Sausenthaler et al., 2007). Two assessed asthma (Maslova et al., 2012; & Miyake et al., 2014), two wheeze (Miyake et al., 2010; & Miyake et al., 2014), three eczema (Miyake et al., 2010; Miyake et al., 2014; & Sausenthaler et al., 2007) and one allergic rhinitis (Maslova et al., 2012). Both studies assessing asthma outcomes found that the incidence of asthma decreased with increased intake of specific dairy products; cheese in one study (Miyake et al., 2014) adjusted OR 0.44 (0.18-0.97) adjusted *p* value for trend 0.052. Maslova et al. (2012) showed an association between asthma outcomes at 18 months and maternal intake of whole milk, adjusted OR 0.85 (0.75-0.97) adjusted *p* value for trend 0.03, semi-skimmed milk, adjusted OR 1.08 (1.02-1.15) adjusted *p* value for trend 0.02 and full fat yoghurt adjusted OR 0.81 (0.56-1.16) adjusted *p* value for trend 0.002. Miyake et al. (2010) showed a decrease in wheeze incidence with increased intake of total dairy adjusted OR 0.45 (0.25-0.79) adjusted *p* value for trend 0.007, milk adjusted OR 0.50 (0.28-0.87) adjusted *p* value for trend 0.02, and cheese adjusted OR 0.51 (0.31-0.85) adjusted *p* value for trend 0.02. Miyake et al. (2014) showed potential for total dairy product intake to decrease eczema outcomes (adjusted OR 0.64 (0.42-0.98) adjusted *p* value for trend 0.054. Maslova et al. (2012) described that increased low-fat yoghurt intake increased the incidence of allergic rhinitis in the narrative but no results tables were shown results for the same are presented as OR 1.40 (1.00-1.97).

Three cohort studies (Table 11) assessed nut intake and the outcomes of interest (Maslova et al., 2012; Sausenthaler et al., 2007; & Willers et al., 2008). Two assessed asthma (Maslova et al., 2012; & Willers at al., 2008), two wheeze (Maslova et al., 2012; & Willers at al., 2008), one eczema (Sausenthaler et al., 2007) and one allergic rhinitis (Maslova et al., 2012). Both studies assessing asthma outcomes measured different nut types. Maslova et al. (2012) found that increased maternal peanut/pistachio (adjusted OR 0.79 (0.65-0.97) adjusted *p* value for trend 0.02) and tree nut (adjusted OR 0.75 (0.67-0.84) adjusted *p* value for trend <0.0001) intake decreased the incidence of asthma at 18 months, but by 7 years of age only increased peanut/pistachio intake decreased asthma

risks adjusted OR 0.66 (0.44-0.98) adjusted *p* value for trend 0.002. Willers et al. (2008) included nut products (predominantly peanut butter) and found increased intake increased the incidence of asthma symptoms adjusted OR 1.47 (1.08-1.99) and wheeze adjusted OR 1.42 (1.06-1.89).

Five cohort studies (Table 12) assessed fat intake and the outcomes of interest (Fitzsimon et al., 2007; Miyake et al., 2009; Miyake et al., 2013; Saito et al., 2010; & Sausenthaler et al., 2007). One assessed asthma (Fitzsimon et al., 2007), two wheeze (Miyake et al., 2009; Miyake et al., 2013), and four eczema (Miyake et al., 2009; Miyake et al., 2013; Saito et al., 2010; & Sausenthaler et al., 2007). Fitzsimon et al. (2007) showed increased added fat intake increased the incidence of asthma. This study has multiple adjustment results given, adjusted *p* value for trend range 0.002-0.003. Miyake et al. (2013) showed that increased eicosapentaenoic acid and eicosapentaenoic assessed together with docosahexaenoic acid decreased the incidence of wheeze adjusted *p* value for trend range for both results 0.02. Increased intake of n-6 polyunsaturated fatty acids and linoleic acid were shown to increase incidence of eczema in Miyake et al. (2009) *p* value for trend range for both results 0.01-0.03, while increased margarine and vegetable oil intakes were shown to increase eczema outcomes in Sausenthaler et al. (2007) adjusted *p* value for trend range for both results 0.017-0.022.

Four cohort studies (Table 13) assessed dietary patterns and the outcomes of interest (Chatzi et al., 2013; Lange et al., 2010; Miyake et al., 2011; Shaheen et al., 2009). Two assessed asthma (Lange et al., 2010; & Shaheen et al., 2009), and all four assessed wheeze and eczema. Miyake et al. (2011) found the 'Western' diet pattern decreased the incidence of wheeze in infants aged 16-24 months adjusted OR 0.59 (0.35-0.98), adjusted *p* value for trend 0.02.

Three cohort studies (Table 14) assessed β-Carotene intake and the outcomes of interest (Litonjua et al., 2006; Miyake et al., 2010; Watson et al., 2014). All three studies assessed wheeze and one eczema (Miyake et al., 2010). Miyake et al. (2010) showed increased intake of β-Carotene was shown to decrease the incidence of eczema adjusted OR 0.52 (0.30-0.89) adjusted *p* value for trend 0.04.

Nine cohort studies (Table 15) assessed folic acid intake and the outcomes of interest (Bekkers et al., 2012; Dunstan et al., 2012 Håberg et al., 2009; Litonjua et al., 2006; Magdelijns et al., 2011; Martinussen, Risnes, Jacobsen & Bracken, 2012; Miyake et al., 2011; Watson, 2014; & Whitrow et al., 2009). Four assessed asthma (Bekkers et al., 2012; Magdelijns et al., 2011; Martinussen et al., 2012, Whitrow et al., 2009), seven wheeze (Bekkers et al., 2012; Dunstan et al., 2012; Håberg et al., 2009; Litonjua et al., 2006; Magdelijns et al., Miyake et al., 2011; Watson, 2014) and four eczema (Bekkers et al., 2012; Dunstan et al.,.2012; Magdelijns et al., 2011; & Miyake et al., 2011) Whitrow et al. (2009) one study found that asthma outcomes were increased in children at 3.5 years of age when mothers had taken increased amounts of folic acid in late pregnancy adjusted, RR 1.26 (1.09-1.47). Wheeze was associated with increased folic acid intake in early pregnancy in Håberg et al. (2009) adjusted risk ratio 1.06 (1.03-1.10). Dunstan et al. (2012) showed that increased intake of folic acid increased the incidence of eczema at one year of age adjusted OR 1.7 (1.0-2.8) *p* value = 0.024.

Four cohort studies (Table 16) assessed Vitamin C intake and the outcomes of interest (Litonjua et al., 2006; Martindale et al., 2005; Miyake et al., 2010; & Watson et al., 2014). All four studies assessed wheeze and three assessed eczema. Martindale et al. (2005) showed that increased intake of vitamin C increased the incidence of wheeze, adjusted OR 2.25 (1.26-4.02) *p* value for trend 0.034. The same study showed increase incidence of eczema when adjusted for vitamin E intake adjusted OR 1.56 (0.99-2.45) *p* value for trend 0.048.

Seven cohort studies (Table 17) assessed vitamin D intake and the outcomes of interest (Allan et al., 2015; Camargo et al., 2007; Devereux et al., 2007; Maslova et al., 2013; Miyake et al., 2010; Miyake et al., 2014; & Watson et al., 2014). Three assessed asthma (Allan et al., 2015; Maslova et al., 2013; & Miyake et al., 2014) five wheeze (Allan et al., 2015; Camargo et al., 2007; Miyake et al., 2010; Miyake et al., 2014; & Watson et al., 2014), three eczema (Camargo et al., 2007; Miyake et al., 2010; & Miyake et al., 2014) and one allergic rhinitis (Maslova et al., 2013). Maslova et al. (2013) showed that low maternal vitamin D intake increased the risk of hospital admissions for asthma after several adjustments were made, adjusted RR 0.99 (0.97-1.00), adjusted *p* value for trend 0.02. Allan et al. (2015) showed that low vitamin D intake increased the incidence of

Doctor confirmed asthma adjusted OR 0.71 (0.45-1.11), *p* value for trend 0.046. Allan et al. (2015) and Camargo et al. (2007) found that increased vitamin D intake decreased the incidence of wheeze, adjusted *p* value for trend range <0.001-0.002.

Seven cohort studies (Table 18) assessed vitamin E intake and the outcomes of interest (Allan et al., 2015; Devereux et al., 2006; Litonjua et al., 2006; Martindale et al., 2005; Maslova et al., 2014; Miyake et al., 2010; & Watson et al., 2014). Three assessed asthma (Allan et al., 2015; Devereux et al., 2006; Maslova et al., 2014), six studies assessed wheeze (Allan et al., 2015; Devereux et al., 2006; Litonjua et al., 2006; Martindale et al., 2005; Miyake et al., 2010; & Watson et al., 2014)., two eczema (Litonjua et al., 2006; Miyake et al., 2010), and one allergic rhinitis (Maslova et al. 2014). Allan et al. (2015) and Devereux et al. (2006) showed increased vitamin E intake decreased the incidence of asthma *p* value for trend range 0.002-0.04. Allan et al. (2015) and Litonjua et al. (2006) found that increased vitamin E intake reduced the incidence of wheeze adjusted *p* value for trend range 0.01-0.05. Vitamin E intake was not shown to affect incidence of eczema or allergic rhinitis.

Four cohort studies (Table 19) assessed zinc intake and the outcomes of interest (Devereux et al., 2006; Litonjua et al., 2006; Miyake et al., 2010; & Watson et al., 2014). One assessed asthma (Devereux et al., 2006), three wheeze (Litonjua et al., 2006; Miyake et al., 2010; & Watson et al., 2014), and two eczema (Devereux et al., 2006, & Miyake et al., 2010). Intake of zinc varied widely within the studies included in this review. Litonjua et al. describe a lowest intake of 6.8mg/day and highest intake of 92.0mg/day, whereas Devereux et al. (2006) describe a lowest quintile range of 4.44-10.19mg/day and a highest of 14.25-30.30. Miyake et al (2010) state that they present as µg/day and median quartile measurements range from 6.1-39µg/day.

Increased zinc intake (Table 19) was shown to decrease ever asthma incidence adjusted OR 0.51 (0.27-0.97), adjusted *p* value for trend 0.04 (Devereux et al., 2006). Devereux et al. (2006) also showed increased intake of zinc decreased the incidence of ever eczema, Doctor-confirmed eczema and current treatment for eczema adjusted *p* value for trend range 0.03-0.05.

The following study results are not presented in SOF tables as there were less than three studies assessing an association. They are included and described in this narrative only. Maslova et al., (2014) assessed maternal intake of vitamin K within the DNBC. Asthma outcomes were assessed using the ISAAC questionnaire and registry data. Results are reported at 18 months and seven years of age. Increased Vitamin K was shown to decrease ever admitted asthma outcomes. Another study reported by Maslova et al., (2013) from the same cohort assessed soft drink intake and asthma and allergic rhinitis outcomes. Artificially-sweetened carbonated and non-carbonated soft drinks were associated with increased ever asthma at seven years old based on registry outcomes. Miyake et al., (2011) assessed B vitamin intake in pregnancy. Wheeze and eczema outcomes were assessed using ISAAC questionnaire questions and there were no associations shown. von Ehrenstein et al., (2015) assessed fast food consumption and asthma and allergic rhinitis outcomes were assessed using the ISAAC questionnaire questions at 3.5 years of age. This study had the highest levels of attrition and the highest risk of bias. They found that increased fast food intake increased the risk of asthma (current, severe and doctor-diagnosed) adjusted *p* value for trend range for the three asthma outcomes 0.0025-0.0236, and hayfever adjusted *p* value for trend 0.0491. Watson et al., (2014) assessed tap water intake, macronutrients and micronutrients. Wheeze was assessed using ISAAC questionnaire questions. Higher water and manganese intake were associated with lower prevalence of wheeze. Presentation of results in this study caused difficulty is interpreting results but the study authors also conclude that higher intake of whole grains and whole grain products and fruit and beverage tea and lower intake of fruit juice, soft drink, cordial, meat, fish, egg and refined grain products may reduce the prevalence of wheeze.

Summary of findings tables

An explanation for the terms included in the SOF tables is presented in Table 2 below. The results are not pooled as discussed in the methods chapter but rather a range is given. The RCT studies are presented according to the recommendations in the GRADE handbook. Presentation of cohort studies in a narrative is not well defined in the handbook and the ranges given for these tables are preferentially the adjusted *p* value for trend, if given, as this allows for a better interpretation of the results due to multiple results given

for the different measurements (i.e. tertiles and quartiles) and their associations with the outcomes.

