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Narrative Review

The role of milk feeds and other dietary supplementary interventions in preventing allergic disease in infants: Fact or fiction?

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SUMMARY

Exclusive breastfeeding ideally up to 6 months of life is the feed of choice for infants and should be promoted by healthcare professionals. However, when human milk is not sufficient or not available, infant formula, generally cow's milk-based, meeting strictly regulated nutritional and safety requirements, are recommended. Human breastmilk feeding has a positive health impact for both mother and child, but there is limited evidence that it has a long-term protective effect on the development of allergic disease. Some studies have found an association of an increased risk to develop cow's milk allergy with early exposure to cow's milk protein in formula milk. As a result, over the last 30 years, partially hydrolyzed formulas (pHF) have gained popularity and, more recently, become embroiled in a debate about their role in the primary prevention of allergic outcomes. Similar debates exist in regards to the potential preventative effects of pre-, pro- and synbiotics as well as nutritional factors, notably vitamin D and omega-3 fatty acids. This paper aims to critically address these aspects, drawing information from published data interpreted by an international expert group in paediatrics, allergy, gastro-intestinal diseases and nutrition.

This group of experts emphasize that human milk is the optimal source of infant nutrition. With regards to pHFs, whilst no harm has been shown with their use and some studies have suggested potential benefit preventing atopic dermatitis in at risk infants, there is insufficient evidence for or against their routine recommendation for primary allergy prevention. The method of hydrolysis differs for every formula. There is insufficient evidence to recommend supplementation with vitamin D, omega-3 LCPUFA, specific prebiotic oligosaccharides or specific probiotic strains during pregnancy, lactation and early life to prevent the development of allergic disease in children. There remains a need for well-designed trials with the currently commercialised pHFs and supplements to allow for better clarity and evidence-based recommendations.

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1. Introduction

Allergic disease has become a major worldwide health concern [1]. Cow's milk allergy (CMA) is one of the most common food allergies in early infancy and forms an important part of the allergic march [1]. Early life inflammation, as occurs in food allergy, may also predispose and contribute to other conditions such as visceral hypersensitivity and functional gastrointestinal disorders [2]. The prevention of CMA should, therefore, in theory, reduce the overall burden of allergic diseases [3,4]. In health care, prevention, if available and feasible, is considered preferable to treatment for most disorders, especially in conditions where subsequent diagnosis and management may be challenging. Primary prevention aims at preventing allergic sensitization and the development of allergic symptoms, whilst secondary prevention focusses on the prevention of progression along the atopic march [5]. Given that the induction of oral tolerance in infants who develop CMA is not yet mainstream practice and since its efficacy is questioned [6], primary prevention remains the preferred option [1].

CMA can be divided into immunoglobulin E (IgE) and non-IgE mediated CMA. In IgE mediated allergy, symptoms have an immediate onset following ingestion, and therefore a clear relationship to the allergen exists with sufficiently reliable diagnostic tests. Conversely, the diagnosis of non-IgE CMA is challenging because of the absence of a clear association with allergen ingestion, specific symptoms or a reliable diagnostic test [1]. As a consequence of this diagnostic ambiguity determining the incidence of true CMA is fraught with difficulties [4,7] and CMA management guidelines have been challenged because they have been deemed to i) be promoting over-diagnosis; ii) negatively impact on breastfeeding, and iii) be influenced by industry [8,9].

CMA has been found to co-occur with other allergies (e.g. asthma, atopic dermatitis) and immunological hypersensitivity disorders, suggesting a shared genetic etiology or a common pathogenic mechanism [10]. Atopic dermatitis, often linked to food allergies such as CMA, is the most common allergic manifestation in infants and young children, and therefore its occurrence is often the main criterion for evaluation of efficacy of clinical trials aimed at reducing allergy burden in infancy [3]. Nutritional intervention soon after birth with a partially hydrolyzed formula (pHF) instead of formula with intact protein was reported to reduce the cumulative incidence of atopic dermatitis up to 16 years of age and, as a consequence, also to reduce health care costs for healthy, high-risk, non-exclusively breastfed infants [11]. In keeping with this, pHFs have been positioned by infant formula manufacturers for the prevention of allergic disease for both primary and secondary prevention [5] in the absence of breastfeeding or in addition to breastfeeding if needed in infants at risk of allergy.

This paper aims to critically reflect on the published data and its interpretation regarding primary prevention of allergic diseases, focusing on the role of pHFs but also reviewing the data on supplementation of the pregnant woman and breastfeeding mother or infant with prebiotics, probiotics, vitamin D and omega-3 fatty acids on the allergy risk for the infant. The use of these dietary components for secondary prevention and the management of functional gastrointestinal disorders is not part of this critical review.

2. Human milk: best feeding and role in allergy prevention

Exclusive breastfeeding is the best and unequalled source of nutrition for optimal growth and development of infants [12]. A meta-analysis published by the Lancet breastfeeding series group, concluded that human milk was associated with protection against

childhood infections, an increase in cognitive function, and, a reduced risk of developing overweight and diabetes. Whilst there is certainty in the benefits of human milk in many areas, the evidence for prevention of allergy is inconsistent [13]. CMA manifests as IgE and non-IgE mediated allergy [14]. Many studies mainly focused on IgE mediated CMA, found that the incidence of CMA is significantly lower in infants exclusively breastfed compared to those fed cow's milk based infant formula with intact protein (<0.5 % vs 2–7.5%), with an incidence of up to 3% in the first year of life [15–18]. In a meta-analysis, the prevalence of CMA as defined by a positive oral food challenge was 0.6% (95% confidence interval [CI]: 0.5–0.8) [19]. CMA has been reported to account for 12–16% of food allergy in French children [20]. Regional differences with Europe were reported [4]. However systematic reviews and meta-analyses concluded that there was absence of evidence for protective effect for food allergy or atopic dermatitis [21–24]. This leads to the hypothesis that some human milk composition may be more suitable than others for food allergy prevention in offsprings [25]. Human milk oligosaccharides (HMOs) and probiotic components of human milk modulate the immune development, gut inflammation and microbiota of the offspring conditioning its allergy susceptibility, and will be discussed in the part on prebiotics and probiotics [26,27].

Human milk is a source of oral exposure to the infant of a wide variety of food allergens such as peanut, wheat, cow-milk and egg-derived allergens and thereby could influence allergic outcomes in offspring [25,28]. There is a great variability in regards to levels of allergens in human milk, which range between pg to ng/ml, in contrast to much higher levels of allergens in food such as beta-lactoglobulin that is found in mg/ml in cow milk. Currently, the mechanisms involved in the determination of the amount of food allergens present in human milk are unknown. In a recent publication Munblit et al. estimated that in 99% of infants with proven CMA, the breast milk of their cow's milk-consuming mothers contained insufficient milk allergen to trigger an allergic reaction [9]. This indicates there is very low risk for a breastfed infant to experience cow milk allergy symptoms while breastfed. Furthermore, mechanistic studies in mice demonstrated the concept of possible immune tolerance induction to food allergen in human milk. Data showed that exposure of offspring to very low levels of allergen (e.g. <1 ng/mL of egg derived antigen, ovalbumin) together with immune modulators found in human milk led to allergy prevention [29]. Recent birth cohort data further validated this concept [30].

