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REVIEW

Optimal timing for solids introduction – why are the guidelines always changing?

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Summary

There have been dramatic changes in timing of first exposure to solid foods for children over the last 40 years, ranging from exposure prior to 4 months of age for most infants in the 1960s, to guidelines recommending delaying solids until after 6 months of age introduced in the 1990s. Infant diet, specifically age of weaning and age at introduction of allergenic foods, has long been thought to play a role food allergy. However, controversy surrounding the relationship between timing of introduction of foods and development of food allergy has lead to a plethora of inconsistent infant feeding guidelines both between and within countries. The aims of this article were to discuss the history of changing guidelines for optimal timing of introduction of solids in general and allergenic solids in particular and the evidence (or lack thereof) underpinning recommendations at each of these time-points. We present the current clinical equipoise with regards to recently revised guidelines published almost simultaneously in the UK, US and Australia and argue that guideline modification about timing of introduction (both for high risk infants but also for the general population) will require careful review of emerging literature to provide a true evidence base to inform public health practice such as infant feeding guidelines.

Introduction

There has been a progressive and dramatic delay in timing of first exposure to solid foods for all children over the last 40 years. In the 1960s most infants had been exposed to solids by 4 months of age with the average age of introduction just 8 weeks of age [1, 2]. The 1970s heralded guidelines recommending delayed introduction of solids until after 4 months, based on the possibly false assumption that the rise in celiac disease was due to early introduction of gluten [3]. By the late 1990s expert bodies began to recommend delaying solids until after 6 months of age [4]. These trends predate, but accelerated with, the rise in food allergy prevalence. Recommendations to delay food introduction (with the associated impact on timing of introduction of allergenic solids) thus do not appear to have been successful in preventing food allergy. In fact, it is even possible that delays in timing of introduction of allergenic foods may have actively contributed to the rising prevalence of food allergy in conjunction with other environmental and genetic factors. World Health Organization (WHO) and similar regulatory bodies offer substantial support for maintaining exclusive breastfeeding for the first 6 months of life. These recommendations are beneficial to children and mothers for a variety of reasons, particularly in the developing world when access to a clean water supply may be limited. However, the role of exclusive breastfeeding in the development of allergic disease in general and food allergy specifically is far less clear.

The aims of this article were to discuss the history of changing guidelines for optimal timing of introduction of solids in general and allergenic solids in particular and the evidence (or lack thereof) underpinning recommendations at each of these time-points. We present the current clinical equipoise with regards to recently revised guidelines published almost simultaneously in the UK, US and Australia and argue that guideline modification about timing of introduction (both for high risk infants but also for the general population) will require careful review of emerging literature to provide a true evidence base to inform public health practice such as infant feeding guidelines.

When are infants developmentally ready for solids introduction?

The first year of life provides a critical developmental opportunity whereby infants move from fluid-based nutrition (i.e. breast milk or a substitute) in the first few months of life to the transition to solid food. This process is developmentally programmed and results from a carefully orchestrated number of factors becoming aligned to enable an infant to achieve nutritional independence from their mother. These factors include the loss of the neonatal gag reflex, an ability to propulse food from entry point to the back of the tongue and an increasing ability to masticate more textured foods with age. Each infant varies with regards to when these factors are aligned but infants in which these processes are either not mature or have been impaired by a neurological condition are at risk of aspiration and inhalation of food during feeding.

During the first 6 months of life the infant develops the readiness to masticate and swallow solid food. Oral immune tolerance, a state of systemic immune unresponsiveness to ingested allergens [5], also develops over the course of the first year of life although the order and interplay between these two sets of developmental processes has not been formally evaluated in humans. There is significant evidence from rodent studies that cessation of suckling results in the alteration and maturation of a number of digestive and absorptive mechanisms including modulation in iron absorption regulatory pathways [6] and increase in gastric acid maturation [7], although the relevance of these findings to humans is unclear. In addition, there is a dramatic transition of intestinal microbiota composition during weaning [8] which is reflected in the transitioning nature of stool composition which is seen clinically by change from a more liquid to a more formed stool often termed transitionary stool, followed by establishment of a more adult-like stooling pattern. In infants the initial colonizing bacteria are facultative anaerobes enterobacteria, coliforms, lactobacilli and streptococci. Colonization with anaerobic genera such as Bifidobacterium, Bacteroides, Clostridium and lactic acid bacteria follows thereafter [9]. The healthy intestinal microbiota in infancy is characterized by a large Gram-positive bacterial population and significant numbers of bifidobacteria, mainly *Bifidobacteria longum*, *Bifidobacteria breve* and *Bifidobacteria infantis*. Infant feeding practices including the use of formula vs. breast milk influence the succession of microbiota colonization, altering the genus, species and species composition, as well as the numbers of bacteria that colonize the infant intestinal tract although there remains controversy around the extent to which breastfed baby stool differs qualitatively from formula fed infants [10].

