


ORIGINAL ARTICLE

WILEY

Clinical Allergy

Association between the age of solid food introduction and eczema: A systematic review and a meta-analysis

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Funding information

NHMRC, Grant/Award Number: APP1041420

Summary

Introduction: Eczema is a common childhood ailment responsible for a considerable disease burden. Both timing of introduction to solid food and allergenic food are believed to be related to childhood eczema. Despite the growing body of evidence, the relationship between timing of any solid food introduction (allergenic and/or non-allergenic) and development of eczema has not previously been systematically reviewed.

Methods: PubMed and EMBASE databases were searched using food and eczema terms. Two authors selected papers according to the inclusion criteria and extracted information on study characteristics and measures of association. Meta-analyses were performed after grouping studies according to the age and type of exposure.

Results: A total of 17 papers met the inclusion criteria, reporting results from 16 study populations. Of these, 11 were cohort studies, 2 case-controls, 1 cross-sectional study and 2 randomized controlled trials. Limited meta-analyses were performed due to heterogeneity between studies. Timing of solid food introduction was not associated with eczema. One randomized controlled trial provided weak evidence of an association between early allergenic (around 4 months) food introduction and reduced risk of eczema.

Conclusions: The available evidence is currently insufficient to determine whether the timing of introduction of any solid food influences the risk of eczema.

KEYWORDS

allergenic food, dermatitis, eczema, solid food, timing/introduction

1 | INTRODUCTION

Eczema is the most common skin disease in childhood,¹ and it causes a considerable amount of distress to both children and parents.² The prevalence of eczema varies globally but is higher in developed countries.² Timing of introduction to complementary food for infants has recently received increased interest,³ as this may impact on the child's immune system⁴ and risk of developing eczema.

Complementary feeding describes the provision of nutrition other than breastmilk.⁵ It may be either in liquid form, typically formula feeding, or in solid form, with introduction of solid food to the infant's diet. Introduction of liquid and solid complementary foods generally occur at different times, responding to different needs. Formula or substitute milk feeding is introduced as a breastmilk substitute until the child can be weaned onto solid foods. Solid food introduction is the start of transition to an adult diet and relies also on developmental readiness.

Adrian J. Lowe and Caroline Lodge jointly supervised the work.

Prolonged exclusive breastfeeding, which is intimately related to the timing of solid food introduction, is widely advocated as a preventive measure for childhood allergic disorders, although there is little clear evidence to support this claim.⁶ Guidelines for the timing of allergenic food introduction also differ, with some authorities recommending introduction between 4 to 6 months, and others before 12 months of age.^{7,8} Currently, there is no consensus concerning the timing of introduction to solid foods with the aim of preventing eczema. The World Health Organization (WHO) guidelines recommend exclusive breastfeeding for 6 months, prior to complementary food introduction.⁵ The food introduced at this time may be solid and/or liquid, but the expectation is that solids will be introduced. The ASCIA (Australian Society of Clinical Immunology and Allergy) guidelines recommend complementary feeding around 6 months and allergenic food within the first year of life.⁹ All other national and international organizations recommend timing complementary feeding around the age of 6 months and not before the age of 4 months.^{10–12}

A recently published systematic review, based on 17 trials and 37 observational studies, investigated the association between allergenic food introduction and eczema, including both liquid and solid allergenic foods.¹³ They found no clear evidence for an association between timing of introduction of any allergenic food and eczema. However, they did not report on the associations between (i) timing of introduction of only solid foods or (ii) the exposure to specific allergenic foods (apart from cows' milk) and the outcome of eczema. Furthermore, the review included multifaceted intervention trials, where the effect of timing of introduction of individual foods could not be determined.¹⁴ Therefore, the literature concerning timing of introduction to solid foods not specifically focussing on allergenic food and the risk of eczema has not yet been systematically synthesized. Understanding this relationship may help inform infant feeding guidelines.

The aim of this article was to appraise all available literature on the association between timing of solid food introduction and the risk of eczema. For the purpose of this review, we have excluded exposure to cows' milk, as it is commonly given as liquid formula before the introduction of complementary solids.

2 | METHODS

PubMed and EMBASE electronic databases were systematically searched using both key words and MeSH terms for solid food, complementary and allergenic food introduction and eczema. We also reviewed the reference lists of included articles. Additionally we searched trial registries (Australian and New Zealand, European, Japanese) and created citation alerts to screen for the most current publications. We included all relevant English-language human studies. Further details of the search terms are provided in the online supplement (S1). The review was prospectively registered in the PROSPERO systematic review registry (CRD42016033473). The final search was performed on the 18 February 2017. Following the final

search, database alerts were established to keep the authors updated on new publications.

2.1 | Inclusion and exclusion criteria

- Types of studies - We included all cohort studies, case-control studies, cross-sectional studies and randomized controlled trials based on general population or high-risk population groups.
- Published in English.
- Study participants—Human.
- Exposures—The exposure of interest was timing of solid food introduction to the child (solid food may be allergenic or non-allergenic). Both the exact age in months and interval cut-offs were considered as suitable for the analysis.
- Outcomes—Diagnosis of eczema (any definition).
- Peer-reviewed publications (conference papers, abstracts and letters to the editor) that did not contain original data were excluded from the review.

2.2 | Selection of studies

Two authors independently reviewed the titles and abstracts (NW and GB). Any disagreements were resolved by consulting a third reviewer (CL) who made the final decision. The list of excluded studies after the full-text review is provided in the online supplement (S2).

2.3 | Data extraction

Two authors independently performed the data extraction (NW and GB). Details of the studies were extracted into a standard table. The fields included the following: first author, year published, exposure and its definition, outcome and its definition, study design, sample size, confounding and moderating factors considered, measures taken to control for reverse causation and effect estimates.

2.4 | Effect estimates

Associations with the dichotomous outcome of eczema vs no eczema were extracted from each paper. Associations were reported as odds ratios/risk ratios or hazard ratios.

2.5 | Quality assessment and risk of bias

Two authors were independently involved in assessing the study quality (NW and GB). Study quality was assessed using Newcastle-Ottawa scale (NOS) for individual studies. The cohort and case-control studies were graded as very good (9–10), good (7–8), satisfactory (5–6) and unsatisfactory (0–4). The Cochrane Review Quality assessment scale was used for quality assessment of randomized controlled trials.

2.6 | Data analysis

Studies that provided the age of exposure and a numerically measured outcome as a risk ratio or odds ratio with 95% confidence interval were included in the meta-analysis. The I^2 was used to assess the heterogeneity of the pooled estimate ($>75\%$ was considered to be high statistical heterogeneity). We performed random effects meta-analysis and studies were grouped according to exposure time in age and also the food groups the child was exposed to. Although early introduction of solids was considered to be when a child was introduced to solids below the age of 4 months, during the analysis we considered different levels of exposure as provided by the included studies. Studies that were not included in the meta-analysis were included in a narrative synthesis.

