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AGE AT INTRODUCTION TO COMPLEMENTARY SOLID FOOD AND FOOD ALLERGY AND SENSITIZATION: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Abstract

Background and Objective

An infant's age at introduction of complementary solids may contribute to food allergy. We aimed to synthesize the literature on the association between age at introduction of complementary solids, excluding milk products, and food allergy and sensitization.

Design

We searched the electronic databases PubMed and EMBASE (January 1946-February 2017) using solid food, allergy and sensitization terms.

Methods

Two authors selected papers according to inclusion criteria, identifying 16 cohort studies, 1 case-control study and 8 randomized controlled trials (RCTs). Pooled effects across studies were estimated using random-effects meta-analysis.

Results

Cohort studies – Introducing complementary solids at age ≥4 months versus <4 months was not associated with food allergy (OR 1.22; 95%CI, 0.76-1.96) but was associated with food sensitization (OR 1.93; 95%CI 1.57-2.38). First exposure from age 4-6 months versus <4 months was not associated with food allergy (OR 1.01; 95%CI, 0.64-1.60) but was associated with food sensitization (OR 2.46; 95%CI 1.55-3.86).

RCTs – Egg exposure from age 4 months was associated with reduced egg allergy (OR 0.63, 95%CI, 0.44-0.90) and sensitization (OR 0.76, 95%CI, 0.51-0.95). Peanut exposure from age 4 months compared to delayed exposure was associated with reduced peanut allergy (OR 0.28, 95%CI 0.14-0.57).

Conclusions

We found no evidence from observational studies that introducing solids before 4 months protected against food allergy, but there was evidence for protection against food sensitization. From RCTs, introducing egg from 4-6 months and peanut from 4-11 months, reduced the risk of egg allergy, peanut allergy and egg sensitization.

PROSPERO systematic review registry (CRD42016033473).

Introduction

There is increasing interest in the timing of solid food introduction to infants as a potentially modifiable cause of the current food allergy epidemic. Solid foods can be separated into non-allergenic and classically allergenic foods. Several randomized controlled trials (RCTs) of introduction to allergenic solid foods found that early introduction, usually from age 4-6 months, reduced the risk of food sensitization and allergic disease[1-3] while other RCTs found no such benefit.[4-6] A recent comprehensive high-quality systematic review and meta-analysis synthesized the evidence from RCTs, finding that early introduction of egg (4-6 months; 5 trials, 1915 participants) was associated with a 46% reduction in the risk of egg allergy (95% confidence interval (CI) 17-66%) and early introduction of peanut (4-11 months; 2 trials, 1550 participants) was associated with a 71% risk reduction of peanut allergy (95%CI 26-89%).[7]

Introducing complementary solid foods is fundamentally different to introducing allergenic foods into an infant's diet. Complementary feeding provides the growing infant with calories, carbohydrates, proteins, fats, vitamins and minerals necessary for optimal growth that can no longer be completely supplied by breast milk or formula feeding. In contrast, early introduction to allergenic foods exposes infants to food allergens during a critical immune developmental window with the aim of inducing tolerance. The current literature on early introduction of allergenic foods may lead to confusion as it may not be appreciated that this is a separate concept with different aims and methods compared to introduction to complementary feeding generally.

Complementary solid feeding is an important infant milestone and is influenced more by child readiness, perceived need for extra nutrition, and parental factors than by guidelines, as evidenced by the low adherence to current guidelines in both low and high income countries.[8, 9] Complementary feeding, although starting with small "tastes" of various foods, usually a choice between fortified cereals, fruits or vegetables, quickly increases so that the child is soon consuming significant amounts. The goal of feeding during the first year is to gradually expand the baby's food repertoire to enable a healthy diet similar to the family's by one year of age.

The optimal age for introduction of complementary feeding is uncertain with conflicting evidence and recommendations from different authoritative bodies.[10] The World Health Organization recommended six months of exclusive breastfeeding with subsequent introduction of solids[11] while a later recommendation from another authoritative body was even more restrictive.[12] More recent guidelines aimed at clear and consistent advice recommend introducing solids by age 6 months but not before 4 months.[13, 14] However, at

least some of these recommendations were based on factors such as the growth rate and maturity of the child and maternal nutritional status[15] as much as on perceived risk of food allergy or sensitization. The timing of complementary food introduction may have an important yet unclear relationship with allergic disease. It would be difficult and perhaps unethical, to conduct an RCT using complementary food as the intervention and no complementary food as the control.

Hence, we aimed to systematically review and synthesise the evidence on the age at introduction of both allergenic and non-allergenic complementary food and compare and contrast the findings on the risk of food allergy and food sensitization.

Methods

PubMed and EMBASE electronic data-bases were systematically searched using key words and MeSH terms based on complementary solid food introduction and food allergy and sensitization. The search was augmented from the reference lists of the included articles and trial registries. The final search was performed on May 20th, 2016 and updated on February 15th, 2017. Further details of the search terms are given in the online supplement (S1). We created citation alerts for more recent publications. The review was prospectively registered in the PROSPERO systematic review registry (CRD42016033473). We note that the systematic review and meta-analysis by Ierodiakonou[7] bears some similarity to this systematic review. However, their search strategy and ours are quite different in timing and scope. The aims and content of their review were directed principally towards RCTs of highly allergenic foods with allergic and auto-immune disease outcomes. On the other hand, our review focused largely on cohort studies of complementary solid food exposure and food allergic outcome. Of the 16 cohort studies included in our review, only five[16-20] were included by Ierodiakonou et al. All but one[5] of the RCTs in our review were also included by Ierodiakonou.

Inclusion and exclusion criteria

We included any RCT, cohort, case-control and cross-sectional studies drawn from general and high-risk populations using human subjects and published in English in a peer-reviewed journal. No ethnic group was excluded. Conference papers, abstracts and letters to the editor were excluded. Studies were included where the exposure was the timing of introduction to complementary solid food or specific allergenic foods, whether timing was expressed as an exact age or as an age range, in months.

Studies with an outcome of food sensitization determined by skin prick test or food specific IgE were included as were studies where the outcome was food allergy determined by food challenge or a physician diagnosis of food allergy.

Study selection

Two authors (JB and NW) independently reviewed study titles and abstracts for detailed review of the full text. All duplicates were removed after the initial search. Any disagreements were resolved by consulting with a third author (CL). Studies were excluded after full text review if they did not meet the inclusion and exclusion criteria.

Data extraction

Two authors (JB and NW) independently extracted data that included the first author, publication year, study name and design, study population, exposure and outcome definitions and ascertainment, details of confounders included in the analysis and author conclusions.

Effect estimates

Odds ratios with 95% confidence intervals for the association between the exposure and outcome were extracted from each included manuscript. Most estimates were presented in tables but occasionally were identified in the text. If dichotomous estimates were not presented, continuous data from two groups were extracted.

Quality assessment and risk of bias

The same authors independently assessed study quality. Cohort study quality was assessed using the Newcastle-Ottawa scale (NOS)[21] and graded as good, fair or poor quality according to the thresholds for converting the NOS to AHRQ standards. The NOS is shown in the online supplement (Table S1). RCTs were assessed according to the Cochrane Review Quality assessment scale.

Data analysis

Studies reporting the infant's age at first exposure to solid foods and the outcome measured as an odds ratio with a 95% confidence interval were considered for inclusion in meta-analyses. A random effects estimate was computed and the I^2 statistic was used to assess heterogeneity. Results from meta-analyses with I^2>80% were not presented. All studies were included in a narrative synthesis. All analysis was performed using STATA 14.1 statistical software package (StataCorp, College Station, Texas. USA).

Results

In total, 1415 articles were identified. Following removal of duplicates, 1097 articles remained. After title/abstract review, 946 articles were excluded leaving 151 articles for full text review which identified 25 studies (16 cohort. one case-control and 8 RCTs) suitable for qualitative synthesis. From these, 9 cohort studies and 7 RCTs were included in meta-analyses. The 126 studies excluded did not provide sufficient detail on exposure and outcome measures. No RCT examined age at introduction of complementary solids and the risk of food allergy or sensitization. Figure 1 shows the PRISMA diagram for study selection.