Table 2 Explanations for SOF table terms

SOF table terms	Meanings/Description	Quality up/down
Study design	In GRADE SOF tables RCT studies start with a high-quality rating while observational studies start with a low-quality rating	
Risk of bias	Determined by previous assessment of ROB and only changes if most of the studies in the table have a high risk of bias.	Down
Inconsistency	Unexplained heterogeneity of results across all the studies for that question and outcome. For example, results with 95% confidence intervals that do not overlap or have similar findings.	Down
Indirectness	Do the studies address the question the SOF table is assessing? Uses PICO to assess differences between the studies and whether the question is addressed	Down
Imprecision	Assesses whether the studies meet optimal information size which describes how the smaller number of events and relative risk reduction the less confidence is felt in the findings. This also addresses the crossing over of the 95% confidence intervals from no effect to showing both potential appreciable benefit and harm.	Down
Other considerations	**Publication Bias**: describes the lack of enthusiasm for presenting negative findings by both study authors and publishing journals. **Large magnitude of an effect:** Describes a significant effect that is rapid, consistent, reverses the previous trajectory of disease or outcome and is supported by indirect evidence. **Dose-response gradient:** studies assess the effect of increased or decreased intake allowing the researcher greater confidence in interpreting findings. **Plausible residual confounding:** describes the effect of biases or confounders on the outcomes that would result in an underestimation of the effect and haven't been adjusted for by the study authors.	Down Up Up
Quality	The quality rating generated by the GRADE database after assessing the study design, risk of bias, inconsistency, indirectness, imprecision and other considerations for each outcome.	
Importance	A numeric scale of one to nine where one is the least important and nine the most important/critical. Hierarchy is determined by the SOF table developer according to research and/or patient perspectives. For this work hospital admissions and effect on quality of life were considered.	

Table 3 Increased fish oil supplementation or fish intake compared to no/low fish oil supplementation or fish intake for pregnant women during pregnancy and/or lactation

Bibliography: Best et al. (2016); Escamilla-Nunez et al. (2014); Furuhjelm et al. (2009); Furuhjelm et al. (2011); Manley et al. (2011); Noakes et al. (2012); Palmer et al. (2012); Palmer et al. (2013); Warstedt et al. (2016)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**increased fish oil supplementation or fish intake**	**no/low fish oil supplementation or fish intake**	**Relative (95% CI)**	**Absolute (95% CI)**		
Asthma (follow up: range 1 years to 3 years)												
3 [a, b, c]	randomised trials	not serious	not serious	not serious	serious [d]	none	133/658 (20.2%)	134/653 (20.5%)	**RR ranged from** 0.95 to 1.05	not estimable	⊕⊕⊕◯ MODERATE	CRITICAL
Wheeze (follow up: range 6 months to 6 years)												
3 [e, f]	randomised trials	not serious	not serious	not serious	serious [d]	none	71/413 (17.2%)	52/373 (13.9%)	**RR ranged from** 0.83 to 1.85	not estimable	⊕⊕⊕◯ MODERATE	IMPORTANT
Eczema (follow up: range 6 months to 6 years)												
6 [a, b, g]	randomised trials	not serious	not serious	not serious	serious [d]	none	143/739 (19.4%)	178/737 (24.2%)	**RR ranged from** 0.41 to 1.29	not estimable	⊕⊕⊕◯ MODERATE	IMPORTANT
Allergic rhinitis (follow up: range 6 months to 6 years)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**increased fish oil supplementation or fish intake**	**no/low fish oil supplementation or fish intake**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [h]	randomised trials	not serious	not serious	not serious	serious [i]	none	89/598 (14.9%)	119/580 (20.5%)	**RR ranged from** 0.41 to 0.77	not estimable	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Furuhjelm (2011) follow on from Furuhjelm (2009). Data from 2011 study used.

b. Best et al. (2016) follow on from Palmer et al. (2012, & 2013). Data from Best et al. used.

c. Furuhjelm (2011) unadjusted RR calculated from incidence data as 1.05 (0.40 to 2.72). Included in summary of findings.

d. Does not meet optimal information size threshold and the 95% CI shows both no effect and appreciable benefit/harm to the extent that recommendations cannot be made

e. Escamilla-Nunez (2014) presented findings as IRR and therefore not included in the summary of findings data. Maternal atopy and wheezing 0.882 (0.642 to 1.211). Maternal nonatopy and wheezing 1.027 (0.828 to 1.275)

f. Noakes (2012) unadjusted RR calculated from incidence data as 1.21 (0.51 to 2.87). Included in summary of findings.

g. Furuhjelm (2011), Noakes (2012), and Warstedt, 2016 Unadjusted RR calculated from incidence data RR ranged from 0.45 to 1.29. Included in summary of findings

h. Furuhjelm (2011) unadjusted RR calculated from incidence data as 1.20 (1.74 to 8.22). Not included in summary of findings as rate of incidence very low and confidence intervals very wide and dissimilar from the other two studies

i. Optimal information size does not meet threshold

Table 4 Increased vitamin D supplementation compared to no Vitamin D (prior to recommendations) or recommended Vitamin D (400IU/day) for women who are pregnant or lactating

Bibliography: Chawes et al. (2016); Goldring et al. (2013); Litonjua et al. (2016)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**increased vitamin D supplementation**	**no Vitamin D (prior to recommendations) or recommended Vitamin D (400IU/day)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Asthma (follow up: 3 years)												
2 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	32/278 (11.5%)	47/271 (17.3%)	**OR 0.82** (0.50 to 1.36)	**27 fewer per 1,000** (from 49 more to 78 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Wheeze (follow up: 3 years)												
3 [a, c]	randomised trials	not serious	not serious	not serious	serious [b]	none	17/108 (15.7%)	7/50 (14.0%)	**OR 1.14** (0.42 to 3.13)	**17 more per 1,000** (from 76 fewer to 198 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Eczema (follow up: 3 years)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**increased vitamin D supplementation**	**no Vitamin D (prior to recommendations) or recommended Vitamin D (400IU/day)**	**Relative (95% CI)**	**Absolute (95% CI)**		
3 [d]	randomised trials	not serious	not serious	not serious	serious [b]	none	30/102 (29.4%)	15/49 (30.6%)	**OR 0.72** (0.32 to 1.61)	**65 fewer per 1,000** (from 109 more to 182 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Allergic rhinitis (follow up: 3 years)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	11/101 (10.9%)	7/49 (14.3%)	**OR 0.69** (0.22 to 2.13)	**40 fewer per 1,000** (from 107 fewer to 119 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Litonjua study presented outcome asthma and/or recurrent wheeze as aHR of 0.80 (0.6 to 1.0). Not included in summary of findings

b. Does not meet optimal information size and the 95% CI shows both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

c. Chawes study presented outcome persistent wheeze as aHR of 0.75 (0.51 to 1.10). Not included in summary of findings

d. Chawes and Litonjua present findings as hazard ratios. Both assess eczema from birth to 3 years of age. Both report hazard ratio of 0.90. Not included in summary of findings.

Table 5 Vitamin C and E supplementation compared to usual or no Vitamin C and E supplementation for pregnant or lactating women in the community
Bibliography: Greenough et al. (2010)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin C and E supplementation**	**usual or no Vitamin C and E supplementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Asthma (follow up: 2 years)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	23/386 (6.0%)	23/366 (6.3%)	**OR 0.94** (0.42 to 2.11)	**4 fewer per 1,000** (from 35 fewer to 61 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Wheeze (follow up: 2 years)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	15/386 (3.9%)	17/366 (4.6%)	**OR 0.81** (0.32 to 2.06)	**8 fewer per 1,000** (from 31 fewer to 45 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Eczema (follow up: 2 years of age)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	98/386 (25.4%)	86/366 (23.5%)	**OR 1.10** (0.70 to 1.74)	**18 more per 1,000** (from 58 fewer to 113 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio
Explanations

a. Does not meet optimal size information threshold and the 95% CI shows both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 6 Probiotic supplementation compared to no probiotic supplementation for women during pregnancy or lactation
Bibliography: Dotterud et al. (2010); Rautava et al. (2012); Simpson et al. (2015)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**probiotic supplementation**	**no probiotic supplementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Asthma (follow up: range 2 years to 6 years)												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b, c]	none	3/136 (2.2%)	1/145 (0.7%)	**OR 3.25** (0.33 to 31.60)	**15 more per 1,000** (from 5 fewer to 173 more)	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 2 years to 6 years)												
1 [a]	randomised trials	not serious	not serious	not serious	serious [c]	none	46/132 (34.8%)	55/142 (38.7%)	**OR 0.85** (0.52 to 1.38)	**38 fewer per 1,000** (from 79 more to 140 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Eczema (follow up: range 2 years to 6 years)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**probiotic supplementation**	**no probiotic supplementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [a]	randomised trials	not serious	not serious	not serious	serious [d]	none	63/224 (28.1%)	80/144 (55.6%)	**OR ranged from** 0.16 to 0.48	not estimable	⊕⊕⊕◯ MODERATE	IMPORTANT
Allergic rhinitis (follow up: range 2 years to 6 years)												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	22/134 (16.4%)	20/145 (13.8%)	**OR 1.22** (0.64 to 2.37)	**25 more per 1,000** (from 45 fewer to 137 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Simpson et al. (2015) follow on from Dotterud et al. (2010). Data from Simpson et al. used.

b. CI are very wide

c. Does not meet the optimal information size criteria and CI shows both no effect and appreciable benefit/harm to the extent that recommendations cannot be made

d. Optimal information size does not meet threshold

Table 7 Higher fish intake compared to lower fish intake for pregnant women in the community

Bibliography: Leermakers et al., 2013; Maslova et al., 2013; Miyake et al., 2009; Miyake et al., 2013; Pele et al., 2013; Romieu et al., 2007; Saito et al., 2010; Sausenthaler et al., 2007; Willers et al., 2007; Willers et al., 2008

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Asthma (follow up: range 18 months to 8 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Willers et al. (2008) found an association between asthma symptoms and daily vs regularly/rarely intake - adjusted OR 1.01 (0.85-1.20). Maslova et al. (2013) findings showed doctor diagnosed asthma was inversely associated with high frequency (reference) vs zero intake of fish adjusted OR 1.30 (1.05-1.63). These findings show that there is a potential dose related protective association between fish intake and the incidence of asthma symptoms (or Doctor diagnosis).	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 12 months to 8 years)									
7	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Romieu et al. (2007) assessed atopic wheeze and persistent wheeze. Atopic wheeze showed a decrease in incidence with greater fish intake adjusted OR 0.55 (0.31-0.96), adjusted *p* value for trend 0.034. Remaining results are similar between studies and no significant associations are found adjusted *p* value for trend range 0.11-0.615 (Leermakers et al., 2013; Maslova et al., 2013; Miyake et al., 2009; Miyake et al., 2013; Romieu et al., 2007). Willers et al. (2008) and Pele et al. (2013) do not present *p* values adjusted OR range 0.68-1.10.	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 12 months to 8 years)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
7 [b]	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Increased fish consumption decreased incidence of eczema in Romieu et al. (2007) adjusted *p* value for trend 0.036 and Willers et al. (2007) found increased fish intake decreased Doctor confirmed eczema adjusted *p* value for trend 0.008 and ever eczema adjusted *p* value for trend 0.50.	⊕⊕◯◯ LOW	IMPORTANT
Allergic rhinitis (follow up: 7 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	No benefits were associated with increased fish intake and prevention of allergic rhinitis. Maslova et al. (2013) results not presented but discussed in narrative and Willers et al. (2007) Doctor confirmed hay fever adjusted *p* value for trend 0.043	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval, **OR:** Odds ratio

Explanations

a. 95% confidence intervals show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

b. Miyake et al. 2009 study is a follow on from Saito et al. 2010 study. Only Miyake et al. data included.