There is also evidence that proteases, predominantly plasmin and trypsin, present in human milk release hundreds of partially pre-digested proteins and numerous bioactive peptides derived from milk proteins [32]. Both plasmin and trypsin are active within the mammary gland and remain active in the infant's stomach where they further contribute to human milk protein digestion [33]. As a result, human milk contains more than 1100 unique peptides derived from 42 milk proteins within the mammary gland and includes 306 potential bioactive peptides [32]. The total amount of peptides in full-term human milk has been estimated to be in average of 11 mg/L, which is around 1000 times lower than the 11–20 g/L true protein in human milk [34–36]. No intact cow's milk gene products were detected in human milk by nanoflow-HPLC-tandem mass spectrometry analysis and Western blotting with anti-beta-lactoglobulin antibody, but dot-blot analysis confirmed the occurrence of beta-lactoglobulin fragments in the enriched peptide fraction [37]. Thus, one could speculate that in addition to the presence of food-derived allergens in human milk, their digestion and the generation of tolerogenic versus immunogenic peptides will condition immune tolerance in breastfed offspring.

In summary, there is no clear evidence that breast-feeding, per se, prevents the development of allergic disease although there is some data pointing to some specific human milk composition(s), which may establish protection. Inter-individual variations of allergens and co-factors in human milk may underlie inconsistent observations on protection in breastfed offspring. Bias may also be induced by lack of randomisation regarding breastfeeding: “very atopic parents” may prefer breastfeeding above formula feeding, what may have a negative impact on the preventive effect of breastfeeding. Future research will need to uncover maternal interventions leading to a human milk composition that is adapted to our modern environment and affords protection from allergy in offspring.

3. Whole cow's milk protein-based infant formula and allergy prevention?

Cow's milk based infant formula with intact protein has historically been considered the first choice for feeding infants who are not exclusively breastfed.

Recent literature suggests that sensitization to food allergens, including CMA and anaphylaxis, may be reduced by avoiding exposure to cow milk antigen for at least the first 3 days of life [38]. However, other papers have contradicted these findings and suggest that exposure to pasteurized fresh cow milk or infant formula with intact protein during the first two weeks of life appears protective for IgE-mediated CMA and promote the acquisition of tolerance [39–43]. A randomized controlled trial (RCT) in infants aged 1–2 months showed a higher incidence of CMA in the group on breast milk with soy formula than in the group receiving breast milk and cow milk based formula (RR 0.12, 95% CI 0.01–0.50; $P < .001$) [44].

According to the Enquiring About Tolerance (EAT) study on a general paediatric population, early introduction of whole cow's milk protein (at the age of 4 months) did not increase the risk of CMA [45]. Findings from the KOALA study indicated that the later the introduction of cow's milk products, the higher risk for eczema [46]. In addition, a delayed introduction of other food products was associated with an increased risk for atopy development at the age of 2 years [46]. None of these studies, however, specifically addressed non-IgE mediated allergy. A systematic review by the European Academy of Allergy, Clinical Immunology Food Allergy, Anaphylaxis Guidelines Group concluded that avoiding conventional cow's milk-based formula may not reduce CMA in infancy or early childhood when the formula is consumed on a recurring basis [47].

In summary, the effect on allergy prevention of early introduction of cow's milk protein-based infant formula during the first three months of life remains unclear, although it formula feeding will have an impact on the duration of exclusive breastfeeding [48]. The role of short-term supplementation with cow's milk in the first days of life on the development of CMA is still debated.

4. Partially hydrolysed cow's milk formula and infant nutrition

pHFs have been commercially available since the 80s. Although there is a lack of agreement regarding the criteria on which to base the classification of hydrolysates, pHF are usually defined as formulas that contain oligopeptides with a molecular weight of generally less than 5 kD (range 3–10 kD) [24]. Several studies have been performed to evaluate the nutritional properties of pHFs. Trials focussing on anthropometry and nutritional serum parameters with different pHFs all demonstrated nutritional safety and adequacy when compared to breastfed infants [49–54]. A systematic review reported that limited data exist on the routine use of pHFs in non-exclusively breastfed infants [55]. Unanimous

consensus was obtained stating that pHFs – for which data were available – are as safe as standard formula with intact protein [55]. Partial hydrolysates have been accepted by the European Food Safety Authority (EFSA) and by the Food and Drug Administration (FDA) in the USA as a suitable protein source for standard infant formula. The EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) emphasises that the safety and suitability of each specific formula containing protein hydrolysates has to be established by clinical studies [56]. In this context, the EFSA Panel notes that one particular formula containing partially hydrolysed whey protein has been evaluated for its safety and suitability by the Panel [57] and has been authorised for use by the Commission Delegated Regulation (EU) 2016/127. Since the process of hydrolyses differs for every hydrolysate, each should be evaluated separately in clinical studies.

5. Partially hydrolysed cow's milk formula and allergy prevention: the rationale for its use from animal models

Different hydrolysed formulas consist of a wide range of peptide sizes, of methods of hydrolysis, and of allergenic characteristics of protein residuals influencing their overall allergenicity [58]. Hydrolyzed formulas may also contain tolerogenic peptides, which actively modulate the intestinal microbiota, permeability and tolerance through different mechanisms via stimulation of Toll-like receptors, increase of regulatory T-cells and cytokines (i.e. IL-10), and decrease some inflammatory molecules (i.e. cyclo-oxygenase 2, NF- κ B, IL-1 β , IL-8, IL-17, TNF- α) [37].

pHF appeared to prevent clinical symptoms in a CMA mouse model and enhance regulatory T and B cells [59]. Whey pHF only partially prevented the further development of CMA in a Th2-biased model [60]. A hydrolysate from both whey and casein fractions has been suggested to be more efficient in one study [60]. In mice fed with a whey protein concentrate or two different whey pHFs, sensitization and development of an allergic reaction were obviated [61]. The acceleration of cytokine release from the spleen and mesenteric lymph node cells or T-cell activation was not evident after beta-lactoglobulin re-exposure [61]. Oral administration of a pHF suppressed specific serum IgE and IgG anti-beta-lactoglobulin antibodies, as well as mediator release from rat mast cells and T-lymphocyte response [62]. This suppression was shown to be antigen-specific and dose-dependent. Oral tolerance induction by whey pHF in sensitized mice was associated with enhanced numbers of Foxp3 (+) regulatory T-cells in the mesenteric lymph nodes [63]. Prior to oral exposure, whey pHF prevented epicutaneous sensitization and subsequent allergic response to beta-lactoglobulin in mice [61]. Similar findings were reported for casein: sensitization and anaphylaxis reaction to casein were significantly suppressed in casein- or casein hydrolysate-fed mice compared to controls [64].