Finally, changes to oral immune tolerance have been hypothesized to dramatically change at the time of weaning [11] possibly in relation to changes to microbial constitution and developmental maturation of the mucosal immune system, termed the Gut Associated Lymphoid Tissues (GALT). The GALT is continuously exposed to diverse antigens, including commensal microorganisms and foods. In the healthy state, there is active induction of tolerance and suppression of immune responses to those antigens required for health. At the same time, the mucosal immune system must recognize and respond to pathogens to protect the host from disease. To facilitate health the host needs to develop immune homeostasis to balance the need to respond to pathogens while maintaining suppressed responses against commensal microbial antigens and food antigens. This modulation is facilitated by commensural intestinal microbiota which is essential for the normal development of the GALT and maintenance of immune homeostasis as evidenced by the failure of mice bred in sterile conditions to develop appropriate oral immune tolerance [12, 13] and normal development of the GALT, with small underdeveloped Peyer's Patches that lack germinal centres, fewer IgA plasma cells and CD4 + T cells in the lamina propria, and fewer intra-epithelial lymphocytes with reduced cytolytic activity. There is a constant interaction between commensal bacteria in the intestinal lumen and the epithelial and immune cells within the gut, and this continuous interaction is central to the maintenance of oral tolerance. The gastrointestinal epithelium and dendritic cells in the gut associated lymphoid tissue are equipped with pattern-recognition receptors (PRRs) which recognize specific conserved molecular patterns on pathogens.

The intestinal epithelium represents the largest interface between the external environment and the internal host milieu and constitutes the major barrier through which molecules can either be absorbed or secreted. Tight junctions between absorptive and secretory cells lining the small intestine appear to play a major role in regulating epithelial permeability by influencing paracellular flow of fluid and solutes. Evidence now exists that tight junctions are dynamic rather than static structures and readily adapt to a variety of developmental, physiological and pathological circumstances and are likely to be substantially modulated through the first year of life in response to a range of dietary and developmental milestones [14].

Together these factors constitute a critical developmental period which has been termed by Prescott et al. [11] a 'window of opportunity' at which time infants are ready to commence solid food in addition to breastfeeding Whether the orchestration of these factors in humans occurs at a pre-determined postnatal time

period of 4–6 months or are modulated by the very event of weaning is not yet fully known.

How do we define weaning and exclusive breastfeeding?

Until relatively recently in the history of medicine infant feeding practices for healthy children were mostly in the domain of child and maternal health nurses which were informed and heavily influenced by cultural and historical norms. Involvement of the medical profession with some notable exceptions was mostly limited to management of feeding in sick and hospitalized infants. Cultural influences still heavily predominate in developing countries such as Africa and India [15] but over the last 50 years the 'science' of infant feeding in Westernized countries has come under the prerogative of public health epidemiologists and clinicians. More recently, the study of infant feeding practices has been regarded as essential to the evolving field of 'Early Determinants of Health and Disease' as it becomes clear that long-term metabolic pathways are critically determined by regulation in early infancy [16].

With increasing interest in this field there have been changes to the definition of types of infant feeding practices with the intent of international standardization to enable better epidemiological comparison between countries. The WHO defines exclusive breastfeeding as the period in which the infant 'only receives breast milk without any additional food or drink, not even water'. Weaning can therefore be defined as the time at which either formula or complementary (solid) foods are introduced into the infant diet. Commonly used weaning foods vary between countries although these are often foods such as fruits and vegetables which are tolerated by most infants. There is also significant variation in the age at which 'allergenic foods', those foods such as cow's milk, eggs, nuts and shellfish, which are often associated with IgE-mediated food allergy, are introduced into the infant diet.