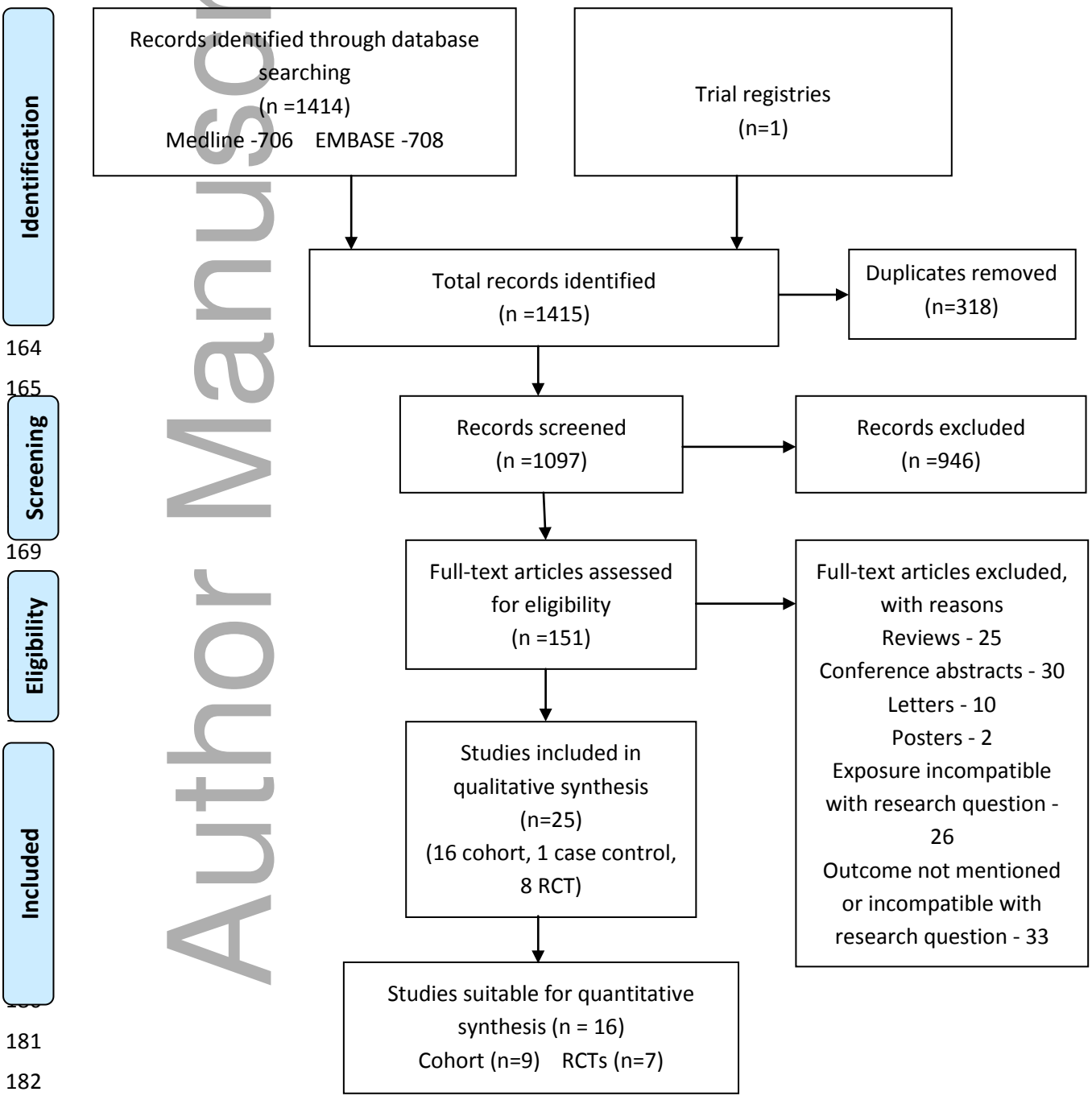

Figure 1

Cohort and Case-Control Studies

The findings from the 16 cohort studies[17-20, 22-33] and the single case-control study[34] are summarized in Tables 1 and 2. All but one study[31] achieved an AHRQ grade that was at least fair on the Newcastle Ottawa Scale (Table S1). The type of food sensitization or allergy examined varied widely, as did the exposures, with some having assessed the outcome in terms of age at introduction to solids generally[25-27, 30-33] while others assessed outcomes in relation to specific allergenic foods.[17-20, 23, 24, 28, 29] Eleven studies[19, 20, 22-24, 27-31, 33] reported that early introduction of solid food influenced later food sensitization or allergy while 5 found no such evidence.[17, 18, 25, 26, 32] Eleven studies[18-20, 23, 25, 28-33] enrolled participants from the general population while 5 enrolled participants at high risk of allergic disease.[17, 22, 24, 26, 27] Study outcomes were food sensitization (9 studies),[19, 20, 23, 27-30, 32, 33] food allergy (4 studies)[18, 22, 24, 25] or both (3 studies).[17, 26, 31] There were important differences in the definition of food allergy. One study used symptoms ± basic SPT,[24] two used physician-diagnosed food allergy ± threshold SPT,[25, 26] and four used oral food challenge.[17, 18, 22, 31] Four studies using oral food challenge found a reduced risk of food allergy from earlier introduction of solids,[31] fish,[17] egg[18] or peanut.[22] The age at which the outcome was determined ranged from 11 months[18] to 6 years[25, 33] although one study determined the outcome at a mean age of 7.3 years.[22]

Fifteen studies involving 20,407 participants gathered data on “solids”, “any solids”, or “solid food” as the exposure of interest from which exposure to specific foods and data on food allergy or sensitization could be extracted. Investigators from the LISA and DIPP cohorts each published two papers which included members of the cohorts twice.[20, 28, 32, 33] DIPP included 994 subjects common to both analyses and LISA included 1123 subjects common to both analyses. Thus, the nett participant number from the studies on allergy and solid foods was 18,290. The remaining study involving 300 participants did not report exposure to solids in general, reporting only exposure to peanut.[22]

Complementary food

Studies finding no association between age at complementary solid food introduction and food allergy or sensitization

Hesselmar et al.[17], classifying “solids” as potatoes, root vegetables or meat, found that those with compared to without documented allergy or sensitization to solids at age 18 months did not differ in the median age when solids were introduced.

Koplin et al.[18] found no association between age at introduction of 'any solid food' and egg allergy at 1 year after adjusting for appropriate confounders.

Luccioli et al.[25] found no association between the age at introduction of complementary solid food and physician-diagnosed food allergy at age 6 years in both 'normal risk' and 'high-risk' infants.

McGowan et al.[26] reported that, in a cohort of high-risk inner-city children, the mean age at introduction of solids was not associated with either food allergy or sensitization at age 5 years.

Studies finding an association between age at complementary solid food introduction and food allergy or sensitization

Kumar et al.[24] separated solids into two groups - rice, wheat and cereal - and the classically allergenic foods egg, peanut, tree nut, shell fish, fish, and sesame. Introduction of the first food group after compared to before age 6 months reduced the odds of allergy to those foods by age 36 months. Introduction of the allergenic food group before compared to after age 1 year was also associated with reduced odds of food allergy at 36 months, an effect not seen when these foods were introduced before and after age 6 months. These findings only applied to children without eczema.

In 2006, Zutavern et al.[32] with a study population of 2,614 reported that delaying the introduction of 8 groups of solids (vegetables, cereal, fruit, meat, dairy products, egg, fish, and 'others') to either age 5 or 6 months or beyond 6 months compared to ≤4 months did not protect against food sensitization at age 2 years. However, in 2008, the same authors reported on 1123 subjects from the same cohort and found that delaying the introduction of the same food groups beyond age 4 months was associated with a significantly increased food sensitization risk at age 6 years with the risk even greater in children without early allergic symptoms or skin disease.[33]

Kull et al.[19] reported on the age at introduction of fish and fish sensitization at age 4 years. They found a reduced fish sensitization risk with early fish introduction which was not seen when infants with eczema or wheeze were excluded.

Joseph et al.[23] studied introduction at <4 months of any solid and/or cow's milk and found that this was associated with significantly reduced peanut sensitization risk at age 2-3 years, but only in high-risk children.

Venter et al.[31] examined the introduction of solids before and after age 16 weeks in terms of food sensitization and food 'hypersensitivity' (determined by oral food challenge) and found that early introduction was associated with a reduced risk of both outcomes at ages 1 and 3 years.