All analyses were performed using STATA 14 statistical package.

3 | RESULTS

Electronic searches identified 1414 records (Figure 1). Following removal of duplicates, 1092 articles underwent title and abstract screening; of these, 987 were excluded. The remaining 105 papers underwent full-text review, and 89 articles were excluded, leaving 17 articles for inclusion. Two studies were added after screening trial registries (Australian and New Zealand trial registry).

Of the 17 papers included in the review, 11 were birth cohort studies.^{3,4,7,8,14–21} As the LISA birth cohort study generated 2 publications,^{17,18} the number of papers exceeds the number of study populations. There was 1 cross-sectional study,²² 2 case-control studies^{23,24} and 2 randomized controlled trials.^{25,26} Among the birth cohort studies, one was a high-risk birth cohort.⁸ The exposure differed considerably among the studies. In some, it was any solid food^{7,8,15,17,18,21} while in others, the exact food item was mentioned^{3,4,14,16,20,27} (Table 1). The age of eczema outcome was also different between studies (1–6 years). Also, the definition used for diagnosis of eczema differed between studies. Some used questionnaire-based diagnosis (the questionnaire identifies whether child had eczema or not),¹⁵ and in others, a clinician diagnosed the condition.^{7,17,18} Some studies adjusted for potential confounding factors such as parental and sibling atopy and type of breastfeeding^{7,8} while others did not.²⁰ Further details of the selected studies are given in Tables 1 to 4.

*ITA—Intention-to-treat analysis.

3.1 | Synthesis of study findings

3.1.1 | Overview of the included studies

The 2 randomized controlled trials of egg introduction did not find evidence that early introduction of egg was protective against eczema^{25,26} (ORs: 0.90(0.65, 1.24) and 0.84(0.57, 1.23), respectively).

Both studies performed the intervention on children <1 year of age. Both trials presented the results of the intention-to-treat analysis but only 1 study adjusted for baseline disparities.²⁵ The diagnosis of eczema in both studies was made by a clinician, and the outcome was assessed during early childhood (1 year).

There were 11 birth cohort studies. Six of these investigated the association between any solid food introduction and eczema.^{3,4,7,8,14–21} All 6 assessed the outcome of eczema in early childhood (below the age of 6 years). Except for the CAPS study,¹² all were population-based cohorts. Only 1 study found that delayed introduction of any solids increased the risk of eczema.⁷ Seven birth cohort studies investigated the introduction of specific allergenic foods such as cereal, fish, eggs or fruits.^{3,4,8,14,16,19,20} From the 3 studies investigating the association between only fish introduction (rather than a multifoed exposure including fish²⁰ and eczema, early vs late introduction of fish was found to have consistent evidence of protection.^{3,14,20} Early fruit or cereal introduction did not show evidence of protection for eczema.^{3,20}

The cross-sectional study did not show any significant association.²² The results from the case-control studies were conflicting.^{23,24} One study found solid introduction before 4 months increased the risk of eczema²³ while the other found a protective effect.²⁴

3.2 | Study quality

The quality of the cohort studies was generally within the range of satisfactory (a minimum score of 5) to very good (a maximum score of 10), while the cross-sectional and case-control studies all achieved a score of more than 6 (tables S1–4). The common area of weakness was how the researchers assessed the exposure and dealt with the possibility of reverse causation in terms of early signs of allergic disease in the children. Most studies did not account for reverse causation based on family history of allergy and breastfeeding. However, even among the studies which accounted for reverse causation, the evidence was inconclusive.

3.3 | Studies that were not included in the meta-analyses

There were 3 observational studies that we could not include in the meta-analysis as risk ratios were not provided.^{3,4,20} Details of these studies are presented in Table 2.

Hesselmar et al³ found that introduction of many food items including allergenic as well as non-allergenic food was delayed among children who had eczema compared to the no-eczema group. Kull et al⁴ investigated the association between the timing of introduction of fish and eczema finding that later exposure to fish increased the risk of eczema at 1 year of age. The other study which investigated early fish exposure and eczema observed a protective effect HR:1.73(0.75, 3.99).

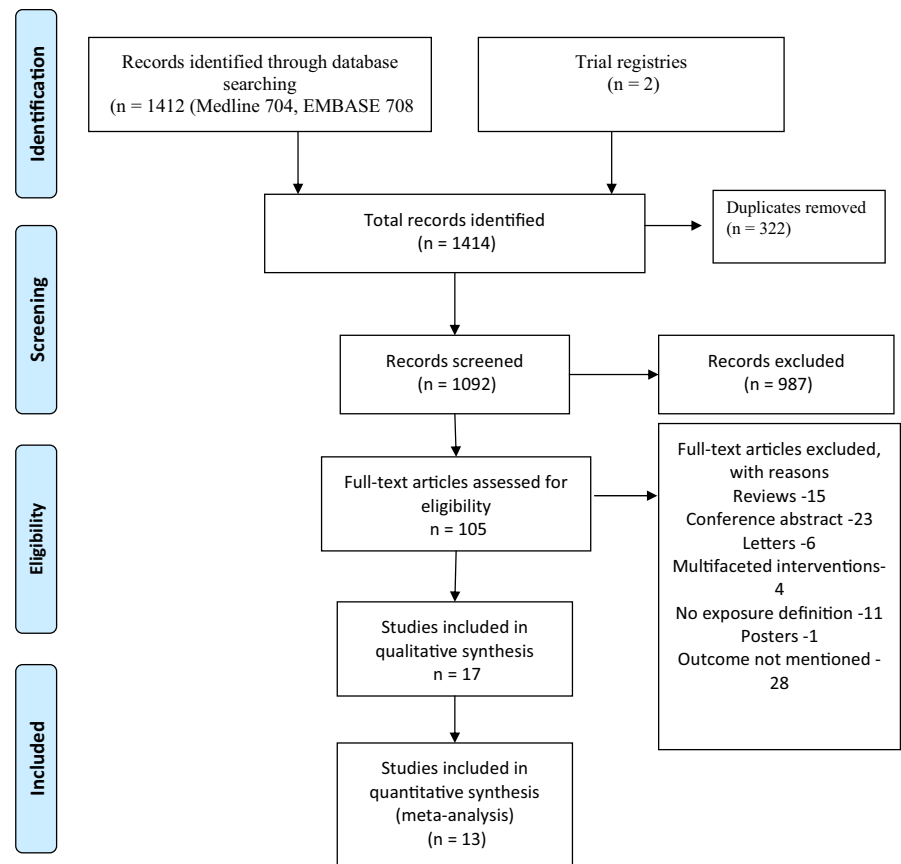


FIGURE 1 The PRISMA flow diagram for selection of studies for the review

3.4 | Studies included in the meta-analyses

3.4.1 | A. Evidence based on RCTs

Introduction to egg

There were 2 randomized controlled trials which investigated the effect of timing of introduction of egg and the risk of eczema (pooled OR: 0.87, 95% CI: 0.68, 1.12, I^2 0.0%) (Figure 2). In 1 trial, the prevalence of eczema among children exposed to egg from 4 to 8 months was not different from the placebo group (RR:0.90, 95% CI: 0.65, 1.24).²⁴ The second trial also found no protective effect in the egg group compared to placebo (0.84 [0.57-1.23])²³; however, when the children with eczema were stratified by atopic status, there was some evidence for a reduction of atopic eczema in the intervention group ($P = .09$).