Although the above definitions have been debated, contested and finally widely accepted in the medical research community with ratification by the WHO there is evidence that both medical practitioners and families themselves do not widely understand them which may at least partly explain why compliance with infant feeding guidelines is often low [17].

The history of infant feeding guidelines – how have they changed over the last 50 years?

Infant diet has long been thought to affect the risk of developing food allergies. While in the 1960s infants were typically given solid foods in the first 3 months of life, the 1970s saw the introduction of guidelines recommending delayed introduced of solids until after 4 months of age because of a perceived link between early introduction of gluten and celiac disease [3]. It is therefore interesting to note that population-based guidelines that were changed due to presumed changes in celiac disease prevalence (which unlike food allergy is not a Th2-mediated disease) may have had unexpected impacts on other population health outcomes such as IgE-mediated food allergy.

By the early 1990s, expert bodies began to recommend delaying solids until after 6 months of age, with further delay in the introduction of allergenic foods such as egg and nuts until at least 2 years of age recommended for infants with a family history of allergy [18]. This did not, however, appear to have the desired effect of reducing the prevalence of food allergy and in 2008, lack of evidence of a protective effect led to the removal of advice to delay the introduction of any foods beyond 4–6 months of age with current guidelines outlined below. Despite widespread interest and research into the area of infant feeding and allergic disease, to date we still lack sufficient evidence to provide definitive recommendations around the best time to introduce solids and particularly allergenic foods to infants.

What is the current controversy regarding solids introduction?

Despite the perceived importance of diet in the development of food allergy, the role of factors including breastfeeding, introduction of foods and maternal diet in preventing food allergy remains unclear. Numerous issues arise when studying the relationship between infant feeding and allergic disease which need to be taken into account in study design and analysis and interpretation of data. Firstly, there is good evidence that the emergence of allergic symptoms in a child, such as eczema or a reaction to cow's milk, leads to changes in infant feeding such as prolonged breastfeeding and removal or exclusion of allergenic foods from the infant and/or the maternal diet [19]. As a result, infants who are showing signs of allergic disease receive different feeding to 'healthy' infants, a phenomenon known as reverse causation. A second issue which has been demonstrated to lead to spurious associations between prolonged breastfeeding or allergen avoidance and allergic disease is confounding by family history of allergy [20, 21]. In this case, changes in infant feeding behaviour result from a history of allergic disease in a parent or sibling, with similar effects as described for reverse causation. Finally, a range of other factors are likely to influence infant feeding, each of which may be independently associated with the outcome of interest, allergic disease. For example, parents who are

aware of and follow current health advice such as infant feeding guidelines may be more likely to obtain medical advice about a child's allergic symptoms and therefore more likely to receive a diagnosis of food allergy from a medical practitioner.

Unfortunately, many observational studies have not adequately addressed these issues when examining the relationship between infant feeding and food allergy, thus raising serious concerns about any reported findings from these studies.

The impact of timing of introduction of solids

A systematic review of the relationship between early introduction of solid foods, defined as introduction before 4 months of age, and allergy, conducted in 2005, identified only one cohort study investigating the relationship between early introduction of solids and food allergy [22]. The one included study, a birth cohort of 135 infants with atopic parents, found that early introduction of solid foods was associated with an increased risk of having reported symptoms of food allergy by 1 year of age. However, no difference was seen in food-challenge confirmed allergy and there was also no difference in allergy to milk, egg or wheat, diagnosed by history and SPT, at 5 years of age.

Two studies published after this review have investigated the relationship between age at introduction of solids and sensitisation to food allergens, although neither of these used symptomatic food allergy as an outcome. One Dutch birth cohort study of 2834 infants found that delayed introduction of solid foods beyond 3 months of age was associated with an increased risk of egg and peanut sensitisation, although the difference was not statistically significant [23]. A key limitation of this analysis was the low percentage of the cohort for which sensitisation data were available (only 782 infants were included in the sensitisation analysis compared with 2510 in an analysis of eczema reported by questionnaire). A second birth cohort of 2600 infants found no evidence that timing of solids introduction was associated with sensitisation to cow's milk, egg, wheat, peanut, soybean or cod fish at 2 years of age [24]. When this cohort was followed up at age six, later introduction of solids was associated with an increased risk of food sensitisation in the complete cohort and also among the subset without early skin or allergic symptoms, indicating that this finding was unlikely to be due to reverse causation. Late introduction of solids increased food sensitisation mainly in children newly sensitized at 6 years who were not sensitized at 2 years. Age at introduction of solids was not significantly associated with sensitisation to egg or milk alone; however, it was significantly associated with sensitisation to peanut.