Table 8 Increased vegetable intake compared to minimal vegetable intake for pregnant and lactating women in the community

Bibliography: Fitzsimon et al. (2007); Miyake et al. (2010); Sausenthaler et al. (2007); Willers et al. (2008)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: range 1 years to 8 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Willers et al. (2008) found no association between maternal intake of vegetables and asthma, adjusted OR 0.98 (0.84-1.14). Fitzsimon et al. (2007) present their findings as fruit and vegetables combined there are multiple adjustments made for confounding covariates and two out of five of these showed an association between fruit and vegetable consumption and decreased incidence of asthma adjusted *p* value for trend range 0.04-0.09.	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 1 years to 8 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	The two studies assessing wheeze found no association between vegetable intake and wheeze. Miyake et al. (2010) assessed total vegetable, green and yellow vegetables and other vegetables intake adjusted *p* value for trend range 0.23-0.81. Willers assessed vegetables adjusted OR 0.97 (0.83-1.12)	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 16 months to 2 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al. (2010) assessed total vegetable, green and yellow vegetables and other vegetables intake whereas Sausenthaler et al. (2007) assessed specific vegetables - raw carrots, cabbage, spinach, celery, raw sweet peppers and salad. Miyake et al. (2010) showed an association between greater intake of green and yellow vegetables and decreased incidence of eczema adjusted *p* value for trend 0.01. Sausenthaler et al. (2007) showed no associations adjusted *p* value for trend range 0.276-0.896.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval, **OR:** Odds ratio
Explanations
a. The 95% CI shows both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 9 Increased fruit intake compared to low fruit intake for pregnant and lactating women in the community

Bibliography: Fitzsimon et al. (2007); Miyake et al. (2010); Sausenthaler et al. (2007); Willers et al. (2007); Willers et al. (2008)

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Asthma (follow up: range 1 years to 8 years)									
3	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Fitzsimon et al. (2007) present their findings as fruit and vegetables combined there are multiple adjustments made for confounding covariates and two out of five of these showed an association between fruit and vegetable consumption and decreased incidence of asthma adjusted *p* value for trend range 0.04-0.09. Willers et al. (2007) show that increased apple consumption decreases the incidence of doctor diagnosed asthma adjusted *p* value for trend 0.008 and ever asthma adjusted *p* value for trend 0.026. Willers et al. (2008) show no association between fruit intake and asthma adjusted OR 0.91 (0.77-1.09).	⊕⊕◯◯ LOW	IMPORTANT
Wheeze (follow up: range 1 years to 8 years)									
3	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al. (2010) showed no association between fruit intake and wheeze adjusted *p* value for trend 0.11.A strong association between increased apple intake and decreased ever wheeze was shown by Willers et al. (2007), adjusted *p* value for trend 0.029. Willers et al. (2008) showed no association between fruit intake and wheeze. adjusted OR 0.89 (0.75-1.04).	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 16 months to 2 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al. (2010) found that increased intake of citrus fruit decreased the incidence of eczema, adjusted *p* value for trend 0.03. Sausenthaler et al. (2007) showed no association between the fruits assessed and incidence of eczema *p* value range 0.338-0.865.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval, **OR:** Odds ratio
Explanations
a. The 95% CI shows both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 10 Increased dairy intake compared to low dairy intake for pregnant and lactating women in the community

Bibliography: Maslova et al. (2012); Miyake et al. (2010); Miyake et al. (2014); Sausenthaler et al. (2007)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: range 18 months to 7 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al. (2014) showed higher intakes of cheese may decrease doctor diagnosed asthma adjusted *p* value for trend 0.052. Maslova showed whole milk (adjusted *p* value for trend 0.03), semi-skimmed milk (adjusted *p* value for trend 0.02) and full-fat yoghurt (adjusted *p* value for trend 0.002) may decrease the incidence of asthma at 18 months. Ever asthma at 7 years assessed through a prescription based medical register showed a decrease of incidence of asthma associated with increased intake of full-fat yoghurt, *p* value for trend 0.01.	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 16 months to 29 months)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al. (2010) and Miyake et al. (2014) studies were undertaken in different prefectures in Japan at different times. Miyake et al. (2010) found strong associations between total dairy (adjusted *p* value for trend 0.002), milk (adjusted *p* value for trend 0.009) and cheese (adjusted *p* value for trend 0.02) intake and a decrease in the incidence of wheeze. While Miyake et al. (2014) showed no strong associations in their findings (adjusted *p* value for trend range 0.11-0.83).	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 16 months to 29 months)									

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
3	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al., (2014) showed the potential for total dairy product intake to decrease incidence of eczema, adjusted *p* value for trend 0.054 while Miyake et al. (2010), and Sausenthaler et al. (2007) showed no further associations, adjusted *p* value for trend range 0.13-0.99.	⊕⊕◯◯ LOW	IMPORTANT
Allergic rhinitis (follow up: range 18 months to 7 years)									
1	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Maslova et al. (2012) found there was very low incidence of hay fever in the population studied it was noted that increased consumption of low-fat yoghurt increased the incidence of self-reported hay fever. Results were reported in the narrative as OR 1.40 (1.00-1.97).	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval, **OR:** Odds ratio

Explanations

a. The 95% CI shows both no effect and appreciable harm and benefit to the extent that recommendations cannot be made

b. Optimal information size does not meet threshold. Results reported narratively as incidence rate very low in the population studied (5%).

Table 11 Increased nut consumption compared to low or no nut consumption for pregnant and lactating women in the community
Bibliography: Maslova et al. (2012); Sausenthaler et al. (2007); Willers at al. (2008)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: range 1 years to 8 years)									
2	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	Maslova et al. (2012) found a decrease in incidence of asthma at 18 months with increased maternal peanut/pistachio, (adjusted *p* value for trend 0.02) and tree nut, (adjusted *p* value for trend <0.0001) intakes but by 7 years of age only increased peanut/pistachio intake decreased asthma risks, *p* value for trend 0.002. Willers et al. (2008) reported that increased nut products (predominantly peanut butter) increased the risk of developing asthma in children assessed at age 1-8 years adjusted OR 1.47 (1.08-1.99)	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 1 years to 8 years)									
2	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	Maslova et al. (2012) found that increased maternal tree nut intake decreased the incidence of wheeze at 18 months, adjusted *p* value for trend 0.001, but by 7 years of age no associations between nut intake and risks of wheeze were shown (discussed no results given). Willers et al. (2008) reported that increased maternal intake of nut products (predominantly peanut butter) increased the risk of developing wheeze in children assessed at age 1-8 years adjusted OR 1.42 91.06-1.89).	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: 2 years)									
1	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Sausenthaler et al. (2007) showed no association between nut intake and eczema *p* value 0.527.	⊕⊕◯◯ LOW	IMPORTANT
Allergic rhinitis (follow up: 7 years)									

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Maslova et al. (2012) used parental report of doctor diagnosis and registry data. Parent reported doctor diagnosis showed no association of either maternal peanut/pistachio (adjusted *p* value for trend 0.06) or tree nut intake (adjusted *p* value for trend 0.21) with allergic rhinitis. Registry data showed an association between increased maternal peanut/pistachio intake and decreased allergic rhinitis adjusted *p* value for trend 0.001.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval, **OR:** odds ratio

Explanations

a. Association measures differ between studies with Maslova et al. (2012) being specific about which nuts are measured and Willers et al. (2008) measuring nut intake overall and nut products (specified as predominantly peanut butter)

b. The 95% CI shows both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 12 Increased fat intake compared to decreased fat intake for pregnant and lactating women in the community

Bibliography: Fitzsimon et al. (2007); Miyake et al. (2009); Miyake et al. (2013); Saito et al. (2010); Sausenthaler et al. (2007)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: 3 years)									
1	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Fitzsimon et al. (2007) used multiple adjustments for different confounding variables and all showed that increased added fats led to increased incidence of developing asthma symptoms, adjusted *p* value for trend 0.003.	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 16 months to 29 months)									
2	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Miyake et al. (2009) found no strong associations between fat intake and the incidence of wheeze, adjusted *p* value for trend range for different fat intakes 0.07-0.74. Miyake et al. (2013) showed an association between decreased wheeze incidence with higher intake of eicosapentaenoic acid, adjusted *p* value for trend 0.02 and eicosapentaenoic acid + docosahexaenoic acid, adjusted *p* value for trend 0.02.	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 16 months to 29 months)									
4 [c]	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Miyake et al. (2009) found an association between increased intake of n-6 polyunsaturated fatty acids and linoleic acid and increased risk of eczema, adjusted *p* value for trend 0.01. Miyake et al. (2013) reported no associations between fat intake and eczema, adjusted *p* value for trend range for different fat intakes 0.19-0.89. Sausenthaler et al. (2007) found associations between increased margarine (*p* value 0.017) and vegetable oil intake (*p* value 0.022) and increased risk of eczema	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval

Explanations

a. Optimal information size does not meet threshold
b. The 95% CI shows both no effect an appreciable benefit and harm to the extent that recommendations cannot be made
c. Miyake et al. (2009) is a follow-on from Saito et al. (2010). Miyake et al. (2009) data used

Table 13 Dietary patterns compared to other eating habits for pregnant and lactating women in the community

Bibliography: Chatzi et al. (2013); Lange et al. (2010); Miyake et al. (2011); Shaheen et al. (2009)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: range 2 years to 7.5 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	none	No associations were found between the identified dietary patterns and asthma outcomes. Lange reported adjusted OR range 0.89-1.08. Shaheen reported adjusted *p* value for trend range 0.27-0.93.	⊕◯◯◯ VERY LOW	CRITICAL
Wheeze (follow up: range 1 years to 7.5 years)									
4	observational studies	not serious	not serious	not serious	serious [a]	none	Three of the four identified studies did not find any associations between wheeze and dietary pattern. Chatzi et al. (2013) reported RR 0.97 (0.77-1.24). Lange et al. (2010) reported adjusted OR range 0.98-1.07. Shaheen et al. (2009) adjusted *p* value for trend range 0.54-0.99. Miyake et al. (2011) the Western diet pattern decreased the incidence of wheeze adjusted *p* value for trend 0.02.	⊕◯◯◯ VERY LOW	IMPORTANT
Eczema (follow up: range 1 years to 7 years)									
4	observational studies	not serious	not serious	not serious	serious [a]	none	The four identified studies found no associations between eczema and dietary pattern. Chatzi et al. (2013), reported RR 1.22 (0.88-1.70). Lange et al. (2010) reported adjusted OR range 0.94-1.06, Miyake et al. (2011) reported adjusted *p* value for trend 0.15-0.92, and Shaheen et al. (2009) reported adjusted *p* value for trend 0.08-0.96.	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval, **OR:** odds ratio

Explanations

a. The 95% confidence intervals show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made.

Table 14 Increased B-Carotene compared to low B-Carotene for pregnant and lactating women in the community

Bibliography: Litonjua et al. (2006); Miyake et al. (2010); Watson et al. (2014)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Wheeze (follow up: range 16 months to 2 years)									
3	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Litonjua et al. (2006), Miyake et al. (2010) and Watson et al. (2015) showed no association between B-Carotene intake and wheeze adjusted *p* value for trend range 0.87-0.971.	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: median 20 months)									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Miyake et al. (2010) showed that increased intake of B-Carotene decreased the incidence of eczema adjusted *p* value for trend 0.04.	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval

Explanations

a. The 95% confidence intervals show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 15 Folic acid or increased dietary folate compared to no/usual folic acid for pregnant or lactating women in the community (does it increase offspring allergy or atopy outcomes?)

Bibliography: Bekkers et al. (2012); Dunstan et al. (2012) Håberg et al. (2009); Litonjua et al. (2006); Magdelijns et al. (2011); Martinussen et al. (2012); Miyake et al. (2011); Watson et al. (2014); Whitrow et al. (2009)

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Asthma (follow up: range 12 months to 8 years)									
4	observational studies	not serious	not serious	not serious	serious [a]	none	Folic acid is not consistently shown to affect asthma outcomes - Bekkers et al. (2012) aPR 1.03 (0.92-1.16), Magdelijns et al. (2011) aOR 1.19 (0.65-2.20), Martinussen et al. (2012) aOR 1.23 (0.73-2.07) and Whitrow et al. (2009) aRR 0.92 (0.77-1.11) (assessed at 5.5yrs, diet and supplement in early pregnancy). But Whitrow et al. (2009) showed that there may be a positive association at 3.5 years of age when folic acid is taken in late pregnancy aRR 1.26 (1.09-1.47).	⊕◯◯◯ VERY LOW	CRITICAL
Wheeze (follow up: range 6 months to 8 years)									
7	observational studies	not serious	not serious	not serious	serious [a]	none	No consistent associations are shown between folic acid intake and wheeze outcomes - Bekkers et al. (2012) aPR 1.07 (0.96-1.20), Dunstan et al. (2012) aOR 1.1 (0.6-2.3), Litonjua et al. (2006) aOR 0.68 (0.38-1.22), Magdelijns et al. (2011) aOR 0.99 (0.80-1.23), Miyake et al. (2011) aOR 1.28 (0.65-2.50) and Watson et al. (2014) *p* value 0.189 (no other results given) Håberg et al. (2009) found that folate supplements in early pregnancy may be associated with increased risk of wheeze aRR 1.06 (1.03-1.10).	⊕◯◯◯ VERY LOW	IMPORTANT
Eczema (follow up: range 12 months to 8 years)									

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4	observational studies	not serious	not serious	not serious	serious [a]	none	Bekkers et al. (2012) aPR 0.98 (0.87-1.09), Magdelijns et al. (2011) aOR 1.16 (0.90-1.48), and Miyake et al. (2011) aOR 1.01 (0.51-2.00) found no consistent associations shown between folic acid intake and eczema. Dunstan et al. (2012) showed increased intake of folic acid increased the incidence of eczema aOR 1.7 (1.0-2.8.	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval, **PR:** Prevalence ratio, **OR:** odds ratio, **RR:** risk ratio