In summary, available data from studies in animal models support the view that pHF is able to induce specific oral tolerance, whereas extensively hydrolysed proteins may not [62]. Furthermore, they strongly suggest that partially hydrolysed casein and whey protein influences the immune system, decreasing the risk for allergenic sensitisation and increasing the development of tolerance.

6. Partially hydrolysed cow's milk formula and allergy prevention: the rationale for its use from studies in infants at high risk

6.1. Systematic reviews

A Cochrane review published in 2003, and updated in 2006, concluded that in high risk infants according to a positive family

history unable to be exclusively breast fed, there was limited evidence that, compared to a cow's milk formula, prolonged feeding with a hydrolysed formula reduced infant and childhood allergy and, specifically, infant CMA [65,66]. A 2018 update of the Cochrane review included additional studies to the previous reviews, and included studies with pHF of different manufacturers. It concluded that there was no evidence to support prolonged feeding with hydrolysed CMP formula compared with that containing intact protein for the prevention of allergic disease in infants [67]. According to the per protocol analysis, the risk ratio was 0.62 with a wide 95% CI ranging from 0.38 to 1.01 [67]. One should not neglect clinical significance when statistical data are interpreted: by consensus a CI crossing 1 is considered as "not beneficial". However, it is unlikely that a confidence interval from 0.38 to 0.99, which would have been considered as proof of benefit, has a different clinical meaning vs. a CI from 0.38 to 1.01. In both situations, the evidence for benefit or no benefit should be considered as extremely weak as very close to 1.00. It should be noted, however, that these figures render the strength of evidence for no benefit (or indeed for benefit) as weak at best. Moreover, it appears that the difference in the Cochrane analyses of 2003, 2006 to the 2018 Cochrane was mainly due to the inclusion of a single study, which found no evidence to support recommending the use of pHF at weaning for the prevention of allergic disease in high-risk infants [68]. This study had a number of key limitations in that it was single blinded, had a telephone interview as the primary endpoint, was published 21 years after initiation, and 16% of the enrolled infants never received the allocated formula and only 50% of infants received the allocated formula by four months of age [68]. Alexander and Cabana concluded in 2010, with regards to the use of a 100% whey pHF in infants, that there was evidence it reduced the risk of developing atopic dermatitis regardless of study design, infant population, follow-up time, or study location, particularly in those with a family history of allergy [69]. In the same year, another meta-analysis was published by Szajewska and Horvath, concluding that the use of this same pHF compared to standard formula was effective in allergy prevention in children at high risk for allergy at most time points, although a lack of methodological rigor was noted in many trials [70]. In 2017, the same authors reported a low certainty of evidence for considering the use of pHF as an option for reducing the risk of any allergic diseases, particularly eczema [71]. The analyses by Alexander and Cabana as well as Szajewska and Horvath focussed on only one type of a 100% whey pHF [69,71]. These effects are likely to be hydrolysate specific. Extrapolation of findings from one hydrolysate to another hydrolysate may therefore not be appropriate.

In 2018, a literature review including as well RCTs as non-RCTs, safety studies, observational studies and epidemiologic studies with a prospective or retrospective design suggested that the risk to develop atopic dermatitis from a population perspective, may be reduced in non-exclusively breastfed infants when supplemented with a specific whey pHF when compared to formula with intact protein during the first 4–6 months of life [72]. The risk of bias should be noted, however, given that among the primary authors are infant formula company employees.

Relevant to this, Boyle et al. identified 37 eligible intervention trials of hydrolysed formula reporting evidence of conflict of interest and high or unclear risk of bias in most studies of allergic outcomes and evidence of publication bias for studies assessing eczema and wheeze [73]. Overall, there was no consistent evidence that pHFs reduced the risk of allergic or autoimmune disorders in infants at high risk of these outcomes [73]. These findings are at least in part explained by: i) including studies with different hydrolysates; ii) allowing double interventions cohort studies; iii) including studies in high-risk and general populations, while not

including studies that were included in the 2009 Cochrane analysis; and iv) considering different end-points of the meta-analyses (Boyle et al. grouped participants who were aged at assessment 0–4, 5–14, and ≥ 15 years) [74]. Boyle and co-workers included in their meta-analysis a negative outcome from a trial they performed testing a specific prebiotic-supplemented pHF [74], which significantly impacted the overall results of the meta-analysis [73]. The differences between Boyle's study and outcomes of other studies may be explained by the following regarding the former: i) a different hydrolysate and thus different peptides were tested; ii) randomisation was done before the age of one month in many studies, thus not at birth as in almost all the other studies, implying that a number of infants had been fed a formula with intact protein before inclusion in the trial [74]. The incidence of eczema at 12 months was 28.7% in the formula fed groups but as high as 44% in the breastfed group [74]. Thus, the incidence of eczema was decreased in the formula groups as compared to the breastfed group [69]. On the other hand, the severity of the eczema was very mild given that the SCORAD scores, which range from 0 to 103, at 12 months were 14 (range 10–23) in the control and 14 (range 9–23) in the active group [74]. Only a few studies evaluated the effect of a pHF on CMA.

In all the systematic reviews detailed above, the strongest evidence comes from the German Infant Nutrition Intervention (GINI) study. The GINI-study, the longest and not-industry sponsored until the 10-year follow-up on the preventive effect of hydrolysates in high-risk children showed that early intervention using different hydrolysed formulas had variable preventative effects on asthma, allergic rhinitis and eczema up to 15 years of age: the cumulative incidence of eczema was reduced in the whey pHF group (in intention-to-treat analysis, RR 0.75, 95% CI 0.59–0.96) [75]. It should be noted, however, that despite the impressive design and long follow up, all the infant formulas tested in the GINI study differed from those currently in the market. Even if the process of hydrolysis may have remained the same, other components such as lipids and probiotics changed.

In summary, the observed effect on allergy prevention is not consistent in the different meta-analyses. This may be explained by varying inclusion criteria, study design and primary endpoints. There is some evidence that meta-analyses focussing on trials with a similar design and one selected hydrolysate may conclude that there is some effect on allergy prevention, mainly atopic dermatitis. However, many of the pHFs have significantly changed in composition since the trials were performed, implying that those findings may not be applicable to currently available formulas.

6.2. Guidelines (Table 1)

In 1999 a joint consensus report of the European Society for Paediatric Allergology and Clinical Immunology and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended, in bottle fed infants with a documented hereditary atopy risk (affected parent or sibling), exclusive feeding using a nutritionally complete formula with confirmed reduced allergenicity to decrease the incidence of adverse reactions to food, especially to cow's milk protein [76]. Five years later, in 2004, an extensive review by a paediatric expert group of the European Academy of Allergy and Clinical Immunology [10] recommended that breast feeding should be the first choice for all infants irrespective of atopic heredity and where this was not possible, formulas with documented reduced allergenicity should be used for at least 4–6 months [24,77,78]. These guidelines focused on food allergy and were updated in 2014, concluding that if breastfeeding is insufficient or not possible, infants at high-risk can be fed for the first 4 months with a hypoallergenic formula with a documented

Table 1
Guidelines of scientific societies.