Snijders et al.[30] studied food sensitization at age 2 years in terms of the introduction of solids including artificial formulas, raw/pasteurized milk, porridge, dairy products, yogurts and other foods such as fruit mash before and after age 3 months. They found that the introduction of solids between 4 and 6 months and at ≥7 months were each associated with an increased risk of sensitization to any food.

Mihrshahi et al.[27] examined introduction of solids generally and, separately, of allergenic foods (cow's milk, egg, nuts or fish) on atopy risk at age 5 years in a high-risk infant cohort. They found that the introduction of solids before compared to after age 3 months and of allergenic foods before compared to after age 9 months were each associated with a reduced atopy risk at age 5 years. However, atopy was defined as the presence of a positive SPT to any food allergen, HDM or inhaled allergen and results directed specifically to food sensitivity were not presented.

Grimshaw et al.[34] published results of a nested case-control study using the UK cohort of the EuroPrevall project.[35] From a multi-variable model, they found that infants with food allergy (double-blind placebo-controlled food challenge) at age 2 years had a 3.42-fold increased odds of food allergy if complementary solids had been introduced before compared to after the age of 16 weeks.

Specific allergenic foods

Egg

Four cohort studies involving 6,019 participants investigated egg exposure and egg allergy or sensitization.

Koplin et al. found that infants introduced to egg at age 10-12 months or >12 months compared to 4-6 months had a 1.6- and 3.4-fold increased risk of egg allergy at age 11 to 15 months.[18]

Hesselmar et al. found that later egg exposure (median 13 months versus 11 months) was moderately associated with a non-significant increased egg allergy risk at 18 months ($p=0.075$).[17] There was no association between age at egg introduction and egg sensitization at 18 months.

Nwaru et al., (2010),[20] found that egg introduced later than age 10.5 months compared to <8.1 months was associated with a 2-fold increased odds of egg sensitization at age 5 years.

In 2013, from a later study that included 994 subjects from the 2010 study, the same authors reported similar findings where egg introduction at 8 months compared to 11 months was significantly associated with 38% less odds of egg sensitization at age 5 years, while introduction of egg earlier than 8 months was associated with a non-significant 18% less odds of egg sensitization at 5 years.[28]

Fish

Three studies (6,472 participants) investigated fish exposure and fish allergy or sensitization outcomes. Hesselmar et al.[17] found that later introduction of fish (median age 13 months vs 9 months) was associated with a reduced risk of fish allergy but not fish sensitization at age18 months. However, Kull et al.[19] found that early introduction of fish (<8 months) was associated with a reduced risk of fish sensitization at age 4 years which became non-significant when children who developed eczema or wheeze during the first year of life were excluded. Nwaru et al.[28] found that the early introduction of fish (< 6 months and between 6 and 9 months vs >9 months) was associated with a reduced risk of sensitization to wheat, eggs and milk at age 5 years.

Peanut –

Bedolla Barajas et al.[22] examined peanut introduction before and after age 2 years in a cohort of 300 Mexican children in terms of peanut allergy (open food challenge). Those challenged had one or both of a positive SPT to peanut or a convincing history of peanut reaction. Introduction of peanut at or after compared to before age 2 years was associated with an 8-fold increased risk of peanut allergy at a mean age of 7.3 years.

Cereal –

Poole et al.[29] examined age at first exposure to cereal grain or rice cereal and wheat allergy (1612 participants). They found that delaying the age of cereal grain exposure to ≥7 months, compared to <7 months, was associated with a near 4-fold increased risk of wheat allergy at age 4 years. However, exposure to rice cereal at ≥7 months was not associated with wheat allergy at age 4 years. Major limitations were the poor objectivity of the definition of wheat allergy which was based on parent report (16 subjects) supported by physician diagnosis (4 subjects, 3 with elevated wheat specific IgE), and the small numbers of events, rendering the study conclusion suspect.

Meta-analyses –

Of the 16 cohort studies in Tables 1, ten[17, 19, 20, 22-24, 26, 28, 29, 32] were not considered for meta-analysis due to reporting the outcome as a mean or median age at introduction[17, 26] or because the age at exposure to complementary solids did not fit with the research question[20, 24, 28, 29] or the complementary food exposure did not fit with our definition of complementary solid food.[19, 22, 23] One excluded study formed the first part of a later, more complete study.[32] The single case-control study[34] was not considered for meta-analysis among the cohort studies.

Meta-analyses of the remaining six cohort studies[18, 25, 27, 30, 31, 33] were then planned where the age at exposure to complementary solids and the comparison age were ≥4 months and <4 months and the outcome was either food allergy or food sensitization. However, four studies [18, 25, 30, 33] presented results for age at complementary solids exposure in one or more age bands (4, 5, 6 and >6 months), each compared to exposure at <4 months. Within each study, we meta-analysed these age-band results to give a pooled estimate of the effect of exposure to complementary solids at age ≥4 months or more compared to <4 months. These pooled estimates were then used in meta-analyses where food allergy or food sensitization was the outcome.

Food allergy

From 3 studies, there was no evidence of association between exposure to complementary solids at age ≥4 months compared to <4 months and later food allergy (OR, 1.22; 95%CI 0.76 – 1.96; I^2=57.0%) (Figure 2). Sensitivity analysis performed by omitting the study by Luccioli (where food allergy was not assessed by food challenge) reduced the I^2 statistic to 28.2% without any change in the pooled estimate (not shown).

Similarly, there was no evidence of association between exposure to complementary solids at age 4-6 months compared to <4 months and later food allergy from 2 studies (OR, 1.01; 95%CI 0.64-1.60, I^2= 9.5%) (Figure 3).

Food sensitization

Exposure to complementary solids at age ≥4 months compared with <4months was associated with an increased risk of food sensitization from 3 studies (OR, 1.93; 95%CI 1.57-2.38, I^2= 0%) (Figure 4). To minimize heterogeneity, this meta-analysis excluded Venter et al. which did not consider confounding. However, a sensitivity analysis with Venter et al included did not alter the pooled estimate (not shown). Similarly, from 3 studies, exposure to

363 complementary solids at age 4-6 months (compared with <4months) was associated with an
364 increased risk of food sensitization (OR, 2.46; 95%CI 1.55-3.86, I^2= 2.2%) (Figure 5).
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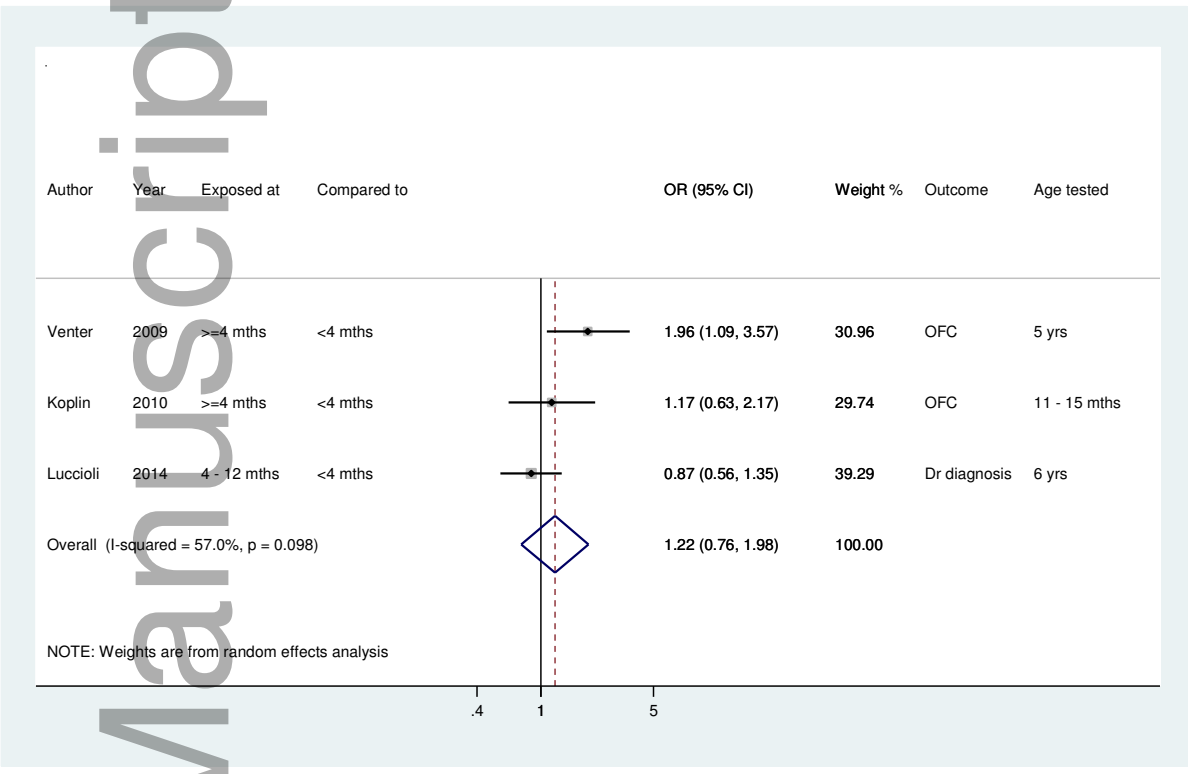
366 **Forest plots – Cohort studies** .