Explanations

a. The 95% CI shows both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 16 Increased Vitamin C compared to minimal intake of Vitamin C for pregnant and/or lactating women in the community
Bibliography: Litonjua et al. (2006); Martindale et al. (2005); Miyake et al. (2010); Watson et al. (2014)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Wheeze (follow up: range 13 months to 24 months)									
4	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Litonjua et al. (2006) Miyake et al. (2010) and Watson et al. (2014) showed no strong associations between vitamin C intake and wheeze outcomes adjusted *p* value for trend range 0.284-0.97. Martindale et al. (2005) found that increased intake of vitamin C may increase incidence of offspring wheeze adjusted *p* value for trend 0.034.	⊕⊕◯◯ LOW	IMPORTANT
Eczema									
3	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Litonjua et al. (2006) Martindale et al. (2005) and Miyake et al (2010) showed no association between maternal intake of vitamin C and eczema adjusted *p* value for trend range 0.115-0.36 (Litonjua et al. (2006) did not present results but discussed in narrative. Martindale et al. (2005) present findings further adjusting for Vitamin E intake that then show increased intake of vitamin C increases incidence of eczema adjusted *p* value for trend 0.048.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval
Explanations
a. The 95% CI show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 17 Vitamin D supplementation or increased dietary intake compared to no supplementation or minimal dietary intake for pregnant or lactating women in the community

Bibliography: Allan et al. (2014); Camargo et al. (2007); Devereux et al. (2007); Maslova et al. (2013); Miyake et al. (2010); Miyake et al. (2014); Watson et al. (2014)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: range 16 months to 10 years)									
3 [a]	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Low maternal vitamin D intake in pregnancy was shown to increase the longitudinal risk of Doctor confirmed asthma at 10 years of age in Allan et al. (2015) adjusted *p* value for trend range 0.046. Maslova et al. (2013) and Miyake et al. (2014) showed no association adjusted *p* value for trend range 0.12-0.90.	⊕⊕⊕◯ MODERATE	CRITICAL
Wheeze (follow up: range 16 months to 10 years)									
5	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Allan et al. (2015) and Camargo et al. (2007) showed that increased intake of vitamin D decreased the incidence of wheeze in offspring adjusted *p* value for trend range <0.001-0.002. Miyake et al. (2010) Miyake et al. (2014) and Watson et al. (2014) showed no strong associations adjusted *p* value for trend range 0.12-0.846.	⊕⊕⊕◯ MODERATE	IMPORTANT
Eczema (follow up: range 16 months to 3 years)									
4	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Allan et al. (2015), Miyake et al. (2010) and Camargo et al. (2007) showed no strong association between Vitamin D intake and eczema adjusted *p* value for trend range 0.13-0.92. Miyake et al. (2014) showed that increased vitamin D intake increased the risk of eczema adjusted *p* value for trend 0.04.	⊕⊕◯◯ LOW	IMPORTANT
Allergic rhinitis (follow up: 7 years)									

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
2	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Maslova et al. (2013) showed no association found between Vitamin D intake and allergic rhinitis adjusted *p* value for trend range 0.53-0.62	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval

Explanations

a. Allan et al., 2014 is a follow on from the Devereux et al., 2007 study. Data from Allan study used.

b. The 95% confidence intervals show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

Table 18 Increased vitamin E intake compared to no or low vitamin E intake for pregnant and lactating women in the community

Bibliography: Allan et al. (2015); Devereux et al. (2006); Litonjua et al. (2006); Martindale et al. (2005); Maslova et al. (2014); Miyake et al. (2010); Watson et al. (2014)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: range 5 years to 10 years)									
3 [a]	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Allan et al. (2015) showed that increased vitamin E intake decreased the incidence of Doctor confirmed asthma (adjusted *p* value for trend 0.027), while Maslova et al. (2014) did not find any associations (adjusted *p* value for trend 0.80).	⊕⊕◯◯ LOW	CRITICAL
Wheeze (follow up: range 16 months to 10 years)									
6 [c]	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Increased intake of Vitamin E reduced the longitudinal incidence of wheeze in Allan et al. (2015) adjusted *p* value for trend 0.002, recurrent wheezing at 2 years of age in Litonjua et al. (2006) adjusted *p* value for trend 0.05 and wheeze at 16-24 months of age in Miyake et al. (2010) adjusted *p* value for trend 0.04. Watson et al. (2014) found no significant associations adjusted *p* value 0.175.	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 16 months to 24 months)									
3	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Vitamin E intake did not affect eczema outcomes in Litonjua et al. (2006) (described in narrative no results given) or in Allan et al. (2015) and Miyake et al. (2010) adjusted *p* value for trend range 0.15-0.93.	⊕⊕◯◯ LOW	IMPORTANT
Allergic rhinitis (follow up: 7 years)									
2	observational studies	not serious	not serious	not serious	serious [b]	dose response gradient	Allan et al. (2015) and Maslova et al. (2014) showed no associations between Vitamin E intake and incidence of allergic rhinitis *p* value for trend range 0.14-0.51.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval

Explanations
a. Allan et al. (2015) is a follow on from the Devereux et al. (2006) study. Allan study data used.
b. The 95% confidence intervals show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made.
c. Allan et al. (2015) is a follow on from the Martindale et al. (2005) and Devereux et al. (2006).

Table 19 Increased intake of zinc compared to low intake of zinc for pregnant and lactating women in the community

Bibliography: Devereux et al. (2006); Litonjua et al. (2006); Miyake et al. (2010); Watson et al. (2014)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Asthma (follow up: 5 years)									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Devereux et al. (2006) found increased zinc intake was associated with decreased incidence of ever asthma adjusted *p* value for trend 0.04.	⊕⊕⊕◯ MODERATE	CRITICAL
Wheeze (follow up: range 16 months to 5 years)									
3	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Miyake et al. (2010)) found no associations between zinc intake and wheeze adjusted *p* value for trend 0.06. Litonjua et al. (2006) report any wheezing *p* value for trend 0.01 and recurrent wheeze *p* value for trend 0.06. Watson et al. (2014) report adjusted *p* value 0.015.	⊕⊕◯◯ LOW	IMPORTANT
Eczema (follow up: range 16 months to 5 years)									
2	observational studies	not serious	not serious	not serious	serious [a]	dose response gradient	Devereux et al. (2006) found that increased zinc intake decreased eczema reporting findings for ever eczema, Doctor-confirmed eczema and current treatment for eczema *p* value for trend range 0.03-0.05. Miyake et al. (2010) found no association *p* value for trend 0.23.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval

Explanations

a. The 95% CI show both no effect and appreciable benefit and harm to the extent that recommendations cannot be made

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Chapter Summary

This chapter has shown the studies identified for analysis in this review and the findings of each study. The characteristics of the included studies and the risk of bias identified for these studies have been presented. A narrative of the results was given and finally the GRADE SOF tables have shown the results for each variable and its effects on the health-related outcomes each study assessed. These findings will now be discussed in the following chapter.

Chapter 4:

Discussion

This chapter will further discuss and explore the findings within the context of the literature base, highlighting key points, strengths, limitations and implications for further research. My conclusions and recommendations will also be presented.

Summary of main results

Overall, 54 studies (16 RCT and 38 cohort) involving 142,487 mother infant pairs were included in this review. Data on vitamin, oligo-element, food groups and dietary patterns during pregnancy and lactation were collected and the effect of these on the health outcomes of asthma, wheeze, eczema and hay fever were assessed.

Although individual studies included in this review did highlight many important associations between maternal diet in pregnancy and lactation and offspring allergy and atopy outcomes, collectively, there were no consistent health outcome findings across the studies reviewed. This finding seems to be in direct contrast to the research originally sourced to inform this review and referred to in the background literature review in chapter one. This reflects the diversity of association and outcome measures utilised within the included studies and the effects of these on the ability to accurately interpret the results collectively. The need for good nutrition during pregnancy is not the issue in question as this has already been established as an important component of maternal and fetal health as demonstrated by the evidence-based nutrition guidelines provided by the government health ministries in many countries. This review assessed the allergy and atopy outcomes in infants and the included studies showed no collectively consistent findings whilst some individual

studies showed that diet or supplements could affect the included allergy and atopy outcomes. This work does present a comprehensive summary and review of the fifty-four identified studies that explored the impact of maternal diet in pregnancy and lactation on allergy and atopy outcomes. Areas of interest and the issues surrounding the interpretation of results are discussed separately below.

A total of 19 studies assessed fish intake or supplement use making this the most frequent diet and supplementation variable assessed in this review (Figure 4). Increased n-3 PUFA through supplements or eating oily fish which has anti-inflammatory and immunomodulatory properties has been shown to have a protective effect on allergic diseases (Palmer, 2017). There were mixed results found in this review with five studies showing increased intake of fish oil decreased asthma, eczema and/or hayfever outcomes (Furuhjelm et al., 2009; Manley et al., 2011; Maslova et al., 2013; Romieu et al., 2007; Willers et al., 2007). Manley et al. (2011) assessed fish oil supplementation during lactation and was the only study in this group that did so; they showed a decreased incidence of hay fever in boys. In 2015, a study conducted by researchers at the Liggins Institute in New Zealand showed that a high proportion of the fish oils supplied to the New Zealand market were oxidised (spoiled) and delivered a lower n-3 PUFA content than advertised (Albert et al., 2015). Studies in the United States of America have shown similar findings to the New Zealand research work (Mason, 2017; Ritter, Budge, & Jovica, 2013). These studies raise the question of the quality of the fish oil supplements used in the included studies and whether this could potentially have affected the findings of the studies. Further research with reported testing of the oxidation levels of the supplemented fish oils are needed. In another murine study conducted by researchers at the Liggins Institute, pregnant rats (dams) were administered high doses of oxidised fish oils, much higher than the equivalent human dose, and found that the offspring of those supplemented rats demonstrated a higher mortality rate with the dams showing increased insulin resistance at the time of weaning; the researchers made the results known early and advised that pregnant women refrain from taking fish oil supplements (Albert et al., 2016).

Other dietary variables assessed in this review included low-fat dairy products and artificial sweeteners used in soft drinks which were shown to potentially affect asthma and allergic rhinitis outcomes according to the results found in the included studies by Maslova, Halldorsson, et al., 2012 and Maslova, Strøm, Olsen, et al., 2013. Very few studies included in this review assessed this dietary variable and further research is needed to determine whether low-fat dairy products and artificial sweeteners increase the incidence of asthma and allergic rhinitis.

One cohort study examined the association between increased fast-food intake and the outcomes of interest in this review. This study showed that increased fast-food intake could potentially increase asthma outcomes (von Ehrenstein, 2015). This study was based in Los Angeles and had the highest risk of bias due to high attrition rates which was attributed to a highly transient population. This means that the findings are less reliable with further well conducted studies with high retention rates needed. These studies with a focus on the use of artificial sweeteners and fast-food provide some support to theories about the change to a more Western or fast food driven diet pattern potentially increasing the incidence of allergic disease (Bengmark, 2013). The whole food and high fruit and vegetable intake that comprises the Mediterranean diet has been studied in this context.

The Mediterranean diet pattern overall was not shown to reduce allergic outcomes in the included Chatzi et al. (2013) and Lange et al. (2010) studies. Both studies assessed diet using FFQs to assess maternal diet and identified the same tool for assessing adherence to the Mediterranean diet. Both studies assessed wheeze and eczema outcomes while Lange et al. (2010) also assessed asthma outcomes. The Mediterranean diet pattern is an area of research that does show potential for improving health outcomes and continues to be well studied. Studies excluded from this review due to quality assessment issues showed that the Mediterranean diet was associated with improved health outcomes (Table 1). The Chatzi et al. (2013) study presented the findings of two cohort studies with one based in Spain and the other in Greece. This study therefore, assessed the diet of participants who would generally be eating a Mediterranean diet as would generations before this, so perhaps the effects of diet would not influence the outcomes as significantly as it might in a population that doesn't

consume high intakes of fruit and vegetables, use olive oil for cooking and eat less dairy products and meat. The Lange (2010) study was based in Massachusetts (USA) and could potentially show greater impact if the diet assessed was an intervention where fruit and vegetable intake was increased, and meat and dairy intake decreased. Instead, this study was an assessment of usual diet and therefore intake of a Mediterranean diet would more likely reflect a more affluent participant recruitment. Another question that remains refers to the quality of the food available. Produce from soils depleted of nutrients will be lower in nutrients than those produced in areas with nutrient rich soils (Pollan, 2008). The widespread use of herbicides and pesticides may further impact the health-related outcomes assessed in this work. The remaining dietary pattern studies included in this review, defined diet patterns differently and this added difficulties to the interpretation and evaluation of dietary pattern impact. Further studies with more uniform definitions of diet types that allow for better evaluation of dietary patterns are needed to determine their effect. The impact of food quality issues as described above could affect many of the variables assessed in this review and have possibly affected the results of the studies exploring dietary patterns. Another variable with the potential to be greatly affected by soil and farming or produce management practices is that of fruit and vegetables.