Venter et al. [25] also examined infant feeding and food allergy in a birth cohort study of 969 infants. Introduction of solid foods occurred prior to 3 months of age in 27% of the cohort and prior to 5 months in 82% of the cohort. Food hypersensitivity and sensitisation to food allergens at 1 and 3 years of age was lower in those weaned before 4 months of age although this analysis was not adjusted for potential confounding factors such as socio-economic status, family history of allergy, birth order and infant history of eczema.

In a recent large observational cohort study in Melbourne, Australia, we found no relationship between timing of introduction of solid foods and challenge-confirmed egg allergy at 1 year of age [26]. Solid foods in this cohort were predominantly introduced between 4 and 6 months of age, with only 4% introducing solids before age 4 months and 5% after 6 months, thus an effect of very early or late introduction of solids cannot be ruled out. However, age at introduction of egg was associated with egg allergy at age 1 year, as described in the following section.

The impact of timing of introduction of allergenic solids such as egg, nuts and milk

There are two main hypotheses regarding the relationship between timing of dietary exposure to allergenic foods and food allergy. The first is that exposure to these foods early in infancy while the immune system is immature or during a stage of increased gut permeability may lead to an immune response and subsequent development of a food allergy. This hypothesis led to early guidelines recommending delayed introduction of allergenic foods such as nuts for as long as 5 years. The second hypothesis states that there may be a period during development when the immune system is predisposed to tolerance development (thought to be within the first 6 months of life) [11] and exposure to a food during this time could lead to persistent tolerance to that food.

Early intervention studies primarily investigated the impact of combined maternal and infant allergen avoidance on the prevalence of food sensitisation and allergy among 'high risk' infants with a family history of allergy. Not surprisingly, the initial reports from these studies showed lower rates of food sensitisation and allergy in infants avoiding allergenic foods, indicating that allergic symptoms did not develop in the absence of exposure to these foods. However, protection did not appear to be maintained after the introduction of allergenic foods into the diet. Later follow-up of the study population in early childhood showed no reduction in the prevalence of food sensitisation and allergy among those with early allergen avoidance, suggesting that these strategies were ineffective in promoting the development of tolerance [27].

More recently, large observational studies have attempted to untangle the impact of timing of introduction of specific foods (such as peanut, egg or cow's milk) and development of allergy to those foods. The relationship between age at introduction of cow milk products and cow's milk sensitisation at age two was investigated in the Dutch birth cohort study described previously [23]. Although there was a trend for a decreased risk of sensitisation with delayed introduction of cow's milk, this did not reach statistical significance. This analysis was also limited by the low percentage of the cohort for which sensitisation data were available and by the lack of a clinically relevant outcome (symptomatic cow's milk allergy). A study of 12 234 newborn infants in Israel with 0.5% prevalence of IgE-mediated cow's milk allergy found that infants exposed to cow's milk in the first 14 days of life were less likely to be cow's milk allergic compared with those first exposed to cow's milk after 14 days [28], although this was not controlled for family history of cow's milk allergy.

Two birth cohort studies designed to investigate risk factors for type 1 diabetes investigated the relationship between timing of food introduction and food sensitisation or allergy [29, 30]. Both studies contained only infants with a family history or personal genetic risk of diabetes. Poole and colleagues found that introduction of wheat after 6 months of age was associated with an increased risk of parent-reported wheat allergy [29]. This finding was based on 16 children with parent-reported wheat allergy, only four of whom had detectable levels of wheat-specific IgE on blood test. The authors also failed to control for a history of eczema in the child, which is likely to be associated with both dietary modifications and an increased risk of food sensitisation. The second study found that introduction of egg after 10.5 months was associated with an increased risk of sensitisation to egg at age five [30]. The relevance of this finding is questionable as neither history of early allergic symptoms in the child nor family history of food allergy or eczema were considered in the analysis, both of which are likely to be important confounders. A recent Turkish study of 1015 infants found no association between age at introduction of egg and egg sensitisation [31], however, the study was relatively underpowered with only 19 egg sensitized infants and, as for the above studies, did not use objectively confirmed food allergy as the outcome.