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368 Figure 2

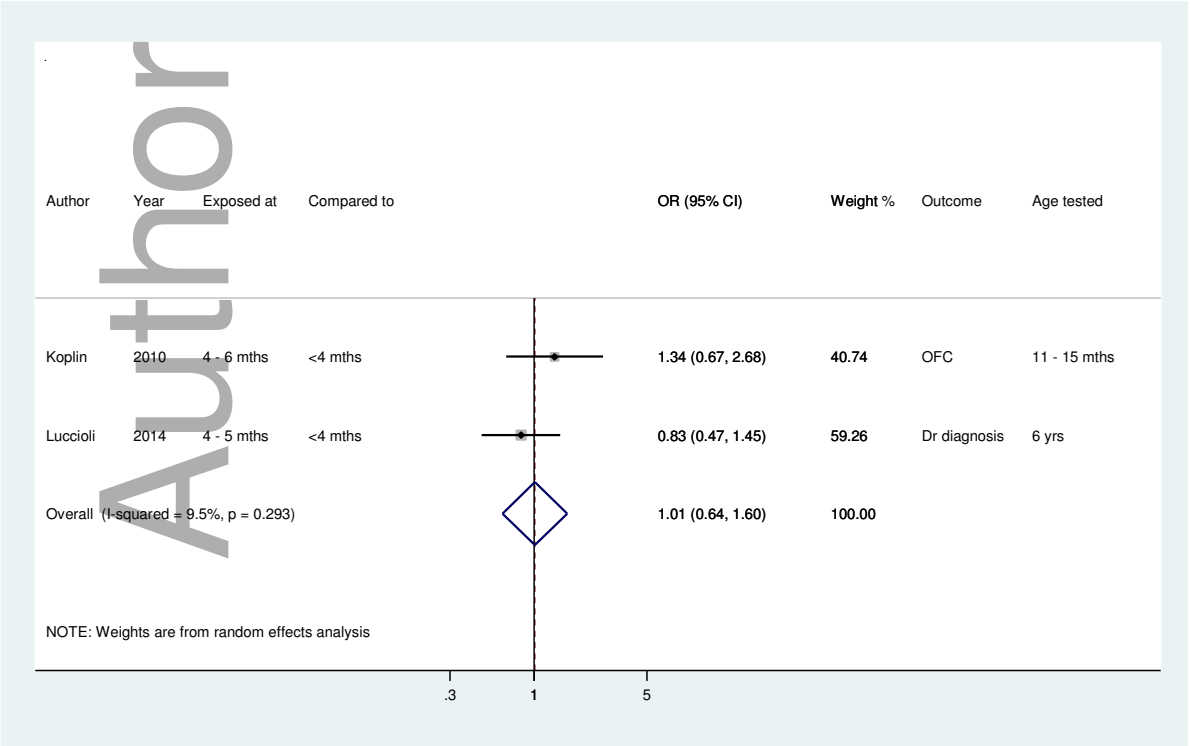

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Figure 3

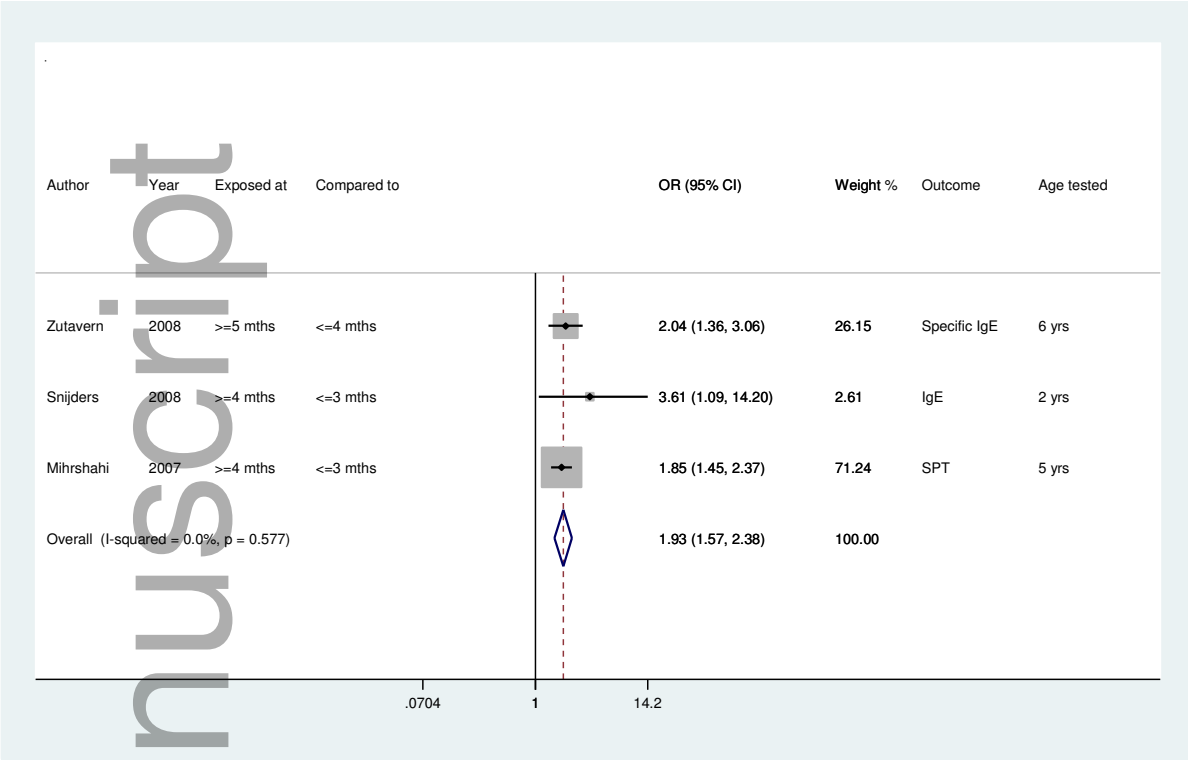

Figure 4

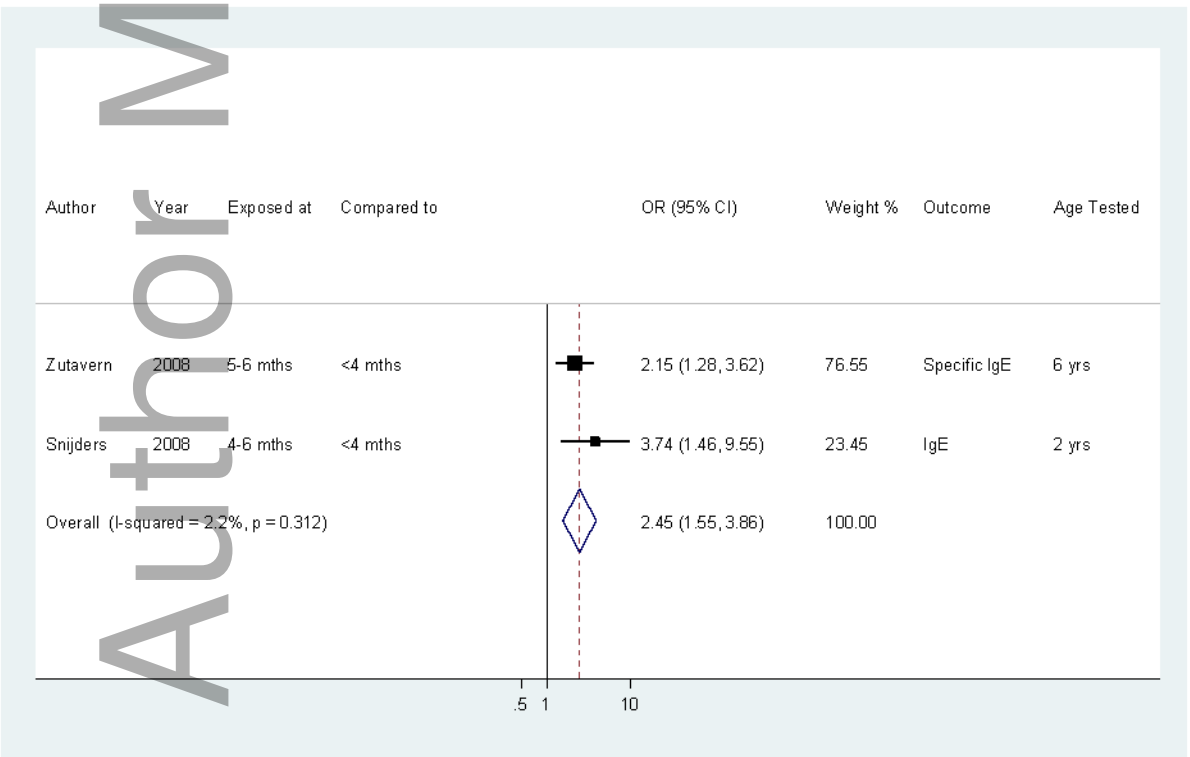

Figure 5

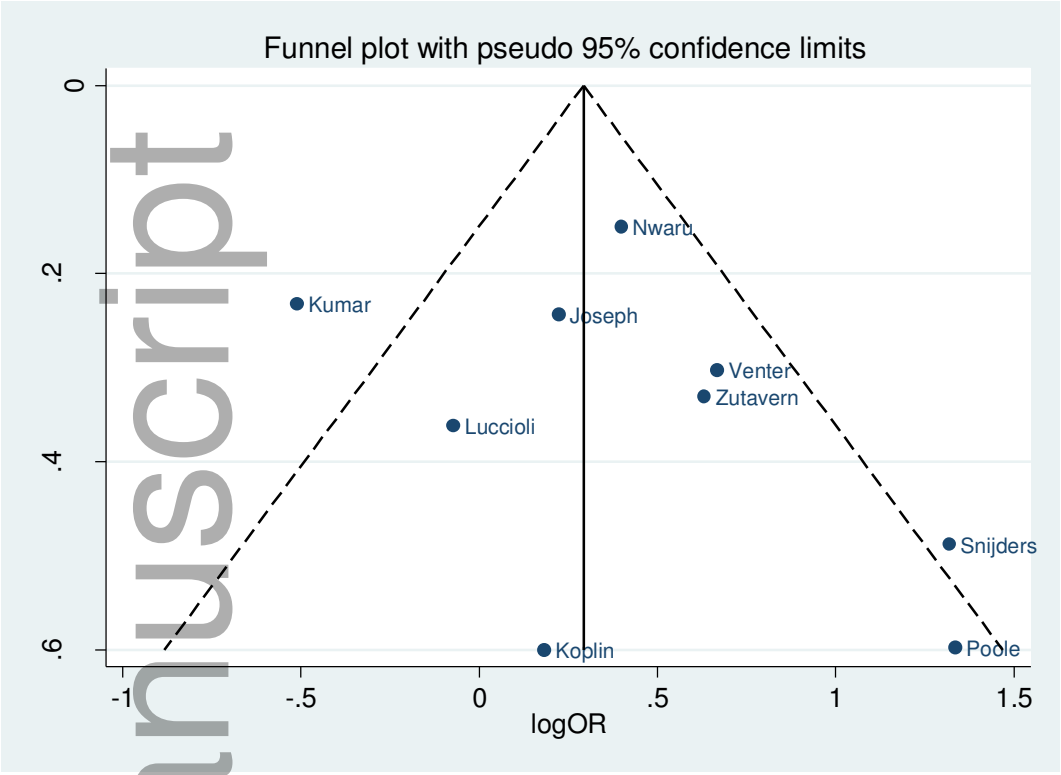

Figure 6

A statistical test to evaluate small study bias was not presented as the number of included studies was small.[36, 37]

Randomized controlled trials

No RCT examined age at introduction of complementary solid food and the risk of food allergy.

There were 8 RCTs that examined early versus late introduction of specific allergenic foods as the intervention.[1, 3-6, 16, 38, 39] Of these, six[3-6, 16, 38, 39] examined egg, one examined peanut[1] and one examined a group of 6 allergenic foods[6] (Table S2 and Figures S1-S3). A detailed summary of the RCTs is included in the supplement.

Five trials of early infant egg exposure commencing at ages from 4-6 months and continuing to an age between 6 and 12 months (Figure S1) demonstrated a protective effect of early egg exposure against egg sensitization at age 12 months [OR 0.76; 95%CI (0.61-0.95)]. Six trials of exposure to egg or food containing egg over similar age ranges (Figure S2) showed a protective effect from early egg exposure against egg allergy measured at the age of 12 months [OR 0.63; 95%CI (0.44-0.90)].

Two trials of early exposure to peanut or allergenic food containing peanut (Figure S3) showed good evidence of a protective effect of early peanut exposure (starting at an age of 3 months[6] or from 4-11 months[1]) against peanut allergy measured at 12 – 36 months or 60 months [OR 0.28; 95%CI (0.14-0.57)]. These results were nearly identical to those presented in a recently published systematic review[7] with differences being explained by our review including the STEP study[5] and not including published abstracts.

Discussion

Cohort studies and food allergy – From a meta-analysis of 3 cohort studies, we found no evidence that the introduction of complementary solid food after the age of 4 months compared to less than 4 months increased the risk of food allergy.

Cohort studies and food sensitization – We found evidence from a meta-analysis of another 3 cohort studies that the introduction of complementary solid food after the age of 4 months compared to less than 4 months appeared to increase the risk of food sensitization.