The literature sourced and perused prior to and during this work created an expectation that increased fruit and vegetable intake would show strong associations with the decrease of allergy and atopy outcomes, but this wasn't consistently reflected within the findings presented in this review. The five included studies that assessed fruit and or vegetable intake are shown in the SOF tables 8 and 9. These studies had varying methods of intake measurement and presented their findings in tertiles or quartiles with variances in how these measurements were combined and compared. Fruit and vegetables are rich in antioxidants but there are two conflicting theories about antioxidant intake, one theory discusses the decline of antioxidant intake and the increase in allergic disease, especially asthma, with the other theory suggesting increased antioxidant intake is causing increased allergic disease (Allan, Kelly, & Devereux, 2009). Other included studies assessed specific antioxidant intakes and their effects on allergic outcomes and will now be discussed further.

Vitamin E intake was assessed in eight studies (Tables 5 & 18). Allan et al. (2015) showed a decrease in longitudinal asthma and wheeze outcomes with increased vitamin E intake. Allan et al. (2015) describe the difficulty in assessing vitamin E effects due to multiple contributory factors, such as potential interactions with other nutrients, and suggest that rather than using vitamin E supplementation, the recommendation should be to increase intake via dietary consumption. This recommendation would mean that the intake of foods with other nutritional benefits would also be increased allowing for the complexity of the interplay between diet and vitamin and mineral uptake.

Zinc intake was assessed by four studies (Table 19). Zinc is an antioxidant that has been shown to potentially affect airway development through its influence on airway proteins, including ADAM33 and metalloproteinase, zinc also has anti-inflammatory, anti-oxidant and pro-survival actions (Zalewski, 2006). Zalewski (2006) specifically discusses the impact of zinc deficiency highlighting murine studies showing that zinc deficiency led to increased airway hyper-responsiveness, and human studies where asthmatic children and adults had significantly lower zinc levels in the plasma or the hair than healthy age-matched subjects. Only one included study assessed zinc intake and asthma outcomes, and confirmed that increased levels of zinc decreased asthma ever, and asthma with wheeze in the previous year (Devereux et al. 2006). Devereux et al. (2006) also found that increased zinc intake decreased eczema outcomes. Ozdemir (2014) describes the impact of the anti-oxidative and anti-inflammatory effects of zinc and how these properties can impact on the development of eczema. The need for further studies examining the effects of increased zinc intake is also highlighted by these potentially positive findings.

Folic acid supplementation is recommended four weeks prior to conception and during the first twelve weeks of pregnancy for the prevention of neural tube defects in New Zealand (MOH, 2008). The nine studies included in this work (Table 15) are from different countries and measured folic acid intake at different time points in pregnancy. Folic acid or folate supplements were not consistently shown to have any effect on asthma, wheeze or eczema outcomes. Haberg et al. (2009) explained that there may be an epigenetic influence on methyl donors which would increase the likelihood of respiratory outcomes in offspring.

This was also the only study that found an increase in any of the identified outcomes in this work when folic acid supplements were taken in early pregnancy; all other studies showed no association when folic acid was taken as recommended by the New Zealand MOH. The MOH guidelines only make recommendations for supplementation of folic acid and iodine but also discuss the importance of vitamin D.

The New Zealand MOH (2008) guidelines discuss the importance of safe sun exposure for increasing vitamin D levels rather than supplementation but a study published by Wheeler et al. (2018) has shown that women living at 45° S latitude (Dunedin) in New Zealand are commonly Vitamin D deficient. Ten studies included in this review assessed vitamin D intake (Tables 4 & 17). There were four cohort studies that showed vitamin D intake, whether by diet or supplement, could decrease the incidence of asthma, wheeze and/or eczema (Allan et al., 2015; Camargo et al., 2007; Devereux et al., 2007; Miyake et al., 2010). These four studies were undertaken in Scotland, Japan and in North America and the study participants were described as predominantly white or Japanese females. There is a higher incidence of vitamin D deficiency in Asian, Northern American and dark-skinned populations (Holick, 2008). There are issues in assessing outcomes of vitamin D intake as sunlight and complementary food intake types are required for better uptake of vitamin D meaning that geographical differences, use of sunscreen, obesity and fortification of foods with vitamin D also influence vitamin D levels (Holick, 2008). The timing of vitamin D intake or supplementation may also affect the outcomes measured as vitamin D has been shown to be involved in fetal lung development and with asthma (Kho et al., 2013). Many of the RCT studies in this work highlight that a limitation of their work as the start date of supplementation (Chawes et al., 2016; Goldring et al., 2013; Litonjua et al., 2016). Lung development begins early in the embryonic stage around the fourth week of gestation and continues post-delivery (Moore, Persaud, & Torchia, 2016). In the studies included in this work the earliest supplement started at ten weeks gestation while the remaining studies started supplementation late in the second trimester. Other supplements that are used widely for their known health benefits and effect on skin conditions are probiotics. These will now be discussed in relation to this review's findings.

Probiotic supplementation was shown by all three studies (Table 6) to lower the incidence of eczema. These studies all supplemented mothers in both pregnancy and during lactation. There is consensus among these studies that both prenatal and postnatal (during lactation) supplementation of mothers has been shown to be more protective than either prenatal or postnatal supplementation alone. Rautava, Kalliomäki and Isolauri (2002) showed an increase in the concentration of immunomodulatory cytokine transforming growth factor (TGF-β2) in breast milk when mothers were supplemented in both pregnancy and lactation. Rautava, et al. (2012) suggest that experimental evidence shows that TGF-β2 modulates immune responses in the immature neonatal gut and promotes immune maturation. The lack of significant findings in relation to asthma, wheeze and allergic rhinitis were explained as either a true effect or possibly due to a lack of power by Simpson et al. (2015) highlighting the need for further, larger studies. A common difficulty expressed by those working in the field of allergy and atopy is the number of different probiotic strains available and the research supporting the use of each of these. The studies included in this review used different probiotic strains and each study utilised more than one identified probiotic strain but found similar positive results for eczema outcomes. A New Zealand based study with results that are soon to be published, the Probiotics in Pregnancy (PiP) study, supplemented participants using one strain of probiotic and included severity of eczema and atopic sensitisation in the outcomes (Barthow et al., 2016). The authors of the published study protocol were contacted via e-mail and a paper is currently being prepared for publication regarding allergic outcomes in infants in the PiP study (Barthow, personal communication, January 2018).

Overall completeness and applicability of evidence

Measurement and definition of outcomes varied amongst studies. Many studies in this review used questions from the ISAAC questionnaire (Asher at al., 1995) and are shown in the characteristics of included studies tables. The ISAAC questionnaire was validated in 6-7 and 13-14-year olds and assessed ISAAC specific outcomes which are, asthma (questions include wheeze), eczema and allergic rhinitis from as young as three months old (Saito et al., 2010). Many of the included studies used the ISAAC questionnaire to assess outcomes

and discussed using a validated tool but didn't highlight that they were using the validated tool for children of an age the tool was not validated for.

Asthma was assessed in offspring from as young as one year old in this work, but a diagnosis of asthma is difficult in this age and is often under- and over-diagnosed in pre-school children (Bakirtas, 2017). Many studies included a wheeze outcome to overcome this issue but wheeze itself is not a good indicator of potential asthma in young children (Bakirtas, 2017), nevertheless, due to the high number of studies that assessed wheeze as an outcome it was included in this work and presented as a separate outcome.

Some studies differentiated between allergic rhinitis and hay fever and others assessed rhinoconjunctivitis. These were all grouped together as allergic rhinitis for the purposes of this review, but this could have affected the ability to determine any associations. Further work could be undertaken with a more specific focus on the effects of maternal diet on allergic rhinitis, and rhinoconjunctivitis outcomes in offspring. This work could provide further insight into the definitions of and differences in these terms as well as answer the question of whether changes in maternal diet affect these outcomes.

Measurement of intervention

The timing of supplementation or diet assessment varied greatly between the reviewed studies. Almost all the RCT studies included in this review administered a supplement to the pregnant or lactating mother. There were differences in the timing in gestation that the supplements were given but all supplements were started in the second trimester of pregnancy. The one RCT study that used a dietary intervention, salmon, increased maternal intake of salmon at around week 20 of gestation.

As discussed in the results chapter most cohort studies utilised a FFQ to determine maternal dietary intake of food or supplements. The FFQ used was usually determined by the country that the study was undertaken in as there are specific nutrient intakes unique to different population groups. One study that assessed the validity of using a FFQ to determine food group intakes showed that a FFQ was not a very reliable way of measuring food group intake

(Barbieri, Crivellenti, Nishimura & Sartorelli, 2015). Another study by Shim, Oh and Kim (2014) evaluated different dietary assessment methods and included 24-hour dietary recall, diet history and FFQ among other methods. This study concluded that each method had differing strengths and weaknesses and the use of a combination of methods to assess intake would be more accurate. Both Barbieri at al. (2015) and Shim, Oh and Kim highlight the issue of recall bias. While there are issues with the accuracy of information gleaned from the use of FFQs, they are cost-effective and easy to use and continue to be the most frequently utilised method of diet assessment (Shim, Oh & Kim, 2014). The variation in timing of diet assessment or supplement intake has been shown in previous discussions to affect the outcomes included in this study. Organ plasticity and the potential for influencing epigenetic changes *in utero* are known to be dependent on timing but further research is needed to understand when those times are (Vickers et al., 2014). There are limitations evident within these studies as embryonic development is a time of great plasticity (Barker, 2002) but the supplementation is started well after the embryonic stage and in some cases the supplementation didn't occur until late in pregnancy. Many studies in this review did highlight the start point of supplementation as a limitation of the study.

The use of mobile phone applications and recording devices to record dietary intake is an area that is beginning to be explored for use in research (Shim, Oh & Kim, 2014). The limitation of assessing diet at a single point in pregnancy is the changing diet patterns of a mother throughout pregnancy. A mother may alter her diet once she finds out she is pregnant or may feel unwell during the pregnancy at different stages and only tolerate certain foods. Other influences may be attributed to cravings or a mother "eating for two", there may be changes in income due to the pregnancy which impact the ability to afford healthier foods. The studies that assessed the diet twice during pregnancy would have achieved a better view of the overall diet during pregnancy than those that assessed only once. McGowan and McAuliffe (2012) assessed diet in each trimester in 285 Irish women and identified two dietary types being healthy and unhealthy. Women in this study were not given any dietary advice and 16% of women who were eating an unhealthy diet changed this dietary pattern by the third trimester.

In summary, the method and timing of measuring dietary intake has a significant impact on the information obtained from the participants in the included studies and therefore impacts the ascertainment of effect on outcomes. Studies assessing the health effects of supplementation in pregnancy may need to devise a method that allows for early commencement of supplement administration to allow for the times of greatest organ plasticity.

There were a wide variety of dietary and supplement variables assessed by the studies in this review and these studies were carried out in many different countries. Further research with a more specific focus may decrease the heterogeneity between included studies and allow for clearer interpretations of findings. Most of the studies included in this work were conducted in countries that were English speaking and most assessed a predominantly white ethnic population apart from the eight Japanese based studies (Miyake et al. 2009, 2010a, 2010b; Miyake, Sasaki, et al., 2011; Miyake, Okubo, et al., 2011, 2013, 2014, Saito et al. 2010). The results from the studies included in this work could not be used to inform populations that are not represented in this work due to differences in food availability and diet types in non-represented countries. The research included in this work was undertaken in developed and industrialised countries and can be generalised for these most affluent populations where the burden of allergy is high (Gunaratne, Makrides, & Collins, 2015).

The differences in how intake was measured and the difference in high and low intake measurements means that the findings of this work require an increased amount of scrutiny to make comparisons.

NZ recommendations and context

As discussed, in the general introduction, Māori and Pasifika populations are consistently shown to have poorer health outcomes in terms of allergy and atopy when compared with non- Māori and non-Pasifika populations in New Zealand. These, and other, inequalities in

health have persisted with few advancements made through health strategies implemented thus far in New Zealand that have impacted successfully to reduce these inequalities (Disney, Teng, Atkinson, Wilson & Blakely, 2017). In addition to applying concentrated efforts to focus on the determinants of health and addressing issues such as access to healthcare and health service provision for Māori and Pasifika populations in New Zealand, a focus on supporting new mothers and encouraging healthy dietary practices would be beneficial.

While the results of the studies included in this review did not show consistent findings for recommendations when being compared with each other collectively, there is evidence shown in individual studies that certain food or supplement intakes can potentially influence allergy outcomes. It is with this knowledge and the understanding that a healthy diet is best for both the pregnant woman and developing fetus that the New Zealand context is discussed and explored further, with an emphasis on the recommendations set forth in the Eating for Healthy Pregnant Women pamphlet (MOH, 2014) which most frequently provides the platform for dietary advice in pregnancy.