3.4.2 | B. Evidence from observational studies

Introduction to first solids

Introduction to solids after 7 months of age compared to early introduction (<4 months)

Pooling 4 birth cohort studies, we found no evidence for an association between increased risk of eczema for late introduction to solids (>7 months) compared to early introduction (<3-

4 months) (OR:1.04 95%CI:0.77, 1.44, I^2 54.5%) (Figure3) (Figure 3 $I^2 = 54.5\%$).

Introduction to solids after 4 months of age compared to early introduction (<4 months)

Pooling 2 case-control studies and 1 cross-sectional study, infants who were exposed to solids after 4 months of age compared to before 4 months demonstrated no evidence of association with eczema risk (OR: 1.14 95% CI: 0.37, 3.58) (Figure 4). The reliability of this estimate is undermined by the high heterogeneity of the pooled studies ($I^2 = 88.1\%$).

Introduction to solids between 4 and 6 months of age compared to early introduction (<4 months)

Meta-analysing 4 birth cohort studies with introduction of solids between 4 to 6 months of age showed no association with risk of eczema (OR: 0.91 95% CI: 0.78, 1.07, $I^2=0.00$) when compared with those who had solids introduced before 4 months (online repository Figure 5, $I^2 = 0.0\%$).

Introduction to allergenic foods (evidence from birth cohort studies)
Introduction to specific allergenic solids (early vs late) and the risk of eczema

Pooling results from 3 birth cohorts (1 high-risk) which had data on earlier (<9 or <6 months) compared to later

TABLE 1 The association between the timing of first food (allergenic) introduction and eczema (randomized controlled trials included in the review)

Author, year, Study name, country and the sample size	Exposure definition	Outcome definition	Confounding factors considered during the analysis	Results	Main findings
Tan et al 2016 ²⁶ BEAT Australia N = 319 infants were randomized, 165 to egg and 154 to placebo	Intervention with egg powder or rice powder between 4 and 8 mo of age 350 mg egg protein daily from 4–8 mo	Modified Hanifin and Rajka criteria 1 y	-	Time-point ITA* 4 mo Intervention started 8 mo Intervention completed 12 mo Eczema evident on examination in Placebo group (n, %) 45/154 (29%) Eczema evident on examination in Egg group (n, %) 37/164 (23%) RR(95%CI) 0.77 (0.53, 1.12) 1.10 (0.78, 1.56) 0.90 (0.65, 1.24)	The prevalence of eczema is the same between the egg exposed and placebo groups
Palmer et al 2016 ²⁵ STEP Australia N = 820 infants with atopic mothers were randomized into 2 groups, egg powder (n = 407) or a colour-matched rice powder (n = 413). (excluded infants who had a history of allergic disease or any previous known direct ingestion of egg)	The intervention (egg powder 0.4 g/d), mixed with carrot, pineapple and rice powders; the control (egg-free), only carrot, pineapple and rice powders were given to infants (starting from age 4 to 6 mo) to 10 mo.	Doctor diagnosed 1 y	City, infant sex, breastfeeding status and paternal history of allergic disease.	ITA* Eczema Atopic eczema Control group 45 of 378 (11.9%) 20 of 379 (5.3%) Allergenic food group 40 of 374 (10.7%) 10 of 372 (2.07%) aRR and 95%CI 0.84 (0.57–1.23) 0.53 (0.26–1.09) P value .37 .09	The prevalence of eczema is the same between the egg exposed and egg-free groups

TABLE 2 The association between the timing of first food introduction and eczema (cohort studies included in the review)

Author & year, Study name, Country, type of population and sample size n/N-(analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) Age How measured	Confounders/selection bias, stratification and reverse causation	Results	Main finding
Cohort Studies					
Chuang et al 2011 ¹⁵ Taiwan Birth Cohort Study Taiwan Population based n/ N = 18 773/24 208	Any solid food and age first solid introduced Measured at 6 and 18 mo Interviewer-administered questionnaire	Parent report of Doctor diagnosis 6-18 mo Questionnaires	Adjusted for infants' gender, birth order, birthweight and gestational age, parents' age, education, allergic history, place of residence, maternal smoking or passive smoking during pregnancy, mould spots, carpet and pets. Considering reverse causality, 2399 children with eczema in the first 6 mo were excluded from the analysis	Introduction of solids and eczema from 6 to 18 mo Time of solid introduction Yes No 41 806 906 15 139 103 1778 aOR (95%CI) 1 1.11 (0.80, 1.53) 1.08 (0.74, 1.57) P value .593 .698	No association between early/late introduction of solid food and eczema from 6-18 mo
Snijders et al 2008 ⁷ KOALA birth cohort Netherlands Population based n/ N = 2434/2558	First food products ingested, measured at 3, 7, 12 and 24 mo by self-administered questionnaire	1. Parent-reported eczema at 3, 7, 12 and 24 mo 2. Eczema defined at the age of 2 y using UK working party criteria 24 mo	Adjusted for duration of breastfeeding, gender of infant, recruitment group (conventional, alternative lifestyle), maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery (in years), maternal education, presence of parental allergic disease and (older) siblings' atopic history. Exclusion of infants with early symptoms of eczema (to avoid reverse causation) did not essentially change results.	Introduction of solid food and infants' Eczema Age at solid introduction 3 4-6 >7 P for trend aOR(95%CI) 1.00 1.28 (0.91-1.81) 2.10 (1.17-3.76) .02 Eczema at 24 mo defined using UK working party criteria aOR(95%CI) 1.00 2.67 (0.80-8.97) 9.46 (2.05-43.61) <.001	Delayed introduction of solids associated with increased risk of eczema

(Continues)

TABLE 2 (Continued)