RCTs and egg allergy – From the RCTs when examined singly, the evidence was that early introduction of egg, usually between 4 and 6 months compared to varying later ages, lessened the risk of egg allergy and egg sensitization. This was supported by the meta-analyses of the RCTs where egg was identified as the exposure of interest. The meta-analyses provided evidence that early exposure to egg, as defined, reduced the risk of later egg allergy and later egg sensitization. The supplement details the evidence from RCTs that the early introduction of certain classically allergenic foods reduced the risk of allergy to these foods.

RCTs and peanut allergy – The literature on early exposure to peanut was small and dominated by DuToit et al.[1] which produced strong evidence that exposure to peanut between 4 and 11 months, compared to peanut avoidance, was associated with a reduced risk of peanut allergy in infants who were either sensitive or not sensitive to peanut at enrolment. This was a strong study with almost no loss to follow-up and excellent adherence to the assigned interventions. Obvious limitations were absence of a placebo control group and lack of generalizability given that the study population was high-risk.

Perkin et al.[6] carried out a pre-specified subgroup analysis of early peanut exposure in their study of early introduction of allergenic foods and found that while there was some evidence for a protective effect in the per protocol analysis, this was not present in the intention-to-treat analysis. Even when considered singly, these studies provided moderate evidence that early exposure to peanut lessened the risk of later peanut allergy, a conclusion strengthened by the meta-analysis which found good evidence for a protective effect against peanut allergy from early peanut exposure.

Complementary solid food guidelines – The recommendations contained in current guidelines state that complementary solid food should be introduced into an infant's diet at or around the age of 6 months but not before 4 months[13, 40] and our findings on age at introduction of complementary solids and food allergy support this.

Unexpectedly, we found evidence that introduction of complementary solids after 4 months compared to before 4 months appeared to increase the risk of food sensitization.

In terms of the guidelines, it is important to note that food sensitization is not a disease and food sensitization and food allergy are not synonymous. While food sensitization is a necessary precursor of food allergy, it is not sufficient for its development. Only some of those sensitized to a specific food allergen will develop allergy to that food. The remainder will develop tolerance, ingesting that food without apparent ill-effect.[41] That said, it is not possible to determine from the data in the included studies whether the observed increased prevalence of food sensitization found in these analyses will translate into food allergy at a later age.