A landmark study by Du Toit et al. [32] compared the prevalence of peanut allergy among Jewish schoolchildren in Israel and the UK. Although the study found that Israel had a lower prevalence of peanut allergy in school-aged children and that in general peanuts were introduced earlier into the diet of infants in that country compared with the UK, the study design did not allow a direct link between age at first peanut consumption and peanut allergy on the individual level. Furthermore, the study was unable to eliminate other environmental factors as the cause of the differing prevalence of peanut allergy, a possibility that is consistent with the study finding a higher prevalence of other food allergies such as egg, tree nut and cow's milk allergy in the UK as well as a difference in prevalence of eczema, a co-associated condition. Interestingly, although there was a higher prevalence of egg allergy in the UK this was not accompanied by a statistically significant difference in age at introduction of egg.

In contrast, the Healthnuts study in Australia found that, compared with introduction at 4–6 months, introducing egg into the diet later was associated with higher rates of egg allergy (adjusted odds ratio 3.4 [95% CI 1.8 to 6.5] for introduction after 12 months). Most interestingly, introduction of cooked egg such as scrambled, baked or fried was more protective than simply introducing egg in baked goods, with those introducing cooked egg at 4–6 months being five times less likely to develop egg allergy than those waiting to the normally recommended time of 10–12 months of age, even after adjusting for confounding factors. There was no protective effect amongst infants who first introduced baked egg into their diet between 4 and 6 months presumably because a lower dose exposure does not provide protection. No other factors such as maternal avoidance or prolonged breastfeeding were associated with altered risk of egg allergy after adjusting for confounders [26].

Early evidence, which requires further investigation, suggests that if a window of opportunity for promoting tolerance exists, it may be different for each food. For example, the optimal timing of introduction of milk appears to be earlier compared with egg. This is supported by findings that infants introduced to milk at 4–6 months were more likely to be milk allergic compared with those introduced to milk later [28], while in a separate study, infants introduced to egg at 4–6 months were less likely to be egg allergic compared with those first exposed to egg after 10 months [26]. Interestingly, Katz et al. found lower rates of cow's milk allergy amongst Israeli infants who were exposed to cow's milk formula within the first 14 days of life, suggesting very early exposure to cow's milk protein might promote tolerance, although this requires further investigation.

Together these studies do not support delaying the introduction of solids in general or allergenic solids in particular for the prevention of food allergy. In fact they suggest that this may even paradoxically increase the risk, although confirmation from randomized controlled trials is required to confirm whether this is truly the case. This is reflected in current guidelines in Australia, the UK, Europe and the US which no longer pro-

vide any recommendations on the best time to introduce potentially allergenic foods citing a lack of evidence base for the prevention of food allergy.

What are the current guidelines?

The recent change in position by specialty allergy bodies around the world has now lead to a contradistinction between government, WHO and peak expert body infant feeding guidelines which is likely to further confuse the public about which guidelines and undermine their credibility. The lack of a consensus is reflected in the myriad different infant feeding guidelines aimed at preventing allergy and with infant feeding guidelines from 18 countries around the world summarized in a recent review by Grimshaw and colleagues [4]. The WHO recommends exclusive breastfeeding for the first 6 months of life, followed by breastfeeding alongside complementary foods up to 2 years of age [33].

In the UK, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), which provides advice to the Food Standards Agency, the Department of Health and other Government Departments and Agencies, produced recommendations for peanut consumption in 1998. These were revised in 2008. Initially, the COT recommended that infants with a family history of allergy should be breastfed exclusively for 4–6 months, peanuts should be avoided by mothers during pregnancy and lactation and by infants until 3 years of age. None of the recommendations about peanut avoidance were retained following the 2008 review [34]. Current guidelines from the Department of Health in the UK recommend exclusive breastfeeding for 6 months and avoidance of potentially allergenic foods (peanuts, other nuts, seeds, milk, eggs, wheat, fish or shellfish) until after 6 months of age [35].