Author & year, Study name, Country, type of population and sample size n/N (analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) definition Age How measured	Confounders/selection bias, stratification and reverse causation	Results	Main finding
Zutavern et al 2008 ¹⁸ LISA birth cohort Germany Population based n/ N = 2073/3097	6 mo, parents reported age of first solid introduction from 1st to the 6th months of age (1st/2nd month, 3rd/4th month, 5th/6th month) reported by mother	Parent-reported Doctor-diagnosed eczema 6 y	Adjusted for study centre, parental allergy, gender, parental education and breastfeeding type. Early life atopic status or parental history of allergy did not alter the association between age of solid food introduction and eczema at 6 y	Introduction of solids and eczema at 6 y of age Timing of solid introduction Ref (0–4 mo) 5–6 mo >6 mo	No association between introduction of solids beyond 4 or 6 mo and eczema at the age of 6 y OR(95%CI) 1 0.92 (0.61, 1.39) 0.82 (0.49, 1.40)
Mihrshahi et al 2007 ⁸ CAPS birth cohort Australia High-risk population n/N = 516/616	Solids given regularly by the age of 3 mo by interviewer-administered questionnaire at 3 mo	By observation eczema at age 5 y by a research nurse/parent-reported combined with seeking medical care/use of steroid cream for eczema 5 y	Adjusted for intervention or control group allocation, mothers and fathers history of asthma, maternal smoking during pregnancy and the gender of the child.-	Association between introduction of solids and eczema at age 5 y Age at solid food introduction By 3 mo Yes compared to no	No association between the timing of solid introduction and eczema. aOR(95%CI) 0.59 (0.33, 1.04)
Zutavern et al 2006 ¹⁷ LISA birth cohort Germany Population based n/ N = 2612/3097	Solids introduced age obtained by a self-administered questionnaire at 6, 12, 18 and 24 mo	Parent-reported doctor-diagnosed eczema 2 y	Adjusted for study centre, parental atopy, child's gender, parental education, birthweight and breastfeeding type. Infants with early skin or allergic symptoms had increased risk of symptomatic eczema (not doctor diagnosed) when exposed to delayed introduction of solids	Association between the introduction of solids and eczema from 0 to 24 mo Timing of solid introduction Ref(0–4 mo) 5–6 mo >6 mo	No association between delayed introduction of solids beyond the 6 mo and prevention of eczema by 2 y of age OR(95%CI) 1 1.02 (0.64, 1.62) 0.96 (0.53, 1.74)

(Continues)

TABLE 2 (Continued)

Author & year, Study name, Country, type of population and sample size n/N-(analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) definition Age How measured	Confounders/selection bias, stratification and reverse causation	Results	Main finding		
				Timing of solid introduction	Non-intervention group (any solid) Symptomatic eczema aOR(95% CI) Doctor-diagnosed eczema aOR (95%CI)	Intervention group(any solid) Symptomatic eczema aOR (95%CI) Doctor-diagnosed eczema aOR (95%CI)	No association between delay in any solid food introduction and eczema.
Filipak et al 2007 ²¹ Birth cohort study Germany Began as RCT investigating hydrolysed vs cow's milk formulae An intervention group n = 2252 and a non-intervention group n = 3739	Solids introduced age obtained by a self-administered questionnaire at the age of 12 mo	Doctor-diagnosed eczema 4 y	Adjusted for family history of eczema and atopy, type of milk feeding such as breastfeeding or formula feeding,	0-4 mo 5-6 mo >6 mo	1 0.86 (0.66-1.12) 1 (0.72-1.40)	1 0.95 (0.69-1.31) 1.00 (0.72, 1.39)	1 1.14 (0.81-1.59) 1.28 (0.91, 1.81)
Niinivirta et al 2014 ²⁰ Probiotic intervention birth cohort Finland high-risk cohort n/N = 256/256	Details of solids given to the child until the age of 1 y by a self-administered food diary	Doctor-diagnosed atopic eczema 4 y	Child's gender, parental perception of child's possible reactions and study group	Timing introduction Fish ≥7 mo Cereal ≥7 mo		HR (95%CI) 1.73 (0.75, 3.99) 1.43 (0.73, 2.80)	No association between delayed introduction and eczema.
Nwaru et al 2013 ¹⁹ DIPP birth cohort Finland high-risk cohort n/N = 3109/3789	Self-administered questionnaire at 3, 6 and 12 mo of age	Parent-reported doctor-diagnosed ever eczema 5 y	Adjusted for sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 y of age, mode of delivery and birthweight Interaction tests for eczema by 6 mo and parental allergic history were performed to evaluate the potential for reverse causality.	Timing of Cereal Introduction <4.5 mo 4.5-5.5 mo 5.5 mo		OR(95%CI) 1.47 (1.10, 1.97) 1.17 (0.88, 1.56) ref	Introduction of cereal <4.5 mo associated with increased risk of eczema

(Continues)

TABLE 2 (Continued)

Author & year, Study name, Country, type of population and sample size n/N-(analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) definition Age How measured	Confounders/selection bias, stratification and reverse causation	Results	Main finding
Tromp et al 2011 ³ Generation R cohort study Netherlands Population based n/ N = 6300/6905	Food frequency questionnaire administered at 6 and 12 mo	Parent reported physician-diagnosed eczema (ISAAC definition) At the ages of 2, 3 and 4 y	Adjusted for sex, mother's socio-economic status, race/ethnicity, smoking during pregnancy, gestational age, birthweight, parity, breastfeeding, parental history of atopy and any of the following from 12 to 24 mo: antibiotics day care attendance, gastroenteritis, respiratory tract infections, over weight A history of cow's milk allergy in the first year of life increased the risk of eczema Parental history of allergy increased the risk of eczema	Introduction of allergenic foods and eczema at ages 2, 3 and 4 y Food group introduced ≤ 6 mo Hen's egg Peanut Tree nuts Soy Gluten 1.10 (0.51-2.32) 1.11 (0.34-3.61) 1.54 (0.35-6.69) 1.33 (0.72-2.44) 0.90 (0.71-1.14) 0.87 (0.69-1.10) 0.99 (0.72-1.36) 1.16 (0.76-1.76) 0.95 (0.75-1.19) 0.90 (0.76-1.06) 1.05 (0.81, 1.35) 0.87 (0.65, 1.16) 1.06 (0.72, 1.56) 0.97 (0.80, 1.17) 1.02 (0.81, 1.27)	No association between delayed introduction of allergenic foods after 6 mo and prevention of eczema
Hesselmar et al 2010 ³ Allergy Flora birth cohort Sweden Population based n/ N = 184/256	Food diaries maintained by the mother at the ages of 0-6 and 6-12 mo	Parent-reported ever eczema 1 y	Adjusted for: maternal and paternal history of allergy, as well as ongoing breastfeeding at 6 mo of age After controlling for reverse causation (eczema ever in the first 6 mo), there was no change in results	Introduction of different food items, in relation to a diagnosis of 'eczema at 18 mo of age Food type Fruit Solids ^a Fish Egg ^a Solids—potatoes, root vegetables and meat Delayed introduction of fish for every 2 moths associated with 16% increased prevalence of eczema (OR 1.16 (95% CI 1.02-1.33), Median age and the IQR at which the food items were introduced Eczema Yes 5 (4, 5) 4 (4, 5) 11 (8, 13) 13 (10, 13) No 5 (4, 5) 4 (4, 4.6) 8 (6, 11) 11 (9, 13) P .859 .971 .004 .070	Early fish introduction protective against eczema
Alm et al 2009 ¹⁴ Birth cohort Western Sweden Population based n/ N = 4941/8176	Food introduction by a self- administered questionnaire biannually	Parent-reported ever eczema 1 y	Maternal eczema, sibling with eczema, bird in the home and cow's milk allergy	Allergenic food introduction By 9 mo Yes compared to no	Early introduction of fish has a protective effect on eczema aOR(95%CI) 0.9% (0.60, 1.54)