In addition, the authors of current guidelines for the age at introduction of complementary solid food have necessarily considered factors other than food allergy and sensitization risk. Such factors include developmental readiness, parental opinion, infant nutritional needs and the risk of developing selective eating habits.[42] Avoidance of food sensitization may not have been a major factor in their deliberations.

Recommendations will also have been influenced by evidence that the timing of complementary food introduction may influence the later risk of infant and childhood obesity, the development of diabetes mellitus and the risk of infant infections, particularly enteral infection.[43, 44] Concerns have also been expressed that the timing of complementary foods could influence the risk of immune disorders including type 1 diabetes mellitus and coeliac disease[45, 46] but meta-analyses by Ierodiakonou et al.[7] did not support these concerns.

The limitations of the cohort studies in this review are important. There was lack of uniformity in the study populations, some drawn from a general population and others from high-risk cohorts, with generalizability from the latter being problematic.

The ascertainment of food allergy as an outcome varied in important ways between studies. We note that the ideal way to ascertain food allergy is by the performance of an oral food challenge (OFC), preferably double blinded.

Among the 16 cohort studies included in this systematic review, food allergy as an outcome was reported by eight.[17, 18, 22, 24-26, 29, 31] Of these, an OFC formed at least part of the diagnostic formulation of food allergy in three[17, 18, 22] and the majority of the participants returning a +ve OFC in these studies were known to be sensitized to one or more food allergens. A fourth study reported “food hypersensitivity” (FHS) as an outcome with an OFC in conjunction with food sensitization forming the FHS construct.[31] Thus, these four studies can be judged to have an objective diagnosis of food allergy.

However, the remaining four studies reported food allergy as an outcome based on descriptors such as typical food allergy symptoms together with documented food sensitivity,[24] maternal report of physician-diagnosed food allergy,[25] allergist clinical diagnosis if symptoms were suggestive or specific IgE >95% of predicted threshold,[26] or parent-report

± physician-diagnosis of wheat allergy.[29] In these instances, the food allergy outcome must be regarded as not objectively verified, and form an important limitation to this systematic review. However, the authors of these four studies have acknowledged this definition limitation, and only one of the 4 studies appeared in a meta-analysis (Figure 2). A sensitivity analysis done by omitting that study[25] did not change the pooled estimate and we believe that the inclusion of these four studies in the systematic review is justified.

While some cohort studies included confounding factors, unrecognized confounding remains an ever-present problem. It should be noted that Venter et al.[31] did not account for any confounding factors so that findings from this study must be regarded with caution. Zutavern *et al.*[33] found that the association between timing of introduction of solids and food sensitization at age 6 years was driven by "late-onset" sensitization (developing after age 2 years) and by cross-sensitivity from pollen sensitization. Further, the association seen with a specific IgE cut-point of 0.35kU/L was not seen with a cut-point of 0.7kU/L. Intuitively, one might expect that an association found at the higher cut-point might more accurately identify true food sensitization. However, the authors commented in their discussion that interpretation of the change in findings was difficult and "has not been linked to clinical conditions".

Further limitations include lack of information concerning whether breast feeding was continued once solid food was introduced and the role of a family history of allergic disease as an effect modifier of observed associations. While some of the included studies considered these factors, this was not universal and unrecognized confounding and effect modification must be considered. In addition, there was lack of uniformity in the ascertainment of food sensitization which was assessed in some studies by skin prick test and in others by specific IgE.

Another concern is possible reverse causation. Infants who appear more mature may be introduced to complementary food at an earlier age. These infants may also have more mature immune systems and be at less risk of food allergy or sensitization. Alternatively, parents concerned about possible evidence of allergy in an infant may delay the introduction of complementary solids to avoid food allergy.

Furthermore, studies published to date have almost exclusively dealt with infants from high income countries and findings may have limited applicability to infants from low-middle income countries.

Conclusions – While acknowledging these limitations, we conclude that this review of cohort studies provides evidence that the current recommendations for the optimal timing of introduction of complementary solid foods do not carry an increased risk of food allergy. Although we found some evidence for reduced risk of food sensitization for infants introduced to solids before compared to after 4 months of age, this should not be taken as

suggesting that current guidelines on age at introduction of solids should change. The evidence was garnered from a small number of studies with important limitations and it is not clear that the estimated reduced risk of food sensitization would necessarily influence food allergy in the older child. Further studies are needed to clarify this.

Author contributions –
Dr John Burgess performed the literature search, played a significant role in the development of the summary tables, performed the meta-analyses and wrote the manuscript.
Professor Shyamali Dharmage assisted in the design of the study, provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.
Professor Katrina Allen developed and obtained funding for the Centre for Research Excellence, assisted in the design of the study, provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.
Dr Jennifer Koplin provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.
Dr Vanessa Garcia-Larsen provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.
Professor Robert Boyle provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.
Dr Nilakshi Waidyatillake performed the literature search, played a major role in the development of the summary tables, provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.
Dr Caroline J. Lodge assisted in the design of the study, resolved disagreements concerning the inclusion or exclusion of certain studies, provided intellectual input to the manuscript and critically evaluated the evidence and the statistical results.

Conflict of interest –
All authors indicate that they have no conflict of interest with this study.

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719

720 **Figure legends**

721

722 Figure1-The PRISMA diagram for study selection

723

724 Figure 2 – Exposure to complementary solids at age 4 mths or more c/w less than 4mths
725 and food allergy.

726

727 Figure 3 – Exposure to complementary solids at age 4 - 6 mths c/w less than 4mths and
728 food allergy.

729

730 Figure 4 – Exposure to complementary solids at age 4 mths or more c/w less than 4mths
731 and food sensitization.

732

733 Figure 5 - Exposure to complementary solids at age 4-6 mths c/w <4mths and food
734 sensitization.

735

736 Figure 6 – Funnel plot of the nine cohort studies considered for quantitative an

Table 1
Cohort Studies from general populations

<table>
<tr><th>Study</th><th>Exposure</th><th>Outcome</th><th>Outcome age</th><th>Confounders</th><th>Results</th><th>Conclusions</th></tr>
<tr><td><u>Koplin</u>
2010
Australia

Population-based cohort (N=2161)

Ref. [18]</td><td>Interviewer questionnaire</td><td><u>Egg allergy</u>- Part-blinded oral egg challenge if preliminary egg SPT +ve</td><td>11-15 mths</td><td>Yes.</td><td>
<table>
<tr><th>Age (mths) egg introduced</th><th>Egg allergy *aOR (95% CI)</th><th>P trend</th></tr>
<tr><td>4-6</td><td>1</td><td><0.001</td></tr>
<tr><td>7-9</td><td>1.3 (0.8,2.1)</td><td></td></tr>
<tr><td>10-12</td><td>1.6 (1.0,2.6)</td><td></td></tr>
<tr><td>>12</td><td>3.4 (1.8,6.5)</td><td></td></tr>
</table>
*Adjusted for FH allergy, infant eczema, parent-reported infant reaction to ≥1 food
</td><td>Egg at ≥10 mths c/w 4-6 mths increased later egg allergy</td></tr>
<tr><td><u>Luccioli</u>
2014
USA

Birth cohort (N=1363)

Ref. [25]</td><td>Parent questionnaire</td><td><u>Food allergy</u> Physician diagnosed food allergy.</td><td>6 yrs</td><td>Yes
.</td><td>
<table>
<tr><th rowspan="2">Age (mths) solids started.</th><th colspan="2">Food allergy present at 6 yrs.</th><th colspan="2">Food allergy present at 6 yrs & not before 1yr.</th></tr>
<tr><th>†aOR</th><th>95% CI</th><th>†aOR</th><th>95% CI</th></tr>
<tr><td>1-3</td><td>1</td><td></td><td>1</td><td></td></tr>
<tr><td>4-5</td><td>0.83</td><td>0.47,1.45</td><td>0.98</td><td>0.53,1.80</td></tr>
<tr><td>6-12</td><td>0.93</td><td>0.45,1.86</td><td>0.87</td><td>0.37,1.89</td></tr>
<tr><td>‡NR</td><td>0.64</td><td>0.21,1.60</td><td>0.84</td><td>0.28,2.29</td></tr>
</table>
†Adjusted for gender, maternal education & smoking, other passive smoking
*Also adjusted for +ve FH food allergy, FH atopy, eczema before age 1 yr
‡Not recorded.
</td><td>No association between age at solid food introduction & physician-diagnosed food allergy at 6 yrs</td></tr>
<tr><td><u>Zutavern</u>
2008
Germany