The discussion points above highlight that there were some positive findings highlighting that some or all of the health outcomes included in this review could potentially be improved with an increased intake of fish or fish oils, vitamin E, zinc and probiotics. The Eating for Healthy Pregnant Women pamphlet (2014) includes all of these except the fish oil and probiotic supplements in their recommendations. This pamphlet highlights the importance of food-based nutrition and states that the only supplements recommended for all pregnant women are folic only and iodine only supplements. Vitamin D is also discussed in this pamphlet with a recommendation to see a general practitioner if daily sun exposure is minimal or higher risk factors are identified.

The Growing Up in New Zealand study published the results of a study assessing women's adherence to the New Zealand nutritional guidelines in pregnancy in 2014 by Morton et al. This paper found that three percent of New Zealand women followed all the recommendations across the four food groups. There have been similar findings in Australia where Malek, Umberger, Makrides and Zhou (2015) found that, in the cohort they studied,

none of the women adhered to the guidelines across all four food groups (fruit and vegetables are separated in the Australian guidelines), Canada – where a study showed that few women came close to meeting Canada's food guide recommendations for daily intake (Jarman, Bell, Nerenberg, Robson, 2017) and Ireland, where O'Keeffe et al. (2016) found adherence to all seven food pyramid guidelines was less than 1%.

In New Zealand, there is a heavy reliance on midwives to provide nutrition support and education during pregnancy as midwives are most likely to be a woman's lead maternity carer (LMC). Around 90% of all New Zealand women register with a community-based LMC midwife or hospital-based midwife (MOH, 2014). A survey of 370/1340 midwives undertaken by Elias and Green (2007) highlighted a lack of formal nutrition education in midwifery but a high level of confidence in dealing with nutritional needs of clients. A further survey in 2014 (Yin, Dixon, Paterson, & Campbell) showed that the midwives who participated delivered tailored nutrition and physical exercise advice. There are four providers of midwifery undergraduate education in New Zealand. Two of these providers offer specific maternal and newborn nutrition courses with one offering the course as an option rather than a core course. The other two remaining institutions do not offer a specific course, but nutrition may be covered within the wider curriculum. The Healthy Start education provided by the Liggins Institute and discussed in the background section of this review is an attempt to address the different approaches in nutrition education and allow for both midwives and other health professionals involved in the care of pregnant women to deliver more fully informed and uniform education tailored to the needs of each woman. The importance for all health professionals who have contact with pregnant women to provide consistent advice that aligns with the information already provided by midwives is a key component of the Healthy Start education.

Okesene-Gafa, Chelimo, Chua, Henning and McCowan (2016), surveyed 422 women in the South Auckland region of New Zealand and concluded that there needed to be more targeted information given to specific ethnic groups regarding nutrition and beliefs around cravings with the 'eating for two' behaviours in pregnancy needing to be addressed for all women when discussing nutrition. The ethnicities that Okesene-Gafa et al. (2016) specified in their

study were Māori, Pacific, Asian and European/Other with Māori and Pacific Island women more likely to report infrequent healthy eating. They also showed that a high number of the women surveyed would consider participating in nutritional interventions if the barriers of transport and childcare could be reduced.

A recent qualitative study that interviewed 12 women living in Dunedin, New Zealand found that the participants felt that women would feel greater motivation to change dietary habits if they knew that the changes would improve outcomes or reduce risk for their baby (Paterson, Hay-Smith, & Trebarne, 2016). This was also highlighted by Gardner et al. (2012) where psychological predictors of dietary intentions in pregnancy were studied and the conclusion made that there needed to be an emphasis on likely positive outcomes in dietary change advice for pregnant mothers. The Healthy Start education for midwives and other health professionals incorporates this into the teaching modules and is an attempt to provide more consistent and easily received information for pregnant women from all health professionals involved in the care of a pregnant women.

Knowing what dietary changes to make during pregnancy and having the ability to make those changes are often foremost in the mind of a pregnant women. There are a growing number of studies assessing diet in pregnancy and the opportunities and barriers to effecting change. A study published in 2009 assessed the cost of healthy living (Boland & Gibbons, 2009). This study took information from the New Zealand healthy eating in pregnancy and breastfeeding guidelines and made a shopping list from these recommendations. The authors then assessed the cost of following these guidelines at three different supermarkets and a rural general store in Dunedin, New Zealand. This study showed that the cost of healthy eating for an individual pregnant woman was closest to the average cost of a weekly shop for a family of three, and for many women was unattainable.

Wennberg, Lundqvist, Högberg, Sandström and Hamberg (2013), used focus groups to describe the experience of dietary information and change during pregnancy for twenty-three women. This study was based in Sweden and showed that most women experienced inconsistency and confusion around the information given to them regarding nutrition advice

and support. The Healthy Start education program is designed to allow for more uniformity in the delivery of nutrition education for New Zealand women. Wall et al. (2016) further explored the dietary patterns of mothers in the 'Growing Up in New Zealand study and concluded that while the NZ eating guidelines for healthy pregnant and breastfeeding women was developed to provide support and to optimise health in pregnancy and lactation these guidelines were not being taken up by all women. They also emphasise that new approaches are needed to target and better engage women in New Zealand to improve the nutrition status of all pregnant women and improve the population's health.

The New Zealand MOH health strategy plan was updated in 2016 (MOH, 2016). One message that could potentially be taken from this health strategy is that there is an emphasis on individual responsibilisation for health with the assistance of technology. Responsibilisation is a term specifically developed in government literature sources that refers to the process of rendering an individual responsible for tasks which are generally perceived as being the responsibility of another (Wakefield & Fleming, 2017). To quote the guiding statement of the strategy "All New Zealanders live well, stay well, get well, in a system that is people-powered, provides services closer to home, is designed for value and high performance, and works as one team in a smart system" (MOH, 2016, p.23). "People powered" is then further discussed as "making New Zealanders 'health smart'" so they can obtain and understand the information provided, there is also an emphasis on mobile phones and the internet 'smart system' (MOH, 2016). The vision then includes people taking "greater control of their own health" and technology being available for everyone to use (MOH, 2016, p. 28). Responsibilisation can be promoted as empowering but there is the risk that people could be held morally responsible for their own health without being given the education and resources needed. Chiapperino and Tengland (2015) discuss this issue and highlight the concern that the basis of responsibilisation sits in the assumption that the people affected are sufficiently free and able to take ownership of their health choices. A chief concern lies in the inability to account for the impact of social structures on an individual's ability to take up this responsibility leading to further health inequalities and disempowerment in already disadvantaged groups within society (Chiapperino & Tengland, 2015). Providing education and technological support for dietary decision making in

pregnancy should not confer responsibility for offspring outcomes onto pregnant women especially when issues such as food affordability and knowledge around food preparation have not been adequately addressed.

In summary, in New Zealand there is an acknowledgement that maternal nutrition has an impact on both maternal and fetal health and is of great importance during pregnancy. Achieving an improvement in maternal dietary patterns in New Zealand is likely to require more than simply encouraging mothers to eat better. A holistic approach would be preferable where, if possible, factors and issues that could potentially influence dietary habits could be successfully navigated and managed. In addition, those interacting with Māori and Pasifika mothers and other groups will need to ensure their engagement and communication are culturally sensitive and appropriate. The government also has a part to play where potential initiatives such as removing easy accessibility to sugar rich and fat loaded foods, implementation of sugar taxes and removal of GST from fruits and vegetables could be implemented.

This work contains many studies that individually show the benefit of a healthier maternal diet on maternal and offspring outcomes. A recent development has been the implementation of nutrition education for health professionals through the Healthy Start programme. This education is provided for all health professionals who have contact with women during their pregnancy with the aim of delivering consistent advice that can be tailored for individual women. New Zealand based studies have also shown that healthy eating during pregnancy needs to be affordable and accessible.

Quality of the evidence

Overall the 16 RCT studies were judged to be of moderate to unclear risk of bias. This was often due to insufficient information presented to allow for a judgement of risk. The main areas where further information was needed, were incomplete outcome data being adequately addressed, knowledge of allocated intervention prevented during study, and other

potential sources of bias. Rautava et al. (2012) was the only RCT within this work judged to be of low risk of bias.

The 38 cohort studies were judged to be of moderate to high risk of bias overall. The main areas where the studies did not meet criteria were representativeness of the exposed cohort, ascertainment of exposure (self-report) and assessment of outcomes (parental/self-report). There was no study that was judged to be of low risk of bias within the cohort studies.

Grade summary of findings tables were used, and studies were assessed for quality within this tool too. Using the GRADE methodology evidence was downgraded based on study limitations (risk of bias), imprecision (predominantly the presence of wide confidence intervals crossing the line of no effect), and inconsistency.

Limitations

A more specifically defined review may provide more detailed and clear findings as this review included many studies assessing a wide variety of associations and multiple outcomes. A potential risk of bias related to author judgement may be present due to some of the elements of this review being undertaken by a lone researcher and may even exist for the elements required to be undertaken by more than one researcher.

The process undertaken in this work is clearly presented and is reproduceable. The PRISMA checklist and the Cochrane handbook and guidelines were used to direct this work. These tools aim for transparency and clarity thus providing a solid basis for this work.

The use of GRADE SOF tables to present the results is a more recent requirement in the Cochrane handbook and while I have needed to learn how to create these independently (with some help from the university statistician and my supervisor) the use of these tables in this work not only improves presentation but allows for easy interpretation of findings in the accepted and more uniform manner encouraged by Cochrane.

Agreements and disagreements with other reviews

There were two previously published systematic reviews with similarities to this work identified (Beckhaus et al., 2015; Netting et al., 2014) and several other systematic reviews that focus on different, more specific, associations. The findings in this work generally reflect those of these previously published studies, where the different methods and measurements employed within each study made evaluation of effects across several studies difficult and potentially added to the inconsistency of findings. None of these reviews looked at the findings in relation to the national recommendations of the country the review authors were based in.

Netting et al. (2014) included 42 studies (many of which were food allergy or food avoidance based), 37 of these were either intervention or control studies and a meta-analysis was conducted of the included studies within subgroups which were predominantly food allergy based. Beckhaus et al. (2015) included only cohort studies and performed a meta-analysis of these cohort studies within subgroups.

Netting et al. (2014) and Beckhaus et al. (2015) also highlighted areas where further study could be beneficial. These recommendations focussed more on specific food types rather than broader methodological recommendations. Netting et al. (2014) suggested further research into the Mediterranean diet pattern and diets high in fruit, vegetables and fish, and further studies focussed on vitamin D intake for positive benefits. Further research was also advised for the negative effects of vegetable oils, margarine, nuts and fast foods. Beckhaus et al. (2015) recommended further studies with a focus on vitamin D, E and zinc intake as these were shown to have the most consistent positive findings.

This review has included more recent studies and did not include food allergen avoidance adding further knowledge around food based nutritional interventions in pregnancy and lactation for the specified outcomes. This review has also explored the impact the findings have within the author's country of interest, New Zealand, providing further support for the MOH (2008) healthy eating in pregnancy guidelines and highlighting the need for consistent,

accessible and tailored education across multiple health professions to further support changes in nutrition for New Zealand women.

Future recommendations

While the importance of a healthy diet in pregnancy has been shown throughout the literature and reinforced throughout the individual studies reviewed as part of this work, the collective impact on the allergic outcomes assessed could not be determined across all the studies included in this review. Nevertheless, this review does offer a valuable resource containing a collection of studies relevant to the local and international context. There were areas where the potential for benefit was highlighted and these areas will need further study. Further studies focused on dietary fish intake or fish oil supplementation would be beneficial but the studies using supplementation would need to ensure the quality of the fish oil supplements used. The New Zealand MOH healthy eating in pregnancy brochure (2014) does not recommend vitamin D supplementation based on the ability to have small amounts of healthy sun exposure in New Zealand but further research into the vitamin D levels of New Zealanders especially Māori and Pasifika populations would be warranted. Probiotics and antioxidants also showed consistent findings in some studies warranting further research into the effects of these variables. The New Zealand MOH guidelines for healthy eating in pregnancy (2008) have been shown to be well researched and supported by literature, however this information is not reaching pregnant mothers in a way that is inspiring an improvement in dietary choices throughout pregnancy as highlighted in the Growing Up in New Zealand Study, Morton et al. (2014).

Summary

This chapter has discussed the findings describing their strengths, limitations and implications. These findings were then related to the New Zealand context showing how they supported the primary source of information provided to mothers in New Zealand but also highlighting that the delivery of this information could be individualised and improved.

Implications for practice

Overall, while this review found that many individual studies highlighted the influence of maternal diet on allergy and atopy outcomes in offspring there was little consistent evidence across the included studies when viewed collectively to support the idea that maternal diet can influence allergy and atopy outcomes in infants. This could be due to the variety of methods and measurements used within the included studies for example the method of food intake measurement, when this was undertaken and how many times during pregnancy it was assessed. Once this data was obtained, the variance in reported intakes was wide across many studies with some studies showing a highest measurement of intake that was included in the lowest measurement intake of another study.