(Continues)

TABLE 2 (Continued)

Author & year, Study name, Country, type of population and sample size n/N-(analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) Age How measured	Confounders/selection bias, stratification and reverse causation	Results	Main finding
Mihirshahi et al 2007 ⁸ CAAPS birth cohort Australia High risk n/N = 516/616	Allergenic food(arbitrarily defined as cow's milk, eggs, nuts or fish) introduction By 9 mo by a by interviewer administered questionnaire at 1, 3, 6, 9 and 12 mo	Dr diagnosed 5 y	Intervention or control group allocation, mothers and fathers history of asthma, maternal smoking during pregnancy and the gender of the child	Introduction of solids and eczema at 1 y of age Age at introduction of fish Before 9 mo After excluding children with eczema during the first year of life, the association of fish consumption ≥2-3/mo compared to ≤1/mo during the first 12 mo associated with increased risk of eczema at 4 y aOR 0.76 (95% CI 0.60-0.98)	Late introduction of Allergenic solids not associated with risk of eczema
Kull et al 2006 ⁴ BAMSE birth cohort Sweden Population based n/ N = 2614/4089	Parent-reported timing of fish introduction to the child at 1, 2 and 4 y	Doctor-diagnosed eczema at 4 y	Adjusted for parental allergic disease, maternal age, maternal smoking and breastfeeding. After excluding infants had eczema during the 1st year of life showed significant association with fish in diet during first 12 mo and eczema at 4 y.	Association introduction of fish during the first 12 mo of age and eczema at age 4 y Reported fish in diet (first 12 mo) Never Once a month 2-3 times a month Once a week ≥Once a week P trend aOR and 95%CI 0.72 0.51-1.00 0.71 0.53-0.95 0.54 0.41-0.70 0.57 0.43-0.76 <.001	Fish in diet during the first year of life is associated with reduced risk of eczema
Cross-sectional studies					
Horwitz et al 2009 ²² United States Children current age of 5 to 18 y and a diagnosis of eczema N = 177	Solid food introduction by both medical record reviewing and parental questioning during the health care visit	Doctor diagnosed At the 5 y, children were divided into 2 groups; persistent eczema and non-persistent eczema (in remission)		Age at solid food introduction Type of atopic dermatitis at the age of 5 y Persistent (not in remission) Non-persistent (in remission) 34 14 15 ref 1.10 (0.47, 2.60) Reference group—children without persistent eczema at the age of 5 y	No association between timing of solid food introduction and persistence of eczema
Case-control studies					

(Continues)

TABLE 2 (Continued)

Author & year, Study name, Country, type of population and sample size n/N-(analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) definition Age How measured	Confounders/selection bias, stratification and reverse causation	Results	aOR(95%CI)	P value	Main finding
Sahakyan et al 2006 ²³ Armania N = 85 cases and 155 controls	Cases: children aged 1-7 y and diagnosed with eczema by a paediatrician Controls: children aged 1-7 y who have never been diagnosed with eczema Information regarding age of first solid food introduction collected using telephone interviews with mother of the child	UK working party's criteria 1 y	Adjusted for: birthweight, gestational age, presence of atopic diseases (eczema, asthma, wheeze, urticaria, allergic reactions to food, contact rashes and hayfever) in the parents, surroundings of child's home and antibiotic use in the first year of life	Age of solid introduction Solid food introduction before 4 mo vs after 4 mo	3.1 (1.4, 6.9)	.006	Solid food introduction before 4 mo increased eczema risk
Sariachvili et al 2010 ²⁴ PIPO cohort Belgium N = 252 cases and 305 controls	Cases: children with 1 or more episodes of parent-reported eczema during the first 4 y of life Controls: children without parent-reported eczema up to 4 y of age Parents provided information about introduction of solid foods when the child was 12 mo old	Parent-reported eczema using ISAAC definition Ever eczema up to 4 y	Adjusted for: child's gender, birthweight and birth order, maternal age, parental allergy and educational level, smoking in pregnancy, passive smoking up to 4 y and breastfeeding. Early introduction of solids reduced eczema significantly among children with parents with allergy	Age of solid introduction Solid food introduction before 4 mo vs after 4 mo	aOR(95%CI) 0.49 (0.32, 0.74)		Early solid introduction has a protective effect towards eczema