Birth cohort (N=1123)

Ref. [33]</td><td>Parent questionnaire</td><td><u>Food sensitization</u>

Specific IgE ≥ 0.35 kU/L</td><td>6 yrs</td><td>Yes</td><td>Food sensitisation
*aOR (95%CI)
<table>
<tr><td>Any solids 0-4 months</td><td>Ref</td></tr>
<tr><td>Any solids 5-6 months</td><td>2.15 (1.28,3.62)</td></tr>
<tr><td>Any solids > 6 months</td><td>1.88 (0.98,3.58)</td></tr>
</table>
*Adjusted for study centre, parental allergy, gender, parental education and breastfeeding type.</td><td>Delaying solids to > 4 c/w ≤ 4 mths was associated with food sensitization at 6 yrs</td></tr>
<tr><td><u>Zutavern</u></td><td>Parent</td><td><u>Food</u></td><td>2 yrs</td><td>Yes</td><td>Food sensitisation</td><td>Delaying</td></tr>
</table>

<table>
<tr>
<td>2006
Germany

Birth cohort
(N= 2612)

Ref. [32]</td>
<td>questionnaire</td>
<td><u>sensitization</u>
Specific IgE
≥ 0.35 kU/L</td>
<td></td>
<td></td>
<td>
<table>
<tr><td colspan="2">aOR (95%CI)</td></tr>
<tr><td>Any solids 0-4 months</td><td>Ref</td></tr>
<tr><td>Any solids 5-6 months</td><td>1.04 (0.71,1.53)</td></tr>
<tr><td>Any solids > 6 months</td><td>0.83 (0.49,1.41)</td></tr>
</table>
*Adjusted for study centre, gender, parental education, parental atopy, birth weight and breastfeeding type
</td>
<td>solids to 5-6 mths or >6 mths c/w ≤4mths not associated with food sensitisation at 2 yrs.</td>
</tr>
<tr>
<td><u>Kull</u>
2006
Sweden

Birth cohort
(N=2614)

Ref.[19]</td>
<td>Parent questionnaire</td>
<td><u>Food sensitisation</u>

Specific IgE
≥ 0.35 kU/L.

(Few had specific IgE ≥ 0.35 kU/L)</td>
<td>4 yrs</td>
<td>Yes</td>
<td>
<table>
<tr><td></td><td>Fish sensitization
aOR (95%CI)</td></tr>
<tr><td>All children</td><td></td></tr>
<tr><td>Fish at ≥ 8 months</td><td>1</td></tr>
<tr><td>Fish at < 8 months</td><td>0.17 (0.04,0.64)</td></tr>
<tr><td>Excluding eczema or wheeze</td><td></td></tr>
<tr><td>Fish at ≥ 8 months</td><td>1</td></tr>
<tr><td>Fish at < 8 months</td><td>0.27 (0.04-1.47)</td></tr>
</table>
*Adjusted for parental allergy, breastfeeding, maternal age and smoking
</td>
<td>Introducing fish at <8 mths protected against fish sensitization at 4 yrs.</td>
</tr>
<tr>
<td><u>Nwaru</u>
2013
Finland

Population-based cohort
(N=3674)

Ref. [28]</td>
<td>Parent questionnaire</td>
<td><u>Food sensitisation</u>

Specific IgE
≥ 0.35 kU/L.</td>
<td>5 yrs</td>
<td>Yes</td>
<td>
<table>
<tr><td></td><td>Any food</td><td>Wheat</td></tr>
<tr><td>Egg</td><td>*aOR (95% CI)</td><td>*aOR (95% CI)</td></tr>
<tr><td><8 mths</td><td>0.78 (0.60,1.03)</td><td>0.71 (0.42,1.17)</td></tr>
<tr><td>8-11 mths</td><td>0.74 (0.56,0.96)</td><td>0.40 (0.26,0.63)</td></tr>
<tr><td>>11 mths</td><td>1</td><td>1</td></tr>
<tr><td>p-value</td><td>0.031</td><td><0.001</td></tr>
</table>
<table>
<tr><td></td><td>Any food</td></tr>
<tr><td>Fish</td><td>*aOR (95% CI)</td></tr>
<tr><td><6 mths</td><td>0.67 (0.50,0.90)</td></tr>
<tr><td>6-9 mths</td><td>0.60 (0.48,0.75)</td></tr>
<tr><td>>9 mths</td><td>1</td></tr>
<tr><td>p-value</td><td><0.001</td></tr>
</table>
*Adjusted - sex, sib number, parent asthma/AR, birth hospital, mother smoking, age/education, birth season, gestation (wks), pets, delivery mode, birth wt.
</td>
<td>Introducing egg no earlier than 8-11 mths c/w >11 mths decreased wheat & ‘any food’ sensitization at 5 yrs. Introducing fish at 9 mths or less decreased ‘any food’ sensitization at 5 yrs.</td>
</tr>
</table>

<table>
<tr>
<td>Nwaru
2010
Finland

Population-based cohort (N=994)

Ref.[20]</td>
<td>Parent questionnaire</td>
<td>Food sensitisation

Specific IgE ≥ 0.35 kU/L.</td>
<td>5 yrs</td>
<td>Yes</td>
<td>
<table>
<tr><th>Age (mths)</th><th>Any food sensitisation</th><th>Egg sensitisation</th></tr>
<tr><td>Egg introduction</td><td>*aOR (95%CI) -</td><td>*aOR (95%CI) -</td></tr>
<tr><td><8.10</td><td>1.00</td><td>1.00</td></tr>
<tr><td>8.10-10.50</td><td>1.01 (0.58,1.76)</td><td>1.02 (0.47,2.22)</td></tr>
<tr><td>>10.50</td><td>1.87 (1.13,3.10)</td><td>2.16 (1.08,4.31)</td></tr>
<tr><td>p-value (overall)</td><td>0.008</td><td>0.017</td></tr>
</table>
*Adjusted for sex, number of sibs, parent asthma/AR, maternal age/education/smoking, delivery mode, pets at home, ponderal index
</td>
<td>Egg introduction at >10.5 mths associated with any food sensitisation and egg sensitisation at age 5 yrs.</td>
</tr>
<tr>
<td>Joseph
2011
USA

Birth cohort (N=594)

Ref. [23]</td>
<td>Interviewer questionnaire</td>
<td>Food sensitisation

Specific IgE ≥ 0.35 kU/L.</td>
<td>2-3 yrs</td>
<td>Yes</td>
<td>
Complementary food (solids &/or cow's milk) at <4 mths.
<table>
<tr><td rowspan="2">§Sensitization at 2-3 yrs</td><td colspan="4">Parental history of asthma and allergy</td></tr>
<tr><td colspan="2">Yes</td><td colspan="2">No</td></tr>
<tr><td></td><td>aOR (95%CI)</td><td>p-value</td><td>aOR (95%CI)</td><td>p-value</td></tr>
<tr><td>IgE egg/milk</td><td>*0.8 (0.5,1.3)</td><td>0.375</td><td>‡1.5 (0.9,2.6)</td><td>0.147</td></tr>
<tr><td>IgE peanut</td><td>†0.2 (0.1,0.7)</td><td>0.007</td><td>**1.3 (0.6,2.7)</td><td>0.544</td></tr>
</table>
§Stratified by parental history of asthma and allergy.
* Adjusted for gender
† Adjusted for gender and race
‡Adjusted for maternal age and household income
**Adjusted for gender and marital status
</td>
<td>For children with FH of asthma or allergy, introduction of solids &/or cow's milk at <4mths reduced peanut sensitization at 2-3 yrs.</td>
</tr>
<tr>
<td>Venter
2009
UK

Birth cohort (N=969)

