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Author/s:

Burgess, JA;Dharmage, SC;Allen, K;Koplin, J;Garcia-Larsen, V;Boyle, R;Waidyatillake, N;Lodge, CJ

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DR JOHN BURGESS (Orcid ID : 0000-0001-7532-5027)

DR JENNIFER JULIA KOPLIN (Orcid ID : 0000-0002-7576-5142)

DR VANESSA GARCIA-LARSEN (Orcid ID : 0000-0002-0003-1988)

PROFESSOR ROBERT J BOYLE (Orcid ID : 0000-0002-4913-7580)

DR NILAKSHI THARANGA WAIDYATILLAKE (Orcid ID : 0000-0003-1434-0308)

DR CAROLINE JANE LODGE (Orcid ID : 0000-0002-2342-3888)

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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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Authors

John A. Burgess¹, Shyamali C. Dharmage^{1,2}, Katrina Allen^{2,3}, Jennifer Koplin², Vanessa Garcia-Larsen⁴, Robert Boyle⁵, *Nilakshi Waidyatillake¹, *Caroline J. Lodge¹

¹ Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Australia

² Centre for Food and Allergy Research, Murdoch Childrens Research Institute, Parkville, Australia

³ Department of Paediatrics, The University of Melbourne, Parkville, Australia

⁴ Department of International Health, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

⁵ Department of Paediatric Allergy, Imperial College London, London, United Kingdom.

*Equal senior author

Corresponding author – Dr John Burgess
Melbourne School of Population and Global Health
The University of Melbourne
Level 3, 207 Bouverie Street, Carlton. 3053 VIC. Australia
Telephone +61 3 90358212
Email jburgess@unimelb.edu.au

1 **Abstract**

2
3 **Background and Objective**

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

7 **Design**

8 We searched the electronic databases PubMed and EMBASE (January 1946-February
9 2017) using solid food, allergy and sensitization terms.

10 **Methods**

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

14 **Results**

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

20 RCTs – Egg exposure from age 4 months was associated with reduced egg allergy (OR
21 0.63, 95%CI, 0.44-0.90) and sensitization (OR 0.76, 95%CI, 0.51-0.95). Peanut exposure
22 from age 4 months compared to delayed exposure was associated with reduced peanut
23 allergy (OR 0.28, 95%CI 0.14-0.57).

24 **Conclusions**

25 We found no evidence from observational studies that introducing solids before 4 months
26 protected against food allergy, but there was evidence for protection against food
27 sensitization. From RCTs, introducing egg from 4-6 months and peanut from 4-11 months,
28 reduced the risk of egg allergy, peanut allergy and egg sensitization.
29 PROSPERO systematic review registry (CRD42016033473).

40 **Introduction**

41 There is increasing interest in the timing of solid food introduction to infants as a potentially
42 modifiable cause of the current food allergy epidemic. Solid foods can be separated into
43 non-allergenic and classically allergenic foods. Several randomized controlled trials (RCTs)
44 of introduction to allergenic solid foods found that early introduction, usually from age 4-6
45 months, reduced the risk of food sensitization and allergic disease¹⁻³ while other RCTs found
46 no such benefit.⁴⁻⁶ A recent comprehensive high-quality systematic review and meta-analysis
47 synthesized the evidence from RCTs, finding that early introduction of egg (4-6 months; 5
48 trials, 1915 participants) was associated with a 46% reduction in the risk of egg allergy (95%
49 confidence interval (CI) 17-66%) and early introduction of peanut (4-11 months; 2 trials,
50 1550 participants) was associated with a 71% risk reduction of peanut allergy (95%CI 26-
51 89%).⁷

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

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

69 The optimal age for introduction of complementary feeding is uncertain with conflicting
70 evidence and recommendations from different authoritative bodies.¹⁰ The World Health
71 Organization recommended six months of exclusive breastfeeding with subsequent
72 introduction of solids¹¹ while a later recommendation from another authoritative body was
73 even more restrictive.¹² More recent guidelines aimed at clear and consistent advice
74 recommend introducing solids by age 6 months but not before 4 months.^{13,14} However, at

75 least some of these recommendations were based on factors such as the growth rate and
76 maturity of the child and maternal nutritional status¹⁵ as much as on perceived risk of food
77 allergy or sensitization. The timing of complementary food introduction may have an
78 important yet unclear relationship with allergic disease. It would be difficult and perhaps
79 unethical, to conduct an RCT using complementary food as the intervention and no
80 complementary food as the control.

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

84 **Methods**

85 PubMed and EMBASE electronic data-bases were systematically searched using key words
86 and MeSH terms based on complementary solid food introduction and food allergy and
87 sensitization. The search was augmented from the reference lists of the included articles and
88 trial registries. The final search was performed on May 20th, 2016 and updated on February
89 15th, 2017. Further details of the search terms are given in the online supplement (S1). We
90 created citation alerts for more recent publications. The review was prospectively registered
91 in the PROSPERO systematic review registry (CRD42016033473). We note that the
92 systematic review and meta-analysis by Ierodiakonou⁷ bears some similarity to this
93 systematic review. However, their search strategy and ours are quite different in timing and
94 scope. The aims and content of their review were directed principally towards RCTs of highly
95 allergenic foods with allergic and auto-immune disease outcomes. On the other hand, our
96 review focused largely on cohort studies of complementary solid food exposure and food
97 allergic outcome. Of the 16 cohort studies included in our review, only five¹⁶⁻²⁰ were included
98 by Ierodiakonou et al. All but one⁵ of the RCTs in our review were also included by
99 Ierodiakonou.

100

101 **Inclusion and exclusion criteria**

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

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

111 **Study selection**

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

116
117 **Data extraction**

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

122
123 **Effect estimates**

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

128
129 **Quality assessment and risk of bias**

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

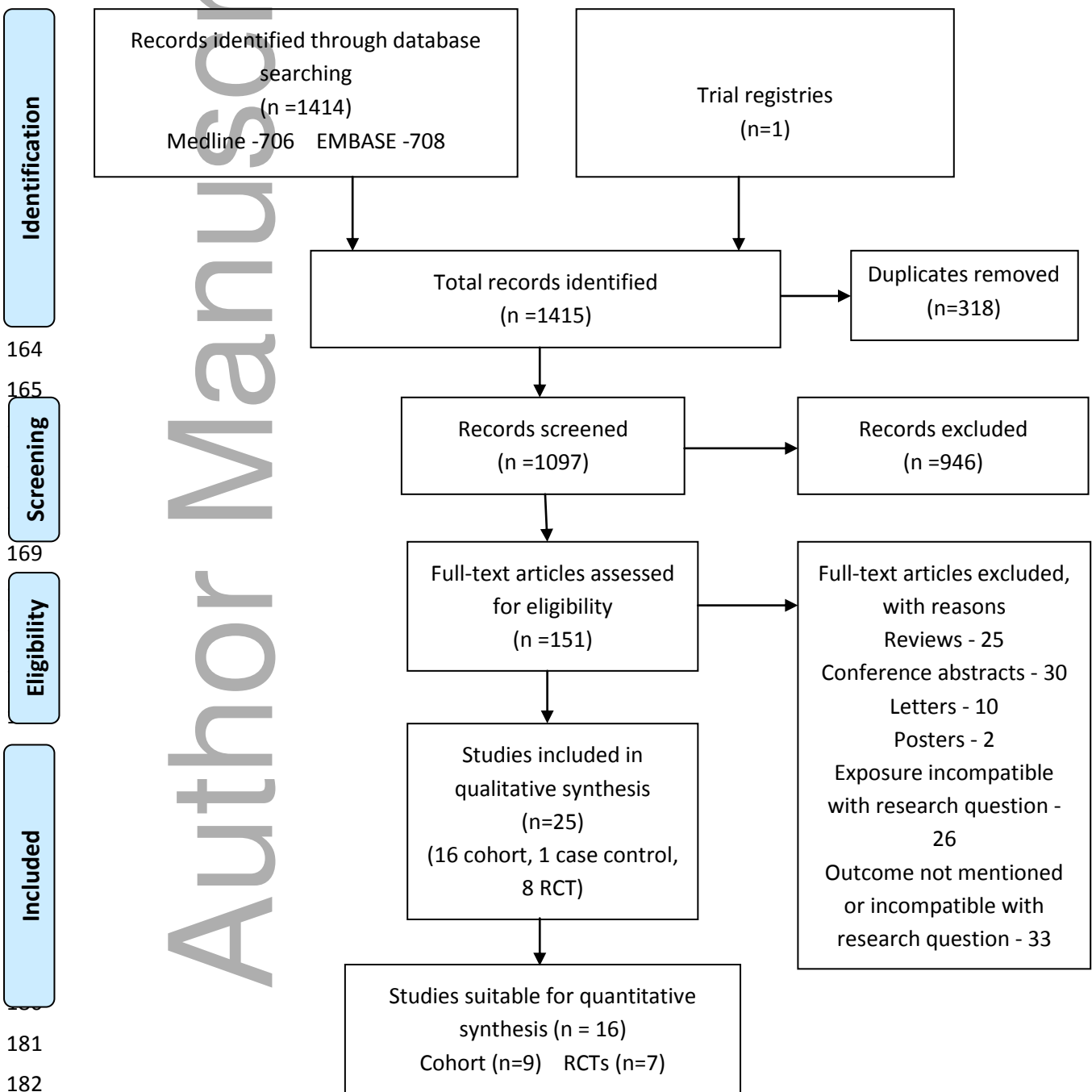
135
136 **Data analysis**

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

143
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148 **Results**

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



181
182
183 Figure 1

184 **Cohort and Case-Control Studies**

185 The findings from the 16 cohort studies^{17-20, 22-33} and the single case-control study³⁴ are
186 summarized in Tables 1 and 2. All but one study³¹ achieved an AHRQ grade that was at
187 least fair on the Newcastle Ottawa Scale (Table S1). The type of food sensitization or allergy
188 examined varied widely, as did the exposures, with some having assessed the outcome in
189 terms of age at introduction to solids generally^{25-27, 30-33} while others assessed outcomes in
190 relation to specific allergenic foods.^{17-20, 23, 24, 28, 29} Eleven studies^{19, 20, 22-24, 27-31, 33} reported
191 that early introduction of solid food influenced later food sensitization or allergy while 5 found
192 no such evidence.^{17, 18, 25, 26, 32} Eleven studies^{18-20, 23, 25, 28-33} enrolled participants from the
193 general population while 5 enrolled participants at high risk of allergic disease.^{17, 22, 24, 26, 27}
194 Study outcomes were food sensitization (9 studies),^{19, 20, 23, 27-30, 32, 33} food allergy (4
195 studies)^{18, 22, 24, 25} or both (3 studies).^{17, 26, 31} There were important differences in the definition
196 of food allergy. One study used symptoms ± basic SPT,²⁴ two used physician-diagnosed
197 food allergy ± threshold SPT,^{25, 26} and four used oral food challenge.^{17, 18, 22, 31} Four studies
198 using oral food challenge found a reduced risk of food allergy from earlier introduction of
199 solids,³¹ fish,¹⁷ egg¹⁸ or peanut.²² The age at which the outcome was determined ranged
200 from 11 months¹⁸ to 6 years^{25, 33} although one study determined the outcome at a mean age
201 of 7.3 years.²²

202
203 Fifteen studies involving 20,407 participants gathered data on “solids”, “any solids”, or “solid
204 food” as the exposure of interest from which exposure to specific foods and data on food
205 allergy or sensitization could be extracted. Investigators from the LISA and DIPP cohorts
206 each published two papers which included members of the cohorts twice.^{20, 28, 32, 33} DIPP
207 included 994 subjects common to both analyses and LISA included 1123 subjects common
208 to both analyses. Thus, the nett participant number from the studies on allergy and solid
209 foods was 18,290. The remaining study involving 300 participants did not report exposure to
210 solids in general, reporting only exposure to peanut.²²

211
212 **Complementary food**

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

215
216 Hesselmar et al.¹⁷, classifying “solids” as potatoes, root vegetables or meat, found that those
217 with compared to without documented allergy or sensitization to solids at age 18 months did
218 not differ in the median age when solids were introduced.

219

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

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

225
226 McGowan et al.²⁶ reported that, in a cohort of high-risk inner-city children, the mean age at
227 introduction of solids was not associated with either food allergy or sensitization at age 5
228 years.

229
230 Studies finding an association between age at complementary solid food introduction and
231 food allergy or sensitization

232
233 Kumar et al.²⁴ separated solids into two groups - rice, wheat and cereal - and the classically
234 allergenic foods egg, peanut, tree nut, shell fish, fish, and sesame. Introduction of the first
235 food group after compared to before age 6 months reduced the odds of allergy to those
236 foods by age 36 months. Introduction of the allergenic food group before compared to after
237 age 1 year was also associated with reduced odds of food allergy at 36 months, an effect not
238 seen when these foods were introduced before and after age 6 months. These findings only
239 applied to children without eczema.

240
241 In 2006, Zutavern et al.³² with a study population of 2,614 reported that delaying the
242 introduction of 8 groups of solids (vegetables, cereal, fruit, meat, dairy products, egg, fish,
243 and 'others') to either age 5 or 6 months or beyond 6 months compared to ≤ 4 months did not
244 protect against food sensitization at age 2 years. However, in 2008, the same authors
245 reported on 1123 subjects from the same cohort and found that delaying the introduction of
246 the same food groups beyond age 4 months was associated with a significantly increased
247 food sensitization risk at age 6 years with the risk even greater in children without early
248 allergic symptoms or skin disease.³³

249
250 Kull et al.¹⁹ reported on the age at introduction of fish and fish sensitization at age 4 years.
251 They found a reduced fish sensitization risk with early fish introduction which was not seen
252 when infants with eczema or wheeze were excluded.

253
254 Joseph et al.²³ studied introduction at < 4 months of any solid and/or cow's milk and found
255 that this was associated with significantly reduced peanut sensitization risk at age 2-3 years,
256 but only in high-risk children.

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

261
262 Snijders et al.³⁰ studied food sensitization at age 2 years in terms of the introduction of solids
263 including artificial formulas, raw/pasteurized milk, porridge, dairy products, yogurts and other
264 foods such as fruit mash before and after age 3 months. They found that the introduction of
265 solids between 4 and 6 months and at ≥ 7 months were each associated with an increased
266 risk of sensitization to any food.

267
268 Mirshahi et al.²⁷ examined introduction of solids generally and, separately, of allergenic
269 foods (cow's milk, egg, nuts or fish) on atopy risk at age 5 years in a high-risk infant cohort.
270 They found that the introduction of solids before compared to after age 3 months and of
271 allergenic foods before compared to after age 9 months were each associated with a
272 reduced atopy risk at age 5 years. However, atopy was defined as the presence of a positive
273 SPT to any food allergen, HDM or inhaled allergen and results directed specifically to food
274 sensitivity were not presented.

275
276 Grimshaw et al.³⁴ published results of a nested case-control study using the UK cohort of the
277 EuroPrevall project.³⁵ From a multi-variable model, they found