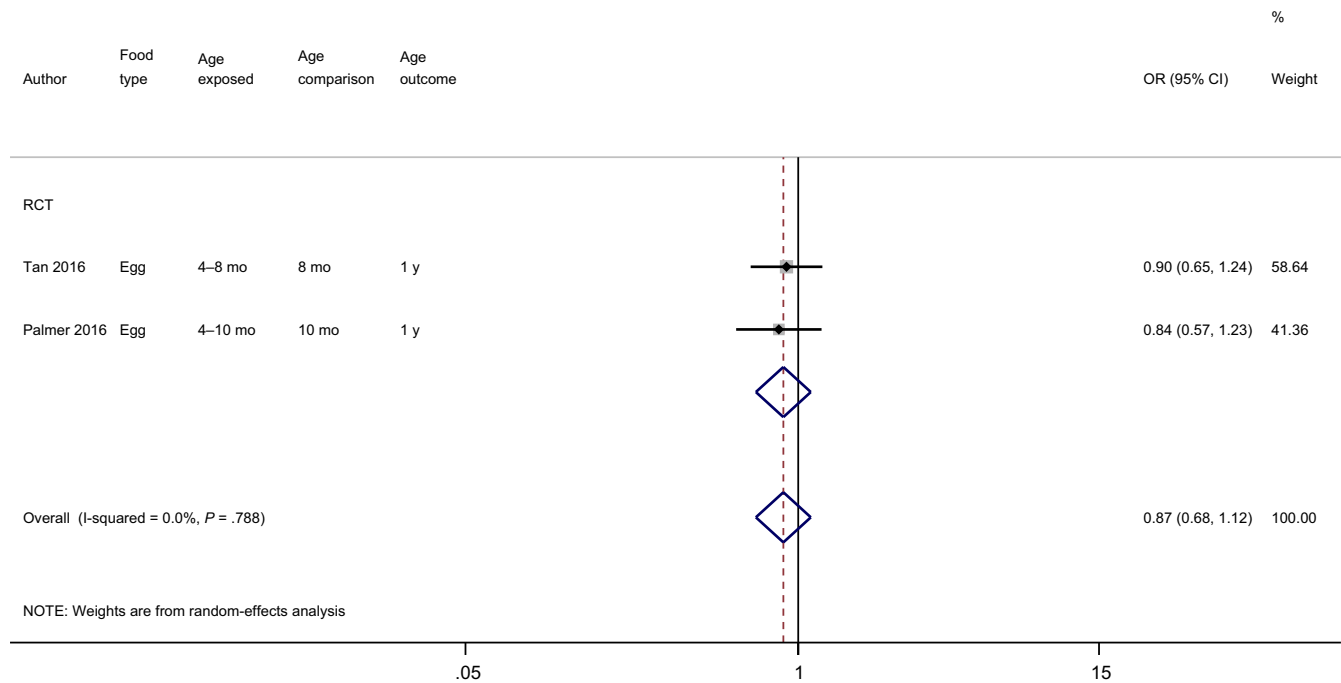


FIGURE 2 Meta-analysis: The association between introduction to egg and eczema

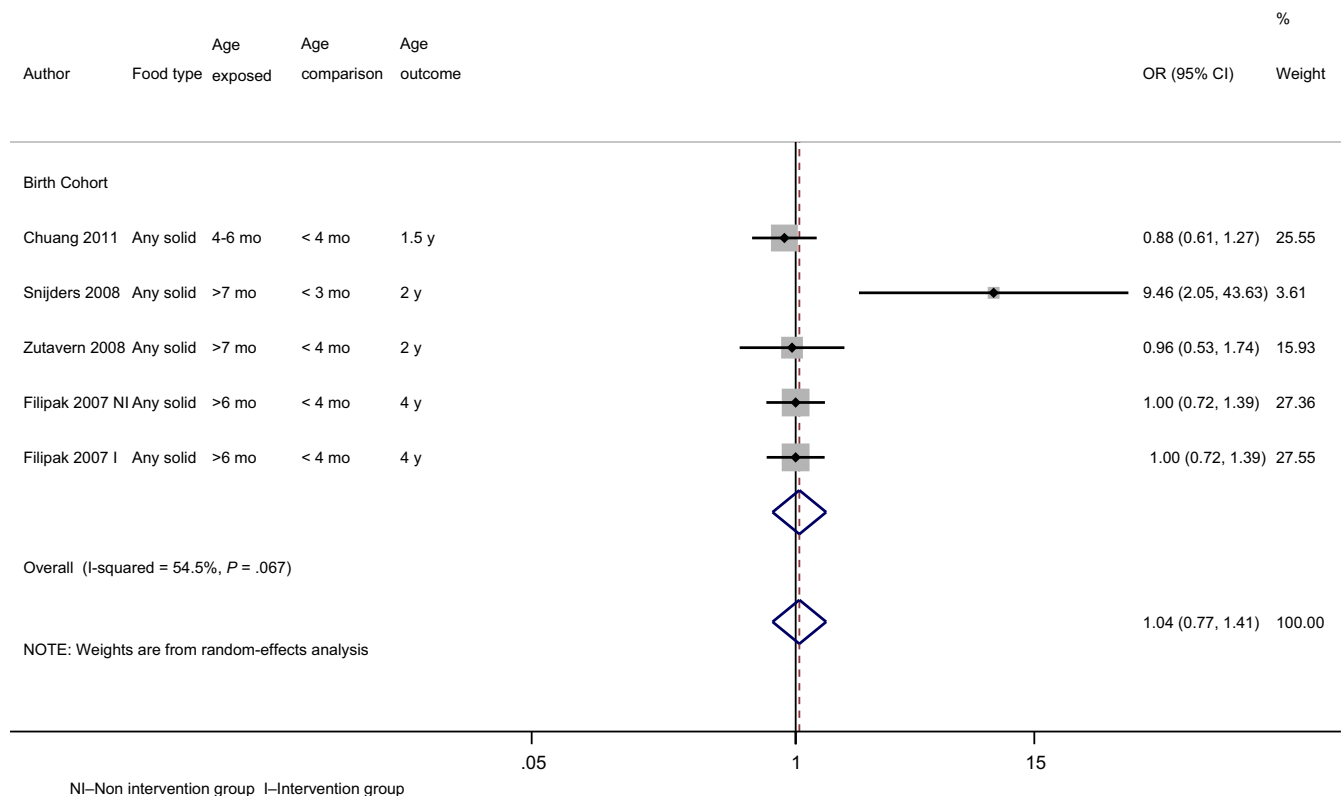


FIGURE 3 Meta-analysis: The association between introduction to solids after 7 mo of age and the risk of eczema

(>6- >9 months) introduction of specific allergenic food (fish and egg) showed a non-significant trend towards increased risk of eczema when allergenic food was introduced later (OR: 1.13 95% CI: 0.91, 1.42) (figure S1), with an I^2 of 45.04%.

Introduction to allergenic food (plant-based) other than fish (early vs late) and the risk of eczema

We confined the meta-analysis to age of exposure to plant-based allergens and, using 2 birth cohort studies, found no