Ref. [31]</td>
<td>Interviewer questionnaire</td>
<td>Food sensitisation SPT

Food hyper-sensitivity (FHS) OFC & SPT</td>
<td>1 & 3 yrs</td>
<td>No</td>
<td>
<table>
<tr><td></td><td>OR (95% CI)</td><td></td><td>OR (95% CI)</td></tr>
<tr><td>At 1 year SPT+ve</td><td>0.25 (0.05-0.94)</td><td>At 3 years SPT +ve</td><td>0.33 (0.11-0.85)</td></tr>
<tr><td>SPT -ve</td><td>ref</td><td>SPT -ve</td><td>ref</td></tr>
<tr><td>FHS yes</td><td>0.41 (0.28-0.89)</td><td>FHS yes</td><td>0.51 (0.28-0.92)</td></tr>
<tr><td>FHS no</td><td>ref</td><td>FHS no</td><td>ref</td></tr>
</table>
</td>
<td>Weaning before 16 wks lessens food sensitization & FHS at 1 & 3 yrs</td>
</tr>
<tr>
<td>Snijders</td>
<td>Parent</td>
<td>Food</td>
<td>2 yrs</td>
<td>Yes</td>
<td>Solids at (mths) | Any food sensitisation</td>
<td>Delaying</td>
</tr>
</table>

<table>
<tr>
<td>2008
Netherlands

Birth cohort
(N=2343)

Ref. [30]</td>
<td>questionnaire</td>
<td><u>Sensitisation</u>

IgE ≥ 0.35 kU/L.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>*aOR (95%CI)</td></tr>
<tr><td>3</td><td>1.00</td></tr>
<tr><td>4-6</td><td>3.74 (1.46,9.55)</td></tr>
<tr><td>>7</td><td>3.94 (1.09,14.2)</td></tr>
<tr><td>P for trend</td><td>0.01</td></tr>
</table>
*Adjusted for breastfeeding, gender, maternal smoking/education/age, infant ETS exposure, family allergy.
</td>
<td>solids to age >3 mths increases “any food sensitisation” at 2 yrs.</td>
</tr>
<tr>
<td><u>Poole</u>
2006
USA

Birth cohort
(N=1612)

Ref. [29]</td>
<td>Interviewer questionnaire (3 mthly to 15 mths then annually).</td>
<td><u>Wheat allergy</u>- Parent report or physician diagnosis.</td>
<td>4 yrs</td>
<td>Yes</td>
<td>
Wheat allergy
<table>
<tr><td>Age exposed to cereal grain</td><td>*aOR (95%CI)</td></tr>
<tr><td><7 months</td><td>1.00</td></tr>
<tr><td>≥7 months</td><td>3.8 (1.18,12.28)</td></tr>
</table>
*Adjusted for FH allergy, duration of breast feeding, age at exposure to rice cereal, any food allergy before age 6 mths.
</td>
<td>Delaying cereal grain to ≥7 mths increased wheat allergy at 4 yrs.</td>
</tr>
<tr><td colspan="6">Cohort Studies from high-risk populations</td></tr>
</table>

<table>
<tr>
<td>Hesselmar
2010
Sweden

Birth cohort
(high risk)
(N=184)
Ref. [17]</td>
<td>Food diaries</td>
<td>Food allergy
Symptoms & OFC &/or SPT or specific IgE >0.35 kU/L.
Food sensitisation
SPT +ve</td>
<td>18 mths</td>
<td>Yes.</td>
<td>
<table>
<tr><td></td><td colspan="6">Median age (mths) (IQR) when food introduced</td></tr>
<tr><td></td><td colspan="3">Allergy</td><td colspan="3">Sensitisation</td></tr>
<tr><td></td><td>Yes</td><td>No</td><td>P</td><td>Yes</td><td>No</td><td>P</td></tr>
<tr><td>Fish</td><td>13 (9.8-13)</td><td>9 (6-12)</td><td>0.01</td><td>9.5 (6-13)</td><td>9 (6-12)</td><td>0.28</td></tr>
</table>
</td>
<td>Age at fish introduction influenced fish allergy but not fish sensitization at 18 mths.</td>
</tr>
<tr>
<td>Kumar
2010
Nth America

High risk cohort
(N=960)

Ref. [24]</td>
<td>Interviewer questionnaire</td>
<td>Food allergy-
Observed food allergy symptoms
+
SPT +ve
or
Specific IgE >0.35 kU/L</td>
<td>36 mths</td>
<td>Yes (stratified by eczema Y/N).</td>
<td>
<table>
<tr><td colspan="2">Food allergy (one or more foods) at 3 yrs*</td></tr>
<tr><td>Timing and food type in those without eczema</td><td>†aOR (95%CI)</td></tr>
<tr><td>Rice, wheat and cereal</td><td></td></tr>
<tr><td>< 6 mths</td><td>1.0</td></tr>
<tr><td>> 6 mths</td><td>0.6 (0.3,1.0)</td></tr>
<tr><td>Egg, peanut, tree nut, shell fish, fish, sesame</td><td></td></tr>
<tr><td>< 1 year</td><td>1.0</td></tr>
<tr><td>> 1 year</td><td>0.5 (0.3,0.95)</td></tr>
</table>
†Adjusted for age, gender, race, caesarean section, pets in 1st year, parent education & income, atopy, FH atopy, first born, breast-feeding, day care.
</td>
<td>Later introduction of solids protective against food allergy at 3 yrs only in children without eczema.</td>
</tr>
<tr>
<td>McGowan
2015
USA

High risk birth cohort
N=609,
Atopic=560)

Ref. [26]</td>
<td>Physician-administered questionnaire</td>
<td>Food allergy-
Allergist clinical diagnosis

Sensitization
Food specific IgE ≥0.35ku/l</td>
<td>5 yrs</td>
<td>Yes</td>
<td>
<table>
<tr><td></td><td colspan="3">Food allergy at age 5 yrs.</td></tr>
<tr><td></td><td>Allergic</td><td>Non-allergic</td><td>p-value</td></tr>
<tr><td>Age solids introduced (wks, mean ± SD)</td><td>13.9 (7.4)</td><td>15.1 (8.9)</td><td>0.27</td></tr>
<tr><td></td><td colspan="3">Food sensitization at 5 yrs.</td></tr>
<tr><td></td><td>Sensitized</td><td>Non-sensitized</td><td>p-value</td></tr>
<tr><td>Age solids introduced (wks, mean ± SD)</td><td>14.8 (8.5)</td><td>15.2 (8.6)</td><td>0.63</td></tr>
</table>
</td>
<td>No association between timing of solid food introduction and food allergy or sensitization at age 5 yrs.</td>
</tr>
<tr>
<td>Mihrshahi
2007
Australia</td>
<td>Interviewer questionnaire</td>
<td>Atopy-
SPT+ve to food or</td>
<td>5 yrs</td>
<td>Yes</td>
<td>
<table>
<tr><td>Atopy
*aOR (95%CI)</td></tr>
</table>
</td>
<td>Early introduction of solids</td>
</tr>
</table>

High risk birth cohort (N=516) Ref.[27]		inhalant allergen or HDM.			Solids by 3 mths - Yes: 0.54 (0.33,0.87) - No: Ref †Allergenic foods by 9 mths - Yes: 0.67 (0.45,1.02) - No: Ref * Adjusted for intervention or control group allocation, parental history of asthma, mother smoking in pregnancy and gender. † Cow's milk, egg, nuts or fish	(≤3mths) and allergenic food (≤9mths) protected against atopy at 5 yrs
Bedolla Barajas 2016 Mexico High risk (N=300) Ref. [22]	Interviewer questionnaire & peanut SPT	Peanut allergy- OFC for those with +ve SPT or convincing history & -ve SPT (n=3/24)	Mean 7.3 ± 3.9 yrs.	Yes	Peanut allergy First peanut exposure: *aOR (95%CI) At age < 2yrs: Ref. At age ≥ 2yrs: 8.0 (1.3-50.0) *Adjusted for age, sex and breast-feeding history.	Later peanut introduction increased peanut allergy risk .

Table 2 - Case-Control Studies

Study	Exposure	Outcome	Outcome age	Confounders	Results	Conclusions
Grimshaw 2013 UK Nested case-control study Cases (n=41) Controls(n=82) Ref.[47]	Food diary "EuroPrevall" questionnaire at 12 & 24 mths.	Food allergy- OFC in those with +ve SPT or specific IgE≥0.35kU/l OR convincing history of food allergy	2 yrs	Yes	Exposure: Food allergy aOR (95%CI) Solids at ≤16 weeks: *3.42 (1.16 – 10.10) Solids at ≤16 weeks: †3.58 (1.03 – 12.50) Solids at ≥17 weeks: Ref. *Adjusted for breast feeding, cow's milk protein, †Additionally adjusted for sex, single child, pets, maternal age/education/asthma & allergy,	Early introduction of solids (≤16 weeks) associated with food allergy.

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Title:
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