Society year (ref)	Recommendation regarding pHF	Summary of evidence	Target population
EAACI 2014 [24] (addressed only IgE-mediated food allergy)	Documented HA formula	Outcome is formula specific	Infants with 1 or 2 parents and/or siblings with a history of allergic disease
CSACI 2014 (149)	No recommendation for or against	It is unclear whether formula-feeding in early infancy has any role in preventing allergic conditions other than atopic dermatitis, and also unclear whether formula feeding has any preventive effect long-term.	Infants who have a first degree relative with an allergic condition
SIPPS, SIAIP, SIP 2016 [147]	No recommendation for or against	There is a lack of evidence that hydrolyzed formula are effective in preventing allergic diseases. The lack of evidence of efficacy does not necessarily imply that some interventions may not be effective, but currently they can't be recommended.	At risk infants
APAPARI 2018 [85]	No recommendation for or against	Focus on complementary feeding.	Healthy infants with a family history of atopy or non-severe eczema.
BSACI 2018 [83]	Intact protein	Using a non-cow's milk based formula (such as soya) or a specialist "low allergy" or hypoallergenic formula has not been consistently shown to prevent food allergy.	High risk: severe eczema Atopic dermatitis or already has a food allergy
AAP 2019 [23]	No recommendation for or against	There is lack of evidence that partially or extensively hydrolyzed formula prevents atopic disease in infants and children, even in those at high risk for allergic disease	Infants with at least 1 first degree relative (parent or sibling) with documented allergic disease.
Middle East 2019 [86]	Documented HA	A proven safe and efficacious pHF is recommended when breastfeeding is not possible or inadequate to prevent allergy, mainly atopic eczema	At risk infant
ASCIA 2019 [82]	Intact protein	Hydrolysed formula is not recommended for the prevention of allergic disease.	Acknowledge that those with family history are at higher risk, but those without history also at risk, so guidelines for everybody

No recommendation: the guideline does not differentiate between intact protein or pHF; HA: hypo-allergenic; CM(A): cow's milk (allergy); (p)HF: (partially) hydrolysed formula; EAACI: European Academy for Allergology and Clinical Immunology; CSACI: Canadian Society of Allergy and Clinical Immunology; SIPPS: Italian Society of Preventive and Social Paediatrics; SIAIP: Italian Society of Paediatric Allergy and Immunology; SIP: Italian Society of Pediatrics; APAPARI: Asia Pacific Association of Pediatric Allergy, Respiriology & Immunology; AAP: American Academy of Pediatrics; BSACI: British Society of Allergy and Clinical Immunology; ASCIA: Asian Society of Clinical Immunology and Allergy.

preventive effect [79]. These guidelines are currently in the process of being updated.

In 2008, the American Academy of Pediatrics (AAP) concluded that there was modest evidence that atopic dermatitis may be delayed or prevented in early childhood by the use of pHFs, compared with cow's milk formula with intact protein [80]. In 2019, the AAP came to different conclusions and revised their 2008 recommendations, stating that there was a lack of evidence that pHFs prevent atopic disease in infants and children, even those at high risk for such disorders [23].

In 2017 the Academy of Breastfeeding stated that when donor human milk is not available or appropriate, protein hydrolysate formulas may be preferable to standard infant formula [81].

However, the Australasian Society of Clinical Immunology and Allergy concluded in 2016 and 2019 that pHF is not recommended for the prevention of allergic disease [82]. Furthermore, the equivalent British Society for Allergy and Clinical Immunology (BSACI) guideline concluded that there was no evidence to recommend infant formula with reduced allergenicity: "Mothers should continue to breastfeed whilst introducing solid foods, if possible" [83]. The equivalent Japanese guidelines also stated that there was insufficient evidence for the usefulness of hydrolysed milk in preventing the onset of food allergy [84]. The Asia Pacific Association of Pediatric Allergy, Respiriology & Immunology (APAPARI) consensus statement focused on complementary feeding and did not discuss hydrolysates [85]. A consensus of the Middle-East region, published in 2019, found pHF to be safe and efficacious for high risk infant when breastfeeding was not possible or insufficient to prevent allergy, mainly atopic eczema [86].

In summary, recent guidelines conclude that there is insufficient evidence to recommend pHFs for the prevention of allergic disease,

with the possible exception of atopic dermatitis as suggested by the results of the GINI study over a period of 16 years with the use of a specific hydrolysate.

7. Partially hydrolysed cow's milk formula for all non-breastfed infants?

Guidelines may be considered contradictory or confusing because they are intended for different target populations (Table 1). Whilst the Australian guidelines are intended for all infants, the guidelines of the British Society for Allergy and Clinical Immunology (BSACI) focus on infants with existing food allergy and/or atopic dermatitis. Also, the guidelines differ in their definitions of who is considered at risk for atopic disease.

Genetic predisposition, evaluated by a family history of atopic disease, is accepted to be a risk factor for a newborn to develop an atopic disease. However, family history of atopic disease identifies less than half of allergic infants [87,88]. In the general population, more infants without history of atopy in their families will develop atopy compared to infants with a positive family history, because the group of non-atopic families is larger. A challenging observation is the finding from the GINI study that an infant born into a family deemed 'non-atopic' at the time of enrolment, but one in which a parent/sibling subsequently becomes allergic later on, behaves the same way as a child with a positive family history at birth [89]. In other words, the genetic background which underpins the risk may be difficult to determine with accuracy at birth. Furthermore, not all allergic patients have a positive family history suggesting that factors other than genes and difficult to identify may be implicated in the development of allergic diseases. In Germany in the '90s, allergic children born to families without allergy risk were more

numerous than those born to families with mono- or bi-parental allergy risk [90] (Table 2). Moreover, the significant increase in allergic disease in 10 years time, as demonstrated by a recent Chinese study, strongly weakens the impact of the family history [91]. Therefore, the indication of the candidate population should consider predictive markers. Some possible neonatal predictors of development of allergic diseases are listed in Table 3.

In a French nationwide cohort study, the use of pHF at two months was not associated with a reduced risk of suffering any of the studied allergy-related symptoms up to the age of two years. In contrast, it appeared to associate with a higher risk of wheezing, food allergy and, to a lesser extent, eczema [92]. Studies on self-selected "exposures" (eg, breast-feeding, introduction of solid food) are well known to be vulnerable to reverse causation [93]. For example, skin symptoms present already in early life might lead to an extension of breast-feeding duration and presumably to a selection of hypoallergenic formula feeding [93].

Regardless of the effectiveness of preventive measures, recommended screening strategies for identifying populations at risk are not followed. Out of 428 French maternity wards included in the Allernaiss survey, only 59% reported to apply a screening strategy for allergic risk in newborns [94]. In cases of detected allergic risk, 90% of these units recommended a pHF in non-breastfed newborns. However, a major problem was the evident non-compliance of parents with this recommendation [95]. In this study, 32.8% of the 597 infants included presented an allergic risk; among the 283 aged under 4 months, 26% were exclusively breastfed and only 5.6% were fed with a pHF [95]. These data were confirmed by other data, also from France, showing that 50% of the infants born with a positive family history were not given a pHF [96].

Finally, the choice of infant formula also clearly relates to decision making around cost versus potential benefit. The cost of infant formula is, no doubt, of major importance in the decision-making process but cannot be discussed here given that the difference in cost between pHF and formula with intact protein differs substantially between countries.

In summary, in case an infant cannot be exclusively be breast fed, pHF is an alternative for cow's milk based infant formula; its use is also dependent on cost.

8. Extensive hydrolysates in non-breastfed infants and allergy prevention

8.1. Data from animal models

Elegant studies in mice demonstrated the need of the developing small intestine to be exposed to a wide source of intact dietary antigens to develop regulatory mechanisms. Feeding mice with a diet made only of amino-acids profoundly affected efficient oral tolerance mechanisms [97,98]. In mice fed an extensive hydrolysate, a suppressive milder effect compared to whey protein concentrate or pHFs, was observed during the development of the allergic reaction [61]. An extensive casein hydrolysate with *Lactobacillus* (L.) *rhamnosus* GG (the name *Lactobacillus rhamnosus* was recently changed to *Lactocaseibacillus rhamnosus* [99]; however, we continued to use the old name as this is how this probiotic is

named in all referenced literature), did not prevent CMA in a mouse model, despite a significantly enhanced humoral and cellular immune response after sensitization with cow milk protein [100]. However, data obtained from infant studies suggest faster acquisition of tolerance if *L. rhamnosus* GG is supplemented to an extensive casein hydrolysate [101]. This contradictory information suggests that extrapolation from data obtained in mouse models to the clinical situation harbors a risk for misguidance.

8.1.1. Data from studies in infants

The results of the 15-year follow-up of the GINI study confirm that the previously reported preventative effect of the extensive casein hydrolysate and whey pHF formulas on eczema are sustained until adolescence without a rebound phenomenon [75]. Among others, differences in exclusive breastfeeding rates and duration in the different study groups in the GINI study may have contributed to the differences in outcome [75]. Between 11 and 15 years, the prevalence of asthma was reduced in the casein based extensive hydrolysate group compared to cow milk formula (OR 0.49, 95% CI 0.26–0.89). Also, the cumulative incidence and prevalence of allergic rhinitis was lower in casein based extensive hydrolysate group (risk ratio (RR) 0.77, 95% CI 0.59–0.99 and OR 0.59, 95% CI 0.41–0.84, respectively [75]). The cumulative incidence and prevalence of eczema were reduced in the casein-based extensive hydrolysate group (RR 0.60, 95% CI 0.46–0.77, and OR 0.42, 95% CI 0.23–0.79, respectively). In high-risk children, early intervention using different hydrolyzed formulas has variable preventative effects on asthma, allergic rhinitis and eczema up to adolescence [75]. Other data suggested that an extensively hydrolysed whey formula was unable to achieve this goal [62,75]. According to the meta-analysis of Boyle et al., extensively hydrolysed formulae, casein and whey grouped together, is ineffective in the prevention of allergic disease [73]. Odds ratios for eczema at age 0–4, compared with standard cows' milk formula, were 0.84 (95% CI 0.67 to 1.07; I² = 30%) for pHFs; 0.55 (0.28–1.09; I² = 74%) for extensively hydrolysed casein-based formula; and 1.12 (0.88–1.42; I² = 0%) for extensively hydrolysed whey-based formula [73]. The AAP concluded in 2008 that there was modest evidence that extensively hydrolysed formula compared with cow milk formula with intact protein may delay or prevent atopic dermatitis in early childhood [80]. However, in 2019, the AAP concluded that extensive hydrolysates do not reduce the risk to develop allergic disease [23]. The Australasian Society of Clinical Immunology and Allergy wrote in 2016 and 2019 that extensively hydrolysed formula would not be recommended for the prevention of allergic disease [82]. Moreover, as we stated for the pHF, also the composition of the extensively hydrolysed formulas evaluated in most of the studies differ often from the ones in the market today. Moreover, extensive hydrolysates are much more expensive than formulas with intact protein or pHF, and are considered too expensive to be used in prevention. Last but not least, according to lessons learned from the studies on peanut, absence of contact with antigens is a risk factor to develop allergy [43]. The same findings were reported for cow milk: daily ingestion of cow milk formula between one and two months of age prevents CMA development [44]. In a group of 491 study participants, the number of CMA cases was 2 (0.8%) of 242 in the cow milk

Table 2

In Germany in the '90s, allergic children born to families without allergy risk were more numerous than those born to families with mono- or bi-parental allergy risk (adapted from Ref. [87]).

Population based lifetime prevalence of asthma in German children at 5 years of life			
Prevalence of parental atopic history	No atopy	A parent atopic	Both parents atopic
	64%	31%	5%
Asthma prevalence in German children (Total 9.3%)	5.3%	3.3%	0.72%

Table 3

Possible predictive allergy markers, beyond a family history of allergic disease, in populations with high growth rates of allergic disease.

General – preconceptional	
High family income	Chong SN, Chew FT. Epidemiology of allergic rhinitis and associated risk factors in Asia. <i>World Allergy Organ J.</i> 2018; 11 (1):17
High family education level	Fiocchi A, Ebisawa M. Avenues for research in food allergy prevention: unheeded ideas from the epidemiology. <i>Curr Opin Allergy Clin Immunol.</i> 2018; 18:210–213
Urban living	Karvonen AM, Lampi J, Keski Nisula L et al. Farm environment during pregnancy and childhood and polysensitization at the age of 31 – Prospective birth cohort study in Finland <i>J Invest Allergol Clin Immunol.</i> 2019; 0455
Low birth order	Upchurch S. Temporal changes in UK birth order and the prevalence of atopy. <i>Allergy</i> 2010; 65: 1039–41
High maternal age	Chieh Yao T. Association Between Maternal Age at Delivery and Allergic Rhinitis in Schoolchildren: A Population-Based Study. <i>World Allergy Organ J</i> 2020; 13 (5)
Gestational	
Allergen exposure	Frazier AL, Camargo CAJ, Malspeis S et al. Prospective study of peripregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. <i>JAMA Pediatr</i> 2014; 168:156–62.
Maternal obesity	Wilson RM. Maternal obesity alters immune cell frequencies and responses in umbilical cord blood samples. <i>Pediatr Allergy Immunol</i> 2015; 26:344–51
Fast prenatal growth trajectory	Wooldridge AL, McMillan M, Kaur M et al. Relationship between birth weight or fetal growth rate and postnatal allergy: A systematic review. <i>J Allergy Clin Immunol.</i> 2019; 144 (6):1703–1713
Use of antibiotics in pregnancy	Zhao D. Prenatal antibiotic use and risk of childhood wheeze/asthma: a meta-analysis. <i>Pediatr Allergy Immunol.</i> 2015; 26:756–764
Low intake of fermented foods during pregnancy	Tuokkola J. Maternal diet during pregnancy and lactation and cow's milk allergy in offspring. <i>Eur J Clin Nutr.</i> 2016; 70:554–559
Low intake of n-3 LCPUFAs during pregnancy	Tuokkola J. Maternal diet during pregnancy and lactation and cow's milk allergy in offspring. <i>Eur J Clin Nutr.</i> 2016; 70:554–559
Low vitamin D levels in pregnancy	Wei Z. Maternal vitamin D status and childhood asthma, wheeze, and eczema: a systematic review and meta-analysis. <i>Pediatr Allergy Immunol.</i> 2016; 27:612–19
Maternal dysbiosis	Jenmalm MC. The mother-offspring dyad: microbial transmission, immune interactions and allergy development. <i>J Intern Med.</i> 2017; 282 (6):484–495
Perinatal	
Prematurity	Chandran U, Demissie K, Echeverria SE, Long JB, Mizan S, Mino J. Food allergy among low birthweight children in a national survey. <i>Matern Child Health J.</i> 2013; 17 (1):165–171
C-section	Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melén E, Ludvigsson JF. Adverse pregnancy outcomes and risk of later allergic rhinitis-Nationwide Swedish cohort study <i>Pediatr Allergy Immunol.</i> 2020; [published online ahead of print, 2020 Feb 14].
First-born	Kikkawa T, Yorifuji T, Fujii Y et al. Birth order and paediatric allergic disease: A nationwide longitudinal survey. <i>Clin Exp Allergy.</i> 2018; 48 (5):577–585.
Autumn-winter season of birth	Tanaka K. The relationship between the season of birth and early-onset food allergies in children. <i>Pediatr Allergy Immunol.</i> 2015; 26:607–613
Intrapartum antibiotic prophylaxis	Carstens LE. Neonatal antibiotics in preterm infants and allergic disorders later in life. <i>Pediatr Allergy Immunol.</i> 2016; 27:759–764
Neonatal	
Neonatal jaundice	Das RR, Naik SS. Neonatal hyperbilirubinemia and childhood allergic diseases: a systematic review. <i>Pediatr Allergy Immunol.</i> 2015; 26:2–11
Use of antibiotics in nursery (e.g., renal dilation)	Carstens LE. Neonatal antibiotics in preterm infants and allergic disorders later in life. <i>Pediatr Allergy Immunol.</i> 2016; 27:759–764

ingestion group and 17 (6.8%) of 249 in the avoidance group (risk ratio: 0.12; 95% CI: 0.01–0.50; $P < .001$) [44]. The risk difference was 6.0% (95% CI: 2.7–9.3) [44]. The challenging findings of this study demand to be repeated elsewhere. Regarding extensive hydrolysates, it can be hypothesized that the more a protein is hydrolysed, the smaller the peptides, the more induction of tolerance may be hindered, as suggested by animal studies [62]. None of the existing guidelines recommends an extensively hydrolysed formula for prevention.

In summary, based on efficacy data, there is no recommendation for or against the use of extensively hydrolysed formula to prevent CMA. However, other factors such as high cost should be considered as well, as acknowledged by the guidelines.

9. Other formula interventions in non-breastfed infants and allergy prevention

Formulas from animals other than cows were considered beyond the scope of this review. The literature on soy based infant formula was not reviewed as there is broad consensus that soy has no indication in prevention of allergy in infants, and its use is not recommended [24,102]. Moreover, recent literature suggests that

contact with cow milk protein in early life decreases the risk to develop CMA [44].

10. Role of pre- and probiotics in allergy prevention

The gut microbiota composition and function early in life is important in the development of food allergy [103]. This is reflected in more than 4000 original research papers focused on gut microbiota and allergy prevention. The gastrointestinal tract plays an important immune function in developing either effector or tolerant responses by balancing the activities of Th1 and Th2 cells as well as regulating Th17 and T regulatory cells in the lamina propria [11]. It is thought, that a reduced gut microbial diversity and dysbiosis may affect this balance and lead to a Th2-skewed immune response, with enhanced IgE responses to food antigens, and/or a defect in mounting proper regulatory T-cell responses [2]. Many environmental factors including caesarean delivery, presence of human milk, medication, including proton pump inhibitors, antibiotics, and diet (including varieties of fibers) can induce gut microbiota dysbiosis, and have been associated with the occurrence of food allergy [103]. Therefore, the manipulation of the microbiota of the infant during pregnancy or after birth, when there is significant immune-plasticity may have an impact on allergy prevention.

10.1. Pregnancy

Before it was thought that the in-utero environment was considered sterile and that the first microbial colonisation occurred during delivery and after the birth. However, several studies now suggest that the placenta and amniotic fluid are involved in the process of colonisation with the ingestion of bacteria present in the amniotic fluid being capable of influencing the foetal gut microbiota [104]. On the other hand, the demonstration of metabolically active and proliferating diverse bacteria within the placental or fetal tissue - what has not been done up to now - will be required to prove the existence of a viable, diverse and unique bacterial community that merits the term microbiota [105,106]. Diet during pregnancy is an important perinatal factor in early life that may impact maternal microbiota; in particular, fiber, lipids and proteins exert a significant effect on the neonatal microbiome and contribute to infant development during the first months of life [107].

10.1.1. Probiotics

Several studies have investigated the supplementation of probiotics during pregnancy, using a variety of probiotic strains, with different atopic markers as outcome, which make assessment of overall success challenging. In 2015, the World Allergy Organisation, based on very low quality evidence that there is a likely net benefit of the use of probiotics in pregnant women at high risk for having an allergic child [108]. This recommendation was substantiated by a systematic review by Garcia-Larsen et al. showing that pooling many studies on probiotic supplementation resulted in a reduced risk to develop eczema, although only 4 out of 21 individual studies resulted in a significant reduction of eczema and 1 out of 12 showing a reduced risk for atopic eczema at 4 years of age [109]. A meta-analysis focusing on *L. rhamnosus* GG concluded that there was no evidence that administration of this specific probiotic would result in a reduction of the risk to develop atopic eczema [110].

10.1.2. Prebiotics

There is paucity of data on allergy prevention with prebiotic supplementation during pregnancy. However, there is currently an ongoing RCT (the PREGALL study) that is recruiting pregnant woman to either a placebo or the prebiotic, galacto-oligosaccharide/inulin and studying the impact on atopic dermatitis. The World Allergy Organisation (WAO) guideline panel therefore chose to provide no recommendation on prebiotic supplementation during pregnancy, owing to lack of experimental and observational studies in which prebiotic supplements were used in pregnant women [111].

10.1.3. Synbiotics

Limited data has been published on the impact of synbiotic supplementation during pregnancy. In 2008 Kukkonen et al. supplemented pregnant woman, 4 weeks prior to delivery with 4 probiotic species (*L. rhamnosus* GG and LC705, *Bifidobacterium breve* BB99, and *Propionibacterium freudenreichii* ssp *shermanii*) and continued to supplement the infants for 6 months [112]. The primary finding of this study was that synbiotic supplementation was safe. Since then a handful of studies have assessed synbiotic supplementation, but none focused on allergy prevention. No official allergy organisation has yet made any recommendation pertaining allergy prevention related to synbiotics.

10.2. Lactation

Human milk oligosaccharides (HMO) are the third most abundant solid component in human milk after lactose and lipids. Studies have shown that a considerable amount of the HMO reach the colon intact and is utilized by gut microbes. In specific, *Bacteroides* and *Bifidobacterium* species that commonly colonize the gut of the breastfed infant, efficiently utilize HMO as carbon sources [113]. In addition, human milk has also been recognised as a source of commensal and probiotic bacteria, contributing towards the colonisation of the gut of the infant. Thereby being both a source of pre- and probiotics [114].

10.2.1. Probiotics

In 2015, Fiocchi et al. identified 13 RCTs that investigated the effect of probiotic supplementation in breastfeeding mothers on allergy. However, only one of those studies focused on intervention during breastfeeding alone, whilst others either supplemented specific probiotics during pregnancy and/or early infancy [108]. Whilst the authors recognised this as a problem with assessing the impact on allergy prevention, overall, they recommended probiotics during breastfeeding in infants at high risk of developing an allergy. However, because of the specificity of probiotics, recommendations should indicate which strains to use. Since then, Wickens et al. published the results of their RCT supplementing mothers from 35 weeks of gestation until 6 months post-partum if breastfeeding and the child until 2 years of age with *L. rhamnosus* HN001 [115]. They found that maternal-only probiotic supplementation did not significantly reduce the prevalence of eczema, wheeze or atopic sensitization in the infant by 12 months, in contrast to the positive impact when the child was given the supplement. In addition, this study also found that HN001 could not be detected in human milk from supplemented mothers, and human milk TGF- β /IgA profiles were unchanged [115].

10.2.2. Prebiotics and synbiotics

There is paucity of data on prebiotic and synbiotic supplementation given to breastfeeding mothers and assessing the impact on allergy prevention.

10.3. Infancy

Studies have shown that gut dysbiosis in infancy is likely to precede atopic disease [116]. In particular germs belonging to the phylum of Proteobacteria (*Haemophilus*, *Moraxella*, *Neisseria* and *Streptococcus pneumoniae*) have been prevalent in children with asthma. In relation to food allergy, a decrease in *Bifidobacterium* and *Lactobacillus* species has been associated with the onset of CMA ([117]). In atopic dermatitis low microbial diversity has been found and some studies have found operational taxonomic units such as *Faecalibacteria* and *Oscillospira* (Firmicutes), *Bacteroides* and *Parabacteroides* (Bacteroidetes) and *Sutterella* (Proteobacteria) associated with atopic dermatitis [118].

As the infant's microbiota is developing, the supplementation of pre, pro and synbiotics as supplement or in addition to infant formula has become a major area of research in allergy prevention. Breastfed and formula fed infants not supplemented with pre-, pro- or synbiotics have distinct gastro-intestinal microbiota signatures, which may underlie the difference in various health outcomes between both groups [119]. Currently, many of the infant formulas contain prebiotics, human-identical or non-human oligosaccharides, probiotics, postbiotics or mixtures - with the intention to stimulate the development of a bifidobacteria dominated microbiota and artificially mimic breastfed infants microbiota [120].

10.3.1. Probiotics

A significant number of probiotic supplementation studies have been published using a variety of strains and different outcome measures. The meta-analysis by Garcia-Larson identified 28 RCT of maternal and infant probiotic supplementation (supplement or infant formula) and pooled them together, making it difficult to make a generalized recommendation [109]. Since then, 3 further RCT have been published assessing the impact on the prevention of atopic disease. The WAO in 2015, concluded based on low certainty and evidence, that there is a likely net benefit of the use of probiotics in infants at high risk of developing allergy [108]. This recommendation has been supported by a recent systematic review by Li et al. [121] who found that probiotic supplementation during infancy has a positive impact on the prevention of atopic dermatitis. The species with most research and benefit, in particular on atopic dermatitis, was *L. rhamnosus* [121]. However, since different *L. rhamnosus* strains were pooled in this systematic review, no specific strain can be recommended [121].

10.3.2. Prebiotics

Data on prebiotic addition to intact protein, partially hydrolysed infant formula and extensively hydrolysed formula has yielded conflicting results. Some show a long-term impact on the prevention of atopic disease, but others have not [73,122,123]. The systematic review by Garcia-Larsen et al. did not find an overall preventative effect of prebiotics, when studies were pooled [109].

10.3.3. Synbiotics

The area of synbiotics, related to allergy prevention is relatively new. To date most research in regard to allergy prevention has focused on a blend of scGOS/lcFOS and *B. breve* M-16V). In a study in 2017, this blend of synbiotics was provided in a formula to infants born via C-section [124]. This study found that the supplementation of this synbiotic, positively modulated the gut microbiota and was associated with the emulation of the gut physiological environment observed in vaginally delivered infants. No official body has provided any recommendations on the routine use of synbiotics for allergy prevention.

10.4. In summary

Whilst *in vitro* data suggest that manipulation of the gastrointestinal microbiota may prevent or alleviate the development of allergic disease, clinical data to confirm this hypothesis are scarce. According to the WAO, currently available evidence on prebiotic supplementation to reduce the risk of developing allergies is very uncertain [111]. Nevertheless, stimulating the development of a balanced gut microbiota is considered to be safe in non-immunocompromised children. Although there are some data to support that supplementation of probiotics during early infancy might decrease the risk to develop atopic dermatitis [108], there is insufficient evidence to recommend supplementation. Evidence regarding the efficacy of specific strains should be further investigated before any recommendation can be formulated.

11. Omega-3 and fish intake and allergy prevention

Omega-3 fatty acids are known for their anti-inflammatory properties via the leukotriene B4 pathways, making it a lucrative nutrient for allergy prevention. In addition, mega-3 LCPUFA rich may modulate immune response toward T helper cell 1-favoured immune response while the omega-6 LCPUFA rich diet exhibited no allergy alleviation with a stronger Th2 polarized immune response [120].

11.1. Fish intake

It is difficult to separate the effect of omega-3 intake from fish/sea food intake, particularly as many studies do not specify the type of fish consumed. Epidemiological studies investigating the association between maternal fish intake during pregnancy and allergic outcomes in infants/children of those pregnancies suggest protective associations, but the findings are inconsistent [126–129]. However, according to a pooled analysis including 18 birth cohorts, there is no evidence supporting a protective association of fish and seafood consumption during pregnancy with symptoms of wheeze, asthma and allergic rhinitis in the offspring from infancy to mid childhood [130].

11.2. Omega-3 fatty acid

11.2.1. Pregnancy

A recent systematic review indicated that based on meta-analysis of a limited number of available RCTs in high and normal risk families, omega-3 fatty acid during pregnancy was associated with reduced offspring outcomes of asthma/wheeze and allergic rhinitis and increased outcomes of atopic dermatitis, food allergy and all allergen sensitization though none of these outcomes reached significance due to the small number of studies [131]. Vadhani et al. assessed the impact of omega-3 supplementation in pregnancy and found that, omega-3 intake significantly reduce allergic sensitization to egg and peanut in the offspring [132].

11.2.2. Lactation

Only one RCT administered omega-3 fatty acids during the lactating period only to normal risk mothers and found no effect on the allergic outcomes studied [133].

11.2.3. Infancy

There is no systematic review reporting on the effect of omega-3 supplementation during infancy on childhood allergy outcomes. A number of studies have however looked at the effect of omega-3 supplementation in the first few months of life. D'Vaz et al. found an association between omega-3 fatty acid supplementation in the first 6 months of life and found a reduction in food allergy, eczema, asthma, and sensitization at 12 months of age [134]. The childhood asthma prevention study (CAPS) reported no difference in the prevalence of asthma or wheeze in these children at 5 years of age. A reduction in cough for atopic children was observed at 3 years of age [135–137]. Wheeze ever, doctor visits for wheeze, bronchodilator use and nocturnal coughing at 18 months were significantly reduced in children in the higher omega-3 fatty acid exposure quintiles. Reduced prevalence of any wheeze and a reduction in prevalence of wheeze of >1 week was reported at 18 months.

11.2.4. Pregnancy, lactation and infancy

Garcia-Larsen et al. summarized omega-3 fatty acids studies using supplementation in pregnancy, and/or lactation and/or early life feeding in their systematic review and meta-analyses and reported reduced sensitization to peanut and egg in the infant and/or child [109].

11.3. In summary

Omega-3 fatty acids may have the potential to prevent allergic outcomes, though the effect on supplementation particularly during pregnancy needs further clarification before supplementation can be recommended. This may be because studies used different doses, duration and time of intervention. Knowledge of pre-study

omega-3 fatty acid intake and maternal/familial risk of allergies may be crucial to interpret study findings.

12. Vitamin D and allergy prevention

Vitamin D is known to have immunomodulatory effects. Supplementation of pregnant women with 4400 IU of vitamin D3 resulted in an enhanced broad-spectrum proinflammatory cytokine response of cord blood mononuclear cells to innate and mitogenic stimuli, a higher gene expression level of TLR2 and TLR9, a greater than 4-fold increase in IL-17A production after polyclonal T-cell stimulation, and an enhanced IL-10 response of cord blood mononuclear cells to dexamethasone treatment in culture [138].

12.1. Pregnancy

A recent systematic review indicated that based on meta-analysis of a limited number of available RCTs, vitamin D intake/supplementation during pregnancy in doses higher than recommended by most countries, may have beneficial effects for prevention of offspring asthma [131]. Vitamin D intake also showed reduced atopic and sensitization though none of these outcomes reached significance due to the small number of studies. Based on observational studies, vitamin D intake was associated with reduced asthma, allergic rhinitis, sensitization. The doses of foods or nutrients studied were however very heterogeneous and we were unable to relate these to current nutrition guidelines. Vadhania et al. also concluded that prenatal supplementation of vitamin D might be associated with reduced odds of recurrent wheezing in children [139].

12.2. Lactation

Norizoe et al. indicated that parental report of doctor-diagnosed food allergy was significantly higher up to age two years in the vitamin D supplemented group (10/39, 25.7%) and did not decrease the severity of eczema at three months of age [140]. The dose given was 800 IU (20 mg) which is higher than recommended by most national guidelines.

12.3. Infancy

In healthy young children with sufficient vitamin D status, increasing vitamin D intakes does not appear to confer additional advantage to immune function [141]. However, low serum vitamin D was associated with persistent blood eosinophilia and symptoms in young infants with CMA [142]. CMA in infants was also related to lower T regulatory cells and vitamin D levels [143]. We identified only one study by Rosendahl et al. indicating that normal risk children receiving a higher dose of vitamin D (30 µg) were more likely to develop cow's milk allergy than children receiving a lower dose (10 µg) which is in agreement with current recommendations [144].

12.4. Pregnancy, lactation and infancy

Garcia-Larsen et al. summarized vitamin D supplementation in pregnancy, and/or lactation and/or early life feeding in their systematic review and meta-analyses and found no preventative effect on any of the allergic outcomes [109].

12.5. In summary

There is no evidence to support the supplementation of vitamin D for allergy prevention [145]. High dose supplementation during

breast feeding and infancy may increase the risk of food allergy and further studies investigation this concern is required.

13. Conclusions

Human milk feeding is the best way to feed infants and has been shown to have long term health benefits. There is no evidence, however, that the incidence of allergic disease differs between human milk fed and formula fed infants. In addition, breast feeding may have a transient protection on atopic dermatitis and prolonged breast feeding may protect against asthma [24]. Infant formula based on intact protein and protein hydrolysates have been reported to be nutritionally safe and adequate to support optimal nutrition and growth in the absence of human milk. However, at present there is insufficient evidence for or against the routine recommendation of pHFs for allergy prevention when compared to intact protein feed. There is some evidence that meta-analyses focussing on trials with a similar design and one selected hydrolysate may conclude that there is some effect on allergy prevention, mainly atopic dermatitis. Similarly, despite their potential health benefits, there is no evidence that supplementation with vitamin D, omega-3 LCPUFA, specific prebiotic oligosaccharides or probiotics during pregnancy, lactation and early life, contributes to the prevention of allergic disease development in children. There remains a need for well-designed trials with the currently commercialised pHFs and supplements to allow for better clarity and evidence-based recommendations.

Uncited reference

[31], [125], [146].

Conflict of interest

YVs has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Biocodex, Biogaia, CHR Hansen, Danone, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, United Pharmaceuticals, Wyeth.

RM has participated as a speaker and/or advisory board member for Nestle, Danone, Abbott and Mead Johnson.

JPC has participated as a clinical investigator, and/or consultant and/or a speaker for Biostime, Mead-Johnson, Nestlé and Nutricia.

CD has participated as advisory board member, and/or consultant, and/or speaker for Nutricia, Nestlé Health Science, United Pharmaceuticals, Nestlé Waters.

AF currently sponsored research by Danone, Sanofi, Hipp, Ferrero. Advisory boards of Danone, Stallergenes, Menarini, Abbott, DBV, Novartis, and Hipp.

SS has participated as advisory board member, and/or consultant, and/or speaker for Bioproject, Danone, Mellin, Nestlé, Novalac.

RS has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott, Danone, Douxmatok, Else, Frutarum, Nestlé Nutrition Institute, Nestle Health Science, NGS, Teva, Ukko, YMINI.

HS has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Danone, Nestlé, Nestlé Nutrition Institute, Nutricia.

NT has participated as a speaker and/or advisory board member, and/or consultant for Danone and Takeda.

CV has provided educational material and review of educational material for Reckitt Benckiser, Abbott Nutrition, Danone, DBV technologies and NNI. She has received research funding from Reckitt Benckiser and the National Peanut Board.

VV has participated as a consultant, and/or speaker for Nestlé Nutrition Institute, Nestlé Health Science, Nutricia, Biostime.

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