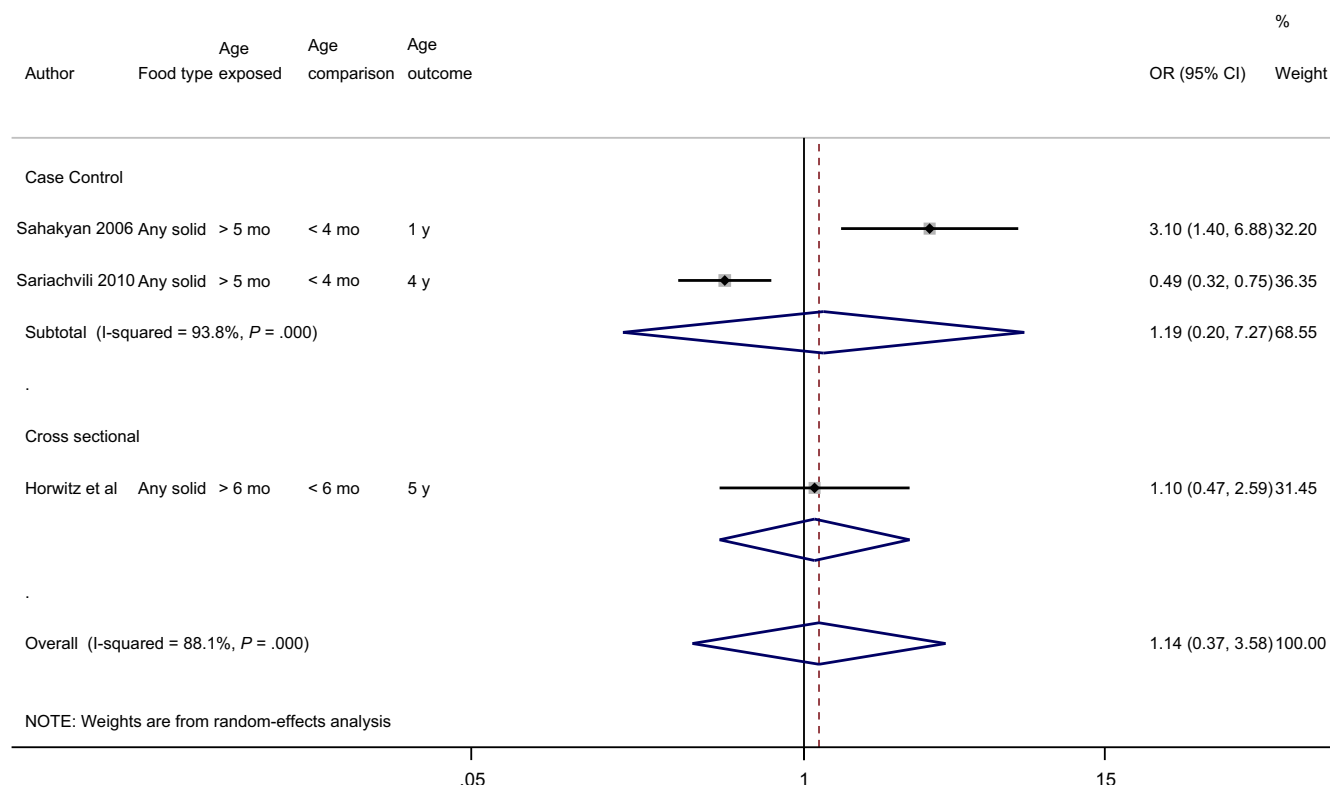


FIGURE 4 Meta-analysis: The association between introduction to solids after 4 mo of age and eczema

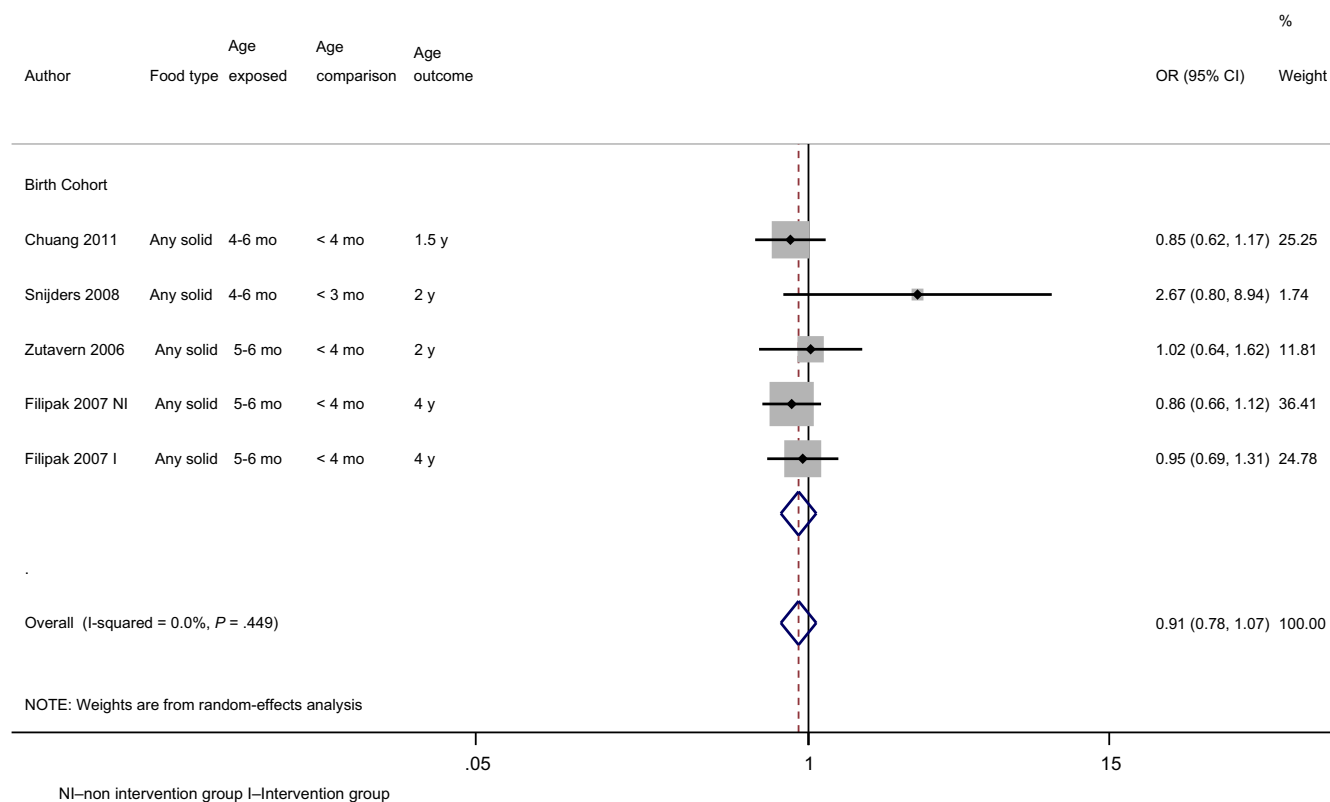


FIGURE 5 Meta-analysis: The association between introduction to solids between 4 to 6 mo of age compared with earlier introduction and eczema

association (OR: 0.82 95%CI: 0.58,1.18) (figure S2), with an I^2 of 74.2%.

4 | DISCUSSION

Overall, we found no strong evidence that early introduction of solid food was associated with less risk of childhood eczema. There was limited evidence of an association for introduction to specific allergenic foods. The evidence from RCTs of egg introduction was limited to 2 trials, 1 of which reported failure to achieve their desired sample size (pooled OR; 0.87, 95%CI; 0.68, 1.12). The observational studies (3 studies) which investigated the association between fish introduction and eczema suggested a protective effect with early introduction. We found no evidence that early introduction of cereal or fruit reduced the risk of eczema.

Although our review focussed on the timing of introduction of any solid food as opposed to allergenic food introduction as in the published systematic review by Ierodiakonou et al,¹³ our results are similar to their findings, despite a different research question and the inclusion of several different studies.¹³ Our review addresses primarily the association between first solids (both allergenic and non-allergenic) and the risk of eczema. Our findings suggest that the associations are similar between timing of introduction of non-allergenic and allergenic foods to infants and eczema.