The European Society of Pediatric Allergy and Clinical Immunology and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have produced joint guidelines. These recommend exclusive breastfeeding for 4–6 months or use of hypoallergenic formulas if exclusive breastfeeding is not possible. In addition, guidelines from ESPGHAN recommend introducing gluten between 4 and 7 months to reduce the likelihood of developing wheat allergy [36].

The American Academy of Pediatrics recommendations now state that there is no evidence to recommend maternal dietary restrictions during pregnancy or breastfeeding. For infants at high risk of atopic disease, there is some evidence that exclusive breastfeeding for at least 4 months is protective against cow milk allergy in first 2 years of life. Atopic dermatitis may be delayed by using hydrolysed formulas instead of cow's milk based formulas early in life. However, there is no evidence that delaying intro of solids including allergenic foods after 4–6 months is protective [37].

In contrast, Australia, which appears to have one of the highest rates of food allergy in the world [38] is plagued by a plethora of infant feeding guidelines including Australian government guidelines (NHMRC) which are essentially WHO compliant but recommend avoiding nuts till 3 years and maternal nut avoidance during pregnancy in the context of a strong family history of nut allergy, a raft of State-based guidelines which are all variations on a theme and the peak allergy specialty body guidelines (ASCIA) which until recently were modelled on AAP guidelines although not as extreme with egg introduction recommended at after age 12 months rather than 2 years.

What is the evidence that guidelines are followed?

Infant feeding practices often do not follow the available guidelines. There is evidence that UK families with a history of allergic disease did not delay the introduction of peanut to infants despite recommendations [39, 40]. Data from the HealthNuts study in Australia show that parents are not following NHMRC guidelines with only 23% exclusively breastfeeding to at least 6 months of age and 54% introducing solid foods prior to 6 months (K Allen and J Koplin, personal communication).

Weaning practices also differ greatly between countries. In a UK-based birth cohort study [25], 27% of infants received solid foods prior to 3 months of age compared with $< 5\%$ in the Australian-based HealthNuts study [26].

How does allergic risk influence adherence to guidelines?

Investigation of the relationship between infant diet and food allergy in observational studies is complicated by the issue of confounding. Past guidelines, which recommended prolonged breastfeeding and delayed introduction of foods for the prevention of food allergy, were primarily aimed at infants with an increased risk of developing allergy because of a family history of allergic disease. If high risk infants are fed according to the guidelines, they may be breastfed for longer and introduced to foods later than infants with a lower risk of developing allergic disease. Dietary decisions may also be influenced by type of family history of allergy. For example, a study of a birth cohort recruited based on a family history of allergy found that a maternal history of food allergy was associated with prolonged breastfeeding [41].

Similarly, there is evidence that those infants who develop signs of allergic disease early in life, while they are still breastfed and before the introduction of allergenic foods into their diet, may be breastfed for longer and introduced to foods later. Signs of eczema occurring during exclusive breastfeeding were associated with prolonged exclusive breastfeeding among a birth cohort with a family history of allergy [41]. A separate population-based birth cohort study found that infants with eczema or other allergic symptoms occurring in the first 6 months of life were more likely to be introduced to egg and milk after 6 months of age [42]. As both these studies involve birth cohorts recruited for the purposes of studying allergy development, these findings may not reflect what happens on a population level. Parents involved in an allergy study might be more aware of signs of allergy in their infant or more likely to seek and obtain information on allergy prevention strategies including prolonged breastfeeding, making dietary modification more pronounced in birth cohorts.