Current nutritional advice provided during pregnancy needs to be delivered in a more cohesive, deliberate and uniform manner. Healthy nutrition as recommended by the New Zealand MOH (2008) should be encouraged by general practitioners, obstetricians, midwives, nurses and the members of the multi-disciplinary health team who have contact with pregnant and lactating women. This means further education will be required and the Liggins Institute's healthy start programme is attempting to bridge this gap. This work provides a comprehensive and current review of studies that have explored the relationship between maternal diet and offspring allergy and atopy outcomes and shows that this is an area of great potential for improving health outcomes as shown by many of the studies individually. Consistent nutritional advice that highlights the benefits of healthy eating for both mother and child delivered in a way that has meaning for the pregnant woman receiving this advice has been highlighted as an important factor in maternal and offspring health outcomes.

Implications for research

A multinational study with predefined intake measurements assessed using a structured interview at multiple points during pregnancy and with outcomes assessed by trained investigators blind to the study hypothesis would assist in gathering data that can be compared.

The health outcomes assessed in this work show that Māori and Pasifika children are the most affected population groups in New Zealand. The reasons for this are likely multifactorial and are incompletely understood and described in the wider New Zealand health literature. Within the context of this review, another important gap identified was the lack of New Zealand based research, that would naturally include Māori and Pasifika participants.

Increased clarity over the best method to assess and measure food and/or supplement associations allowing for the interplay of differing nutrients and how these complement each other is needed to allow for better informed dietary and supplement recommendations to be made.

Further research with a focus on how to deliver nutrition advice in pregnancy in a way that women will engage with is needed to improve the health outcomes of both mother and developing fetus.

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Appendix 1:

Systematic review protocol

Systematic review protocol

Background

One of the major findings originating from "The Growing up in New Zealand" longitudinal birth cohort study reported that only three percent of pregnant New Zealand women adhere to the recommended guidelines for healthy eating in pregnancy across all four food groups (Moreton et al. 2014). These recommendations were introduced by the New Zealand Ministry of Health and are distributed in pamphlets that are offered to women during pregnancy (Ministry of Health, 2014). With this statistic in mind, the literature was explored to identify information concerning the impact of maternal diet on early development and formation of the human gut and immunology.

The work of Barker and colleagues (2002) reported associations between the maternal environment during pregnancy and the lifetime health outcomes of offspring. Neu's (2015) work challenged the well accepted theory that the fetal gut was sterile at birth and describes the impact and influence of the maternal microbiome on the developing fetus. Neu also reported that maternal intestinal microbes could be found in the fetus and uterus, further highlighting the importance of the maternal microbiome which is directly affected by maternal diet. The presence of these microbes in the amniotic sac led to the hypothesis that the fetal immune system develops within the womb and that the swallowing of amniotic fluid is one of the initial mechanisms by which the gut is prepared and colonised to promote establishment of a healthy microbiome (Campbell, Boyle, Thornton, & Prescott, 2015; Neu, 2015; Thum et al., 2012). This swallowing of amniotic fluid occurs prior to twelve weeks'

gestation and increases during development (Aikat, Roy & Bhattacharya, 2016). Fetal T cells develop during the second trimester making this gestational stage one of critical importance in the development of the immune system and one of elevated susceptibility to epigenetic changes due to environmental influences (Jenmalm & Duchén, 2013). West Jenmalm and Prescott (2015) report that it is likely that both pre- and postnatal microbial stimulation are important factors that contribute to optimal Th1 and T regulator pathway development. Immune development is, therefore, epigenetically regulated and with strengthening interest in the potential to restore and rebalance immune development to enhance neonatal immune responses.

These factors are all interlinked with a common theme being the impact of maternal diet on fetal development. Harding and Johnston (1995) state maternal nutrition during pregnancy impacts fetal growth and the development of the physiological functions of all organ systems making nutrition the most influential environmental factor in the development of the fetus. What has been reinforced by this literature review is the importance of maternal diet in fetal immunological development and the lack of maternal uptake of recommended dietary guidelines. The need for a systematic review to support the knowledge base within this area and potentially improve nutrition information for pregnant women is also highlighted.

Summary of existing literature

Two systematic reviews exploring the impact of maternal diet on offspring allergies and atopy were identified firstly by Beckhaus et al. (2015), and secondly by Netting, Middleton, & Makrides (2014). The review by Beckhaus et al., did not include studies that measured maternal intake during lactation or vitamin or oligo-element supplementation of the pregnant women and identified and reviewed cohort studies only. Netting's work included diet during lactation but did not include studies that measured the effect of dietary supplements or intake expressed as nutrients. Various study methodologies were reported and included within the Netting review. The Beckhaus review specified asthma and wheeze during childhood as being the primary outcomes of interest with eczema, allergic rhinitis or other atopic condition as secondary outcomes. Netting et al. prespecified primary outcomes as child eczema, asthma, hayfever, and food allergy. Secondary outcomes were described as allergy

symptoms, atopy or atopic disorder, dyspnoea, hay fever (allergic rhinitis or allergic rhinoconjunctivitis), wheeze (and recurrent wheeze), cough, food hypersensitivity (IgE – mediated food allergy or food intolerance), and sensitization (e.g., milk, egg, nut, food, inhalant).

Research question and aims

This review aims to evaluate research that has investigated the question of whether diet (food-based or supplement) in pregnancy or lactation affects allergy and atopy in offspring. I will analyse the findings of the studies reviewed and aim to use those findings to inform maternal education and further research in New Zealand.

Methods

Search strategy

Databases to be utilised in the search include: PubMed via helicon (advanced search), ProQuest (MEDLINE) via helicon, CINAHL Complete (EBSCO host via helicon), The Cochrane Library, The Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar. Limits were "humans". The key search terms were 'diet' or 'supplements', 'pregnancy' or 'lactation', 'allergy' or 'atopy' or 'asthma; NOT 'elimination' or 'avoidance'. The studies were restricted to studies published in English only.
Other sources included are The Liggins Institute's research themes and recent publications, World Health Organisation (WHO) website, clinical trials databases, published proceedings of recent conferences/symposiums attended or aware of and hand searching through the reference lists of the studies and reviews already identified.

Screening and selecting studies
Studies

The included studies will be randomised controlled trials and cohort studies in the English language.

Participants

Pregnant or lactating women with outcomes assessed in the offspring.

Interventions

Assessment of maternal diet or supplement intake during pregnancy or lactation using a systematic recording of intake.

Outcome measure categories

Asthma, wheeze, eczema and hay fever are the outcomes of interest identified for this work. The titles and abstracts of the studies identified will be screened using the search strategy and screening criteria outlined above ensuring that any studies that may be questionable for inclusion remain included for full text assessment. The full text assessment will then be undertaken with any uncertain for inclusion or exclusion studies being reviewed by my supervisor with reasoning for exclusion documented. This method of screening and selecting studies is acceptable for a master's thesis systematic review but will mean that it will not be able to be published as the screening by two or more people during this process is a pivotal part of the systematic review process. This limitation will be addressed in the thesis.

Data extraction

The Cochrane Public Health Group template for data extraction will be used for the randomised controlled trials and an adapted version for the cohort studies. The tables are displayed in Table [] and []. Two pilot RCT and five pilot cohort data extractions will be completed to ensure that the template is understood and is fulfilling the purpose. These will be reviewed by the primary supervisor and alterations will be made at this point if necessary.

Cochrane Public Health Group Data Extraction and Assessment Template RCT

Study ID:	**Report ID:**	Date form completed:
First author:	Year of study:	Data extractor:
Citation:		

1. General Information

Publication type Journal Article ☐ Abstract ☐ Other (specify e.g. book chapter) _____	
Country of study:	
Funding source of study:	Potential conflict of interest from funding? Y / N / unclear

2. Study Eligibility

Study Characteristics			**Page/ Para/ Figure #**
Type of study RCT	☐ Randomised Controlled Trial (RCT)	http://ajcn.nutrition.org/	
	Does the study design meet the criteria for inclusion? Yes ☐ No ☐ →**Exclude** Unclear ☐		
	Description in text:		
Participants Pregnant or lactating mothers with outcomes assessed in offspring	Describe the participants included:		
	Are participants defined as a group having specific social or cultural characteristics?	Yes ☐ No ☐ Unclear ☐ Details:	

	How is the geographic boundary defined?	Details: Specific location (e.g. state / country):	
	Do the participants meet the criteria for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐	

Types of intervention Measured supplement or dietary intake.	Strategies included in the intervention			
	Focus of the intervention			
	Does the intervention meet the criteria for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐		
Duration of intervention	Start date:	Stop date:	Intervention duration:	
	Is the duration of intervention adequate for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐		
Types of outcome measures Offspring health outcomes of asthma, wheeze, eczema and allergic rhinitis.	List outcomes:			
	Outcome measured at a population level or individual level?	Details:		
	Do the outcome measures meet the criteria for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐		

Summary of Assessment for Inclusion

Include in review ☐ Exclude from review ☐	
Independently assessed, and then compared? Yes ☐ No ☐	Differences resolved Yes ☐ No ☐
Request further details? Yes ☐ No ☐	Contact details of authors:

Notes:

DO NOT PROCEED IF PAPER EXCLUDED FROM REVIEW

3. Study details

Study intention	**Descriptions as stated in the report/paper**	**Page/ Para/ Figure #**
Aim of intervention	*What was the problem that this intervention was designed to address?*	
Aim of study	*What was the study designed to assess? Are these clearly stated?*	
Equity pointer: Social context of the study	*e.g. was study conducted in a particular setting that might target/exclude specific population s? See also Inclusion/exclusion criteria under Methods, below.*	
Start and end date of the study	*Identify which elements of planning of the intervention should be included*	
Total study duration		

Methods	**Descriptions as stated in the report/paper**	**Page/ Para/ Figure #**
Method/s of recruitment of participants		

(How were potential participants approached and invited to participate? Where were participants recruited from? Does this differ from the intervention setting?)		
Inclusion/exclusion criteria for participation in study		
Representativeness of sample: Are participants in the study likely to be representative of the target population?		
Total number of intervention groups		
Assumed risk estimate (*e. baseline or population risk noted in Background)*	*References:*	
Sample size calculation: What assumptions were made? Were these assumptions appropriate?	*(Yes/No/Unclear)*	
What was the unit of randomisation? Allocation by individuals or cluster/groups		
What was the unit of analysis? **Is this the same as the unit of randomisation?**	*(Yes/No/Unclear)*	
Statistical methods used and appropriateness of these methods	*(Check with your statistician if unsure about appropriateness)*	

Results

Participants *Include if relevant*	**Include information for each group (i.e. intervention and controls) under study**	**Page/ Para/ Figure #**
• What percentage of selected individuals agreed to participate?		
• Total number randomised		
• Number allocated to each intervention group (no. of individuals)		
• Where there any significant baseline imbalances?	Yes ☐ No ☐ Unclear ☐ Details:	
• Number and reason for (and sociodemographic differences of) withdrawals and exclusions for each intervention group		
• Were patients who entered the study adequately accounted for?		
• What percentage of patients completed the study?		
• What percentage of participants received the allocated intervention or exposure of interest?		
• Is the analysis performed by intervention allocation status (intention to treat) rather than the actual intervention received? Have any attempts been made to impute missing data?		
• Age (median, mean and range if possible)		
• Sex		

• Race/Ethnicity		
• Principal health problem (incl. stage of illness)		
• Diagnostic criteria		
• Co-morbidity		
• Other sociodemographics (e.g. Educational level, literacy level, socio-economic status, first language. Also consider possible proxies for these e.g. low baseline nutritional status)		
• PROGRESS categories reported at baseline (indicate letters of those reported: Place of residence, race, occupation, gender, religion, education, SES, social capital)		
Subgroups	*Enter a description of any participant subgroups from this paper to be analysed in the review.*	

Intervention Group 1

Group name:	*(State brief name for this intervention group.)*	**Page/ Para/ Figure #**
Details of intervention or control condition (*Include if relevant in sufficient detail for replication)*		

• Setting *eg multicentre, university teaching hospitals, rural, metropolitan, school, workplace, community, GP clinic, etc.*		
• Content (list the strategies intended and delivered)		
• Did the intervention include strategies to address diversity/disadvantage?	*Enter a description of any relevant strategies*	
• Delivery (e.g. Stages (sequential or simultaneous), timing, frequency, duration, intensity, fidelity – process indicators)		
• Providers (who, number, education/training in intervention delivery, ethnicity etc. if potentially relevant to acceptance and uptake by participants		
• Co-interventions		
Duration of intervention		
Duration of follow-up		
Subgroups	*Enter a description of any intervention subgroups from this report to be analysed in the review.*	

Do the authors describe any political or organisational context?	*List relevant dot points*	
Was a process evaluation conducted?	*What components were included in the process evaluation? (e.g. dose, frequency, consistency, implemented as intended etc)*	
Control/comparison (what information is provided about what the control or comparison group received?)	*Enter a description of what was provided for the control group, if applicable*	

Outcomes

Question	**Outcome 1**	**Page/ Para/ Figure #**	**Outcome 2**	**Page/ Para/ Figure #**
Is there an analytic framework applied (e.g. logic model, conceptual framework)?				
Outcome definition (with diagnostic criteria if relevant)				
Type of outcome: Is this a modifiable variable (Community level, neighbourhood level, individual level) or desired health outcome				
Time points measured				
Time points reported				
Is there adequate latency for the outcome to be observed?				

Is the measure repeated on the same individuals or redrawn from the population / community for each time point?				
Unit of measurement (if relevant)				
For scales – upper and lower limits and indicate whether high or low score is good				
How is the measure applied? Telephone survey, mail survey, in person by trained assessor, routinely collected data, other				
How is the outcome reported? Self or study assessor				
Is this outcome/tool validated?				
…And has it been used as validated?				
Is it a reliable outcome measure?				
Is there adequate power for this outcome?				
Were PROGRESS categories analysed by outcome? Indicate the letters of those that outcomes were analysed by (place of residence, race, occupation, gender, religion, education, SES, social capital)				

Results

For RCT/CCT

Dichotomous **outcome**

page/para/fig

Comparison		
Outcome		

Subgroup					
Timepoint					
Results	**Intervention**		**Comparison**		
	Events	No. participants	Events	No. participants	
No. of missing participants and reasons					
Any other results reported					
Reanalysis required? (specify - (e.g. correlation adjustment)					
Reanalysis possible?	*yes/no/unclear*				
Reanalysed results					

Other relevant information

Were outcomes relating to harms/unintended effects of the intervention described? Include any data for these in the outcomes tables above		
Potential for author conflict *i.e. evidence that author or data collectors would benefit if results favoured the intervention under study or the control*		
Key conclusions of the study authors		
Could the inclusion of this study potentially bias the generalisability of the review? Equity pointer: Remember to consider whether disadvantaged populations may have been excluded from the study.		
Is there potential for differences in relative effects between advantaged and disadvantaged populations? (e.g. are children from lower income families less likely to wear bicycle helmets)		
Are interventions likely to be aimed at the disadvantaged? (e.g. school meals aimed at poor children).		

Issues affecting directness (*Note any aspects of population, intervention, etc. that affect this study's direct applicability to the review question)*	
References to other relevant studies	
Additional notes by review authors	
Correspondence required for further study information (from whom, what and when)	

Risk of bias assessment

Domain	**Review authors' judgement***	**Description**	**Page/ Para/ Figure #**
Was the allocation sequence adequately generated?	**Yes / No / Unclear**	***Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.***	
Was allocation adequately concealed?	**Yes / No / Unclear**	***Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.***	
Were baseline outcome measurements similar?	**Yes/No/Unclear**	***Note whether baseline outcome measurements were reported and whether there were any important differences between groups. If***	

		there were important differences between groups, note whether appropriate adjusted analysis was performed to account for this.	
Were baseline characteristics similar?	**Yes/No/Unclear**	***Note whether baseline characteristics were reported and whether there were any important differences between groups.***	
Were incomplete outcome data adequately addressed? ***Assessments should be made for each main outcome (or class of outcomes).***	**Yes / No / Unclear**	***Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.***	
Was knowledge of the allocated intervention adequately prevented during the study? ***Separate assessments should be made for relevant groups of***	**Yes / No / Unclear**	***Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective, or whether blinding was appropriate.***	

people involved in the study i.e. participants, outcome assessors, investigators, data assessors etc		• Participants – yes, no, unclear *[record supporting statement from study]*. • Investigators – yes, no, unclear *[record supporting statement from study]*. • Outcomes assessors – yes, no, unclear *[record supporting statement from study]*. Data assessors – yes, no, unclear *[record supporting statement from study]*.	
Was the study adequately protected against contamination?	**Yes/No/Unclear**	***State whether and how the possibility of contamination was minimised by the study design/implementation.***	
Are reports of the study free of suggestion of selective outcome reporting? ***Assessments should be made for each main outcome (or class of outcomes).***	**Yes / No / Unclear**	***State how the possibility of selective outcome reporting was examined by the review authors, and what was found.***	

Other sources of bias •	**Yes / No / Unclear**	***State any important concerns about bias not addressed in the other domains in the tool.***	

Cochrane Public Health Group Data Extraction and Assessment Template Cohort group

Study ID:	**Report ID:**	Date form completed:
First author:	Year of study:	Data extractor:
Citation:		

1. General Information

Publication type Journal Article ☐ Abstract ☐ Other (specify e.g. book chapter)	
Country of study:	
Funding source of study:	Potential conflict of interest from funding? Y N unclear

2. Study Eligibility

Study Characteristics			**Page/ Para/ Figure #**
Type of study Cohort		☐ Cohort study ☐ Retrospective ☐ Prospective	

	Does the study design meet the criteria for inclusion? Yes ✓ No ☐ →**Exclude** Unclear ☐		
	Description in text:		
Participants Pregnant or lactating women with outcomes assessed in offspring	Describe the participants included:		
	Are participants defined as a group having specific social or cultural characteristics?	Yes ☐ No ☐ Unclear ☐ Details:	
	How is the geographic boundary defined?	Details: Specific location (e.g. state / country):	
	Do the participants meet the criteria for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐	

Types of measurement Measured dietary or supplement intake.	Strategies included in the study			
	Focus of the study			
	Does the intervention meet the criteria for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐		
Timeframe of study	Gestation at recruitment:	Timing of diet assessment:	Age at follow up:	
	Is the timeframe of the study adequate for inclusion?	Yes ☐ No ☐ →**Exclude** Unclear ☐		
	List outcomes:			

Types of outcome measures Offspring asthma, wheeze, eczema and allergic rhinitis	Outcome measured at a population level or individual level?	Details: individual	
	Do the outcome measures meet the criteria for inclusion?	Yes ☐ No ☐ **→Exclude** Unclear ☐	

Summary of Assessment for Inclusion

Include in review ☐ Exclude from review ☐	
Independently assessed, and then compared? Yes ☐ No ☐	Differences resolved Yes ☐ No ☐
Request further details? Yes ☐ No ☐	Contact details of authors:
Notes:	

DO NOT PROCEED IF PAPER EXCLUDED FROM REVIEW

3. Study details

Study intention	**Descriptions as stated in the report/paper**	**Page/ Para/ Figure #**
Aim of study	*What was the study designed to assess? Are these clearly stated?*	
Equity pointer: Social context of the study	*e.g. was study conducted in a particular setting that might target/exclude specific population s? See also Inclusion/exclusion criteria under Methods, below.*	
Start and end date of the study	*Identify which elements of planning of the intervention should be included*	

Total study duration		

Methods	**Descriptions as stated in the report/paper**	**Page/ Para/ Figure #**
Method/s of recruitment of participants *(How were potential participants approached and invited to participate? Where were participants recruited from?)*		
Inclusion/exclusion criteria for participation in study		
Representativeness of sample: Are participants in the study likely to be representative of the target population?		
Total number of outcomes measured		
Variables (*outcomes, exposures, predictors, potential confounders and effect modifiers).*		
Describe how each outcome was measured		
Study size explanation		
Bias		
Quantitative variables (*how was quantitative data grouped and is it defined in study?)*		
Statistical methods used and appropriateness of these methods	*(Check with your statistician if unsure about appropriateness)*	

Results

Participants *Include if relevant*	**Include information for each group (i.e. intervention and controls) under study**	**Page/ Para/ Figure #**
• What percentage of selected individuals agreed to participate?		
• Total population at the start of the study		
• Number and reason for (and sociodemographic differences of) withdrawals and exclusions		
• Were participants who entered the study adequately accounted for?		
• What percentage of participants completed the study?		
• Age (median, mean and range if possible)		
• Sex		
• Race/Ethnicity		
• Gestation when recruited		
• Other sociodemographics (e.g. Educational level, literacy level, socio-economic status, first language. Also consider possible proxies for these e.g. low baseline nutritional status)		

Cohort Group *(copy and paste table as needed)*

Group name:		**Page/ Para/ Figure #**
Details of cohort conditions *(Include if relevant in sufficient detail for replication)*		
• Setting *eg multicentre, university teaching hospitals, rural, metropolitan, school, workplace, community, GP clinic, etc.*		
• Content (list the strategies intended and delivered)		
• Delivery (e.g. Stages (sequential or simultaneous), timing, frequency, duration, intensity, fidelity – process indicators)		
• Providers (who, number, education/training in intervention delivery, ethnicity etc. if potentially relevant to acceptance and uptake by participants		
Duration of cohort follow-up and times of previous follow up		
Were any partnerships referred to?	*List these as dot points*	

Outcomes

Question	**Outcome 1**	**Page/ Para/ Figure #**	**Outcome 2**	**Page/ Para/ Figure #**
Outcome definition (with diagnostic criteria if relevant)				

Type of outcome: Is this a modifiable variable (Community level, neighbourhood level, individual level) or desired health outcome				
Time points measured				
Time points reported				
Is there adequate latency for the outcome to be observed?				
Unit of measurement (if relevant)				
How is the measure applied? Telephone survey, mail survey, in person by trained assessor, routinely collected data, other				
How is the outcome reported? Self or study assessor				
Is this outcome/tool validated?				
…And has it been used as validated?				
Is it a reliable outcome measure?				
Is there adequate power for this outcome?				

Results

For Cohort Studies

Association:				
Outcome:				
Timepoint				
Measure 1	Measure 2	Measure 3	Measure 4	Measure 5

Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Number of missing participants and reasons:									
Any other results reported:									
Adjustments made:									
Presented as:									

Other relevant information

Potential for author conflict *i.e. evidence that author or data collectors would benefit if results favoured the intervention under study or the control*		
Key conclusions of the study authors		
Limitations discussed		
Could the inclusion of this study potentially bias the generalisability of the review? Equity pointer: Remember to consider whether disadvantaged populations may have been excluded from the study.		
Is there potential for differences in relative effects between advantaged and disadvantaged populations? (e.g. are children from lower income families less likely to wear bicycle helmets)		
Are interventions likely to be aimed at the disadvantaged? (e.g. school meals aimed at poor children).		
Issues affecting directness (*Note any aspects of population, intervention, etc. that affect this study's direct applicability to the review question)*		
References to other relevant studies		

Additional notes by review authors	
Correspondence required for further study information (from whom, what and when)	

Quality assessment of included studies

The quality assessment of the RCT studies is included with the RCT data extraction table above and is based on the Cochrane risk of bias table. The cohort studies will be assessed using the Newcastle-Ottawa Scale which is shown in table []

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

- a) truly representative of the average pregnant (country of study) women in the community*
- b) somewhat representative of the average pregnant (country of study) women in the community –
- c) selected group of users eg nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort*
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (e.g., surgical records)*
- b) structured interview*
- c) written self report
- d) no description

4) Demonstration that outcome of interest was not present at start of study

- a) yes
- b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for maternal history of allergy or atopy *
- b) study controls for maternal smoking during pregnancy* (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blind assessment*
- b) record linkage*
- c) self report
- d) no description

2) Was follow-up long enough for outcomes to occur

- a) yes (select an adequate follow up period for outcome of interest) *
- b) no

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for*
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > 70% follow up, or description provided of those lost *
- c) follow up rate < 60% and no description of those lost
- d) no statement

/9 ★

Adapted from Wells, G. A, Shea, B., O'Connel, D. et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www ohrica/programs/clinical_epidemiology/oxford htm 2009 Feb 1

Levels of evidence, error and bias

The Grades of recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) (Guyatt et al., 2008, Guyatt et al., 2011) developed a system to

assign grades to the quality of evidence. This approach groups studies according to the association and the outcome of interest and then assigns levels of evidence for each grouping of studies. The GRADE Summary of Findings tables will be used to present the quality and the findings within each grouping of studies. The levels of quality will be shown according to the GRADE approach quality ratings.

Table []: Levels of quality of a body of evidence in the GRADE approach

Underlying methodology	**Quality rating**
Randomised trials; or double upgraded observational studies	High (further research is very unlikely to change our confidence in the estimate of effect)
Downgraded randomised trials; or upgraded observational studies	Moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate)
Double-downgraded randomised trials; or observational studies	Low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate)
Triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports	Very low (an estimate of effect is uncertain)

Adapted from Schünemann, H.J., Oxman, A.D., Vist, G.E., Higgins J.P.T., Deeks, J.J., Glasziou, P., Guyatt G.H. Interpreting results and drawing conclusions. In: J.P.T. Higgins, & S. Green (Eds), *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0 updated March 2011). Retrieved from http://handbook.cochrane.org/

Data analysis

The summary of findings table mentioned above will inform much of the analysis. This table analyses the quality and findings of the studies reviewed according to their groupings by methodology, association and outcomes.

If there is sufficient homogeneity within the studies a meta-analysis will be performed. If there is not sufficient homogeneity, then a narrative synthesis will be undertaken.

Acknowledgements

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