In 2008, Prescott et al²⁸ described a critical window for development of maximum immune tolerance, which could have an impact on overall allergic disease outcomes of the child. It has been suggested that this critical window may span from 4 to 6 months of age, but this is controversial. This critical window is important as introduction of solids during this period and onset of eczema and persistent eczema may predict other allergic outcomes such as asthma and allergic rhinitis in later childhood.²⁹ With the increasing global prevalence of food allergy, introduction of allergenic food to infants has recently received much interest.¹⁷ Allergenic food introduction may have an impact on the child's immune system and this may be modified by other predisposing factors such as pre-existing allergic disease of the child and family history of allergy.^{17,18}

Part of the difficulty in assessing the relationship between solid food introduction and eczema is that there may be multiple forms of eczema or phenotypes, with common physical appearances, but different aetiological risk factors. In support of this concept was the stronger relationship between age of introduction to egg for atopic eczema, as opposed to non-atopic eczema. Additionally, there are many other factors that may be related to introduction of food that could also influence the risk of eczema,^{17,25} which may be potentially confounding or modifying the associations seen. Duration of exclusive breastfeeding, duration of total breastfeeding, formula introduction and the type of formula introduced prior to solid food introduction are some of the factors which are intimately related to solid food introduction and could also have an impact on the immune system and the risk of eczema.³⁰ Not all the studies have

commented on these factors. Other factors, such as family history of allergic disease and cultural beliefs are important, as these could have an impact on the feeding behaviour of the parents and influence risk of allergic disease in the child.³¹ Moreover, early symptoms of allergic disorders during infancy may influence the timing of solid food introduction³² as there is a belief in some communities that extended duration of exclusive breastfeeding (thus delaying the introduction of solid foods) is protective against childhood allergic disorders. As this belief may influence allergic families to delay solid introduction, it could lead to an association through reverse causation. Failure to account for this reverse causation will bias the association between later solid introduction and eczema. Therefore, the methodological quality of the studies in assessment of potentially confounding and modifying factors and reverse causality will be important in interpreting the study findings. Among the studies included in this review, only a few have looked at reverse causation with respect to duration of breastfeeding and allergic diseases (family history and childhood allergies)^{7,15,17,18} and these studies did not find evidence for reverse causation. All these factors have contributed to a significant amount of heterogeneity. Furthermore, we could not comment about the quantity of food introduced or any allergic reaction which occurred following food introduction as these data were not available.

We have limited evidence to comment on early life egg exposure and the risk of eczema. There was weak evidence from 1 RCT that early introduction of egg may reduce the risk of atopic eczema.²⁵ Two studies^{14,20} based in Scandinavian countries identified that earlier introduction of fish might be associated with reduced risk of eczema. Unfortunately, we do not have adequate details on the type of fish and the quantity introduced. Therefore, we are unable to comment in terms of n-3 fatty acids which have been postulated to reduce the risk of allergic disease. It is possible that n-3 fatty acids, which are rich in some fish, might cause such an effect. Despite the biologic plausibility that n-3 fatty acids may modulate the immune response, there is currently no consistent evidence that they reduce the risk of allergic disease. A number of observational studies have investigated breastmilk PUFA (poly unsaturated fatty acids) and their association with eczema in infants, but findings have not been consistent. Some studies showed a protective effect³³ associated with increased n-3 fatty acid levels in breastmilk while others did not.³⁴

In terms of "best evidence," if you had to choose between 1 RCT and a meta-analysis of birth cohort studies, the guidelines pertaining to hierarchy of evidence would suggest that the RCT carries more weight. Evaluation of this conundrum is not always straightforward. It would depend upon objective measures of the individual studies contributing evidence, including size, quality and risk of bias. The RCT involved may be small, non-representative of the target population and have extensive loss to follow-up introducing bias and lack of external validity, whereas the birth cohort studies may be relatively free from bias except from unknown confounders. The conclusion of this paper was based on evidence from both RCTs and birth cohort studies. An overall assessment of the "quality of evidence" for any meta-analysis could be estimated in a more objective

manner using the GRADE criteria;³⁵ however, it is difficult to know how you would then compare this to the quality of evidence contributed by 1 RCT.

Based on this review, we do not have adequate statistical evidence to say that solid food introduction at 4 months is better compared to introduction at 6 months or whether the timing of allergenic food introduction protects against development of eczema. Also, there is no consistency of results among the studies suggesting an unaccounted source of heterogeneity between the studies/study populations. As eczema is a disease which is closely related to other allergic diseases, there might be a strong genetic component³⁶ which could mask the true association with solid food introduction.

4.1 | Strengths and limitations of this review

This review contains all available peer-reviewed papers up to the final search date on food introduction and its association with eczema. Mostly, the evidence in this paper comes from birth cohort studies which are the strongest observational study design in which to assess potential causation as these studies use prospectively collected data and are therefore not affected by recall bias. Although different outcome definitions were used by the included studies, all of them were standard definitions developed by the researcher or clinicians. Creating different forest plots according to different age exposure categories has enabled us to get an overview of the available studies on timing of solid food introduction and allergic disease outcomes. All the studies in the review are of reasonably good quality according to the Newcastle-Ottawa scale. The disadvantage of different definitions was that we could not combine the outcome of atopic eczema with the other outcomes. Furthermore, multifaceted intervention studies were not included in the review as there were multiple exposures. Not all studies adjusted for important confounding factors, such as family history of allergic disease, gender and allergic disease of the child or looked for reverse causation. Also, we were unable to comment on the quantity of the food introduced to the child or any adverse reactions to that food. Furthermore, we have not included studies which investigated infant foods and exacerbations of existing eczema. The majority of the evidence we found was based on observational studies. Therefore, we are unable to comment on inherent biases and unknown confounding factors which may have influenced outcomes. While the evidence from well-conducted randomized controlled trials is robust, there is currently limited evidence.

4.2 | Future directions based on our findings

The available evidence is currently insufficient to determine whether the timing of solid food introduction influences the risk of eczema. Our review indicates that findings from RCTs and well-conducted observational studies are similar. Large observational cohorts can complement the evidence from RCTs as they are more likely to be representative of the target population for a universal population exposure such as introduction of solids. Future directions for individual studies may include better characterization of exposures in terms

of quantities, better characterization of outcomes in terms of phenotyping eczema, and a way to measure the cultural and familial reasons for the individual differences in timing of solid food introduction.

5 | CONCLUSION

The available evidence is inconclusive regarding the association between timing of any solid food introduction and the risk of eczema. There is currently no clear evidence to determine whether weaning at 4 months, between 4-6 months or after 6 months of age is better in terms of eczema risk. There is no impetus to alter current guidelines. All of which support the introduction of complementary food around or at 6 months of age with a spectrum of food items and the introduction of allergenic foods by 1 year with the aim of prevention of allergic diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Waidyatillake NT, Dharmage SC, Allen K, et al. Association between the age of solid food introduction and eczema: A systematic review and a meta-analysis. *Clin Exp Allergy*. 2018;48:1000-1015.
<https://doi.org/10.1111/cea.13140>