Ongoing intervention studies

Several intervention studies currently in progress have the potential to provide high-quality evidence about the role of infant feeding in food allergy as results become available over the next few years. Two studies are currently underway in the UK, the LEAP and EAT studies. The LEAP study aims to examine the effect of early peanut consumption on peanut allergy [43]. The study design involves enrolling 640 children aged 4–10 months at high risk of peanut allergy (defined as a history of egg allergy or severe eczema), without current peanut allergy (SPT< 4 mm on study entry and no history of reaction to peanut). Infants will be randomized to either regular consumption of peanut protein (2 g in three serves per week) or peanut avoidance and the prevalence of peanut allergy in the two groups will be assessed and compared at 5 years of age. The EAT study aims to examine the effect of early consumption of a range of potentially allergenic foods on IgE-mediated allergy to any of these foods. The EAT study will involve 2 500 infants with mothers recruited during pregnancy [44]. The intervention arm will introduce six potentially allergenic foods into the infants' diets prior to 6 months of age (cow's milk, egg, wheat, sesame, fish and peanut). The control arm will follow standard UK government advice (exclusive breastfeeding until 6 months of age and no introduction of allergenic foods – egg, wheat, peanuts, tree nuts, seeds, fish and shellfish - before 6 months of age). The outcomes examined will be IgE-mediated food allergy to the six intervention foods between 1 and 3 years of age.

There are also studies underway which involve the use of a placebo control. In Germany, the Hen's Egg Allergy Prevention (HEAP) study will involve 800 children, randomized to receive either hen's egg or a placebo at 4–6 months of age, with the effect on egg allergy measured at 12 months of age [45]. The STAR and STEP trials in Australia will include 200 infants with moderate to severe eczema and 1500 infants without eczema but with atopic mothers respectively [45]. Infants will receive either whole egg powder or a placebo (rice powder) from 4 to 6.5 months of age.

Could the rise in food allergy be explained by the change to timing of intro of solids – in particular allergenic solids?

The prevalence of food allergy is widely believed to have increased over the past few decades in line with other allergic diseases. This increase has occurred too rapidly to be explained by genetics alone, suggesting that environmental factors also play a role in determining food allergy risk. Unfortunately, the timing of this increasing prevalence of food allergy is difficult to substantiate as studies documenting the population prevalence of food allergy prior to the 1980s are not available to provide baseline data.

Evidence for an increase in the prevalence of food allergy comes from two types of studies. The first consists of examining hospital records to assess the prevalence of hospitalization for more serious allergic food reactions. In Australia, there has been a 5.5-fold increase in the hospitalization rate for food-related anaphylaxis in children under the age of five over the last decade [46]. An increase in food allergy admissions has also been observed in the UK [47] and the US [48] over a similar time period.

The second line of evidence for an increase in food allergy prevalence is data from population-based studies measuring changes in the same population over time. To date the limited number of population-based studies that exist have mainly focused on peanut and tree nut allergy. In a UK study, Grundy et al. [49] found that peanut sensitisation varied from 1.3% to 3.3% to 2.0% in three sequential early childhood cohorts from the same geographic area, each surveyed 6 years apart, while reported peanut allergy increased from 0.5% to 1.4% then 1.2%. While there was evidence that both peanut sensitisation and allergy were significantly more common in the second cohort (born in 1994–1996) compared with the initial cohort (born in 1989), there was no evidence of a further increase in prevalence in the third cohort (born in 2001–2002). Between three United States-wide phone surveys conducted in 1997, 2002 and 2007, the prevalence of self-reported peanut and/or tree nut allergy increased from 0.6% to 1.2% to

2.1% among children, though no change was observed for adults [50]. However, this increase in reported allergy was paralleled by a decreasing response rate across surveys (42% response rate in 2007), raising questions about whether these prevalence figures can be generalized to the wider population.

Changes in the timing of food introduction may contribute to but unlikely to completely explain recent increases in the prevalence of food allergy. Existing studies show that some children will develop food allergy despite early introduction of potentially allergenic foods while others do not develop food allergy despite the delayed introduction of these foods, providing evidence that other environmental or genetic factors play a role in the development of food allergy. Genetic factors have been shown through twin and family studies to be important in determining food allergy risk although the specific genes which are involved in food allergy have not yet been conclusively identified [51, 52]. Future studies will need to investigate environmental factors including timing of introduction of solids in the context of individual genetic risk (gene-environment interactions).

Conclusions

Behaviour with regard to introduction of first solid foods and allergenic solids has undergone dramatic changes over the last several decades. There is as yet insufficient evidence to inform the question as to whether changing in feeding practices may contribute to the rise in food allergy. More evidence about the role of infant diet in the development of food allergy will be become available in the next few years with the impending completion of several randomized controlled trials around the world.

Conflicts of interest

The authors declare no conflicts of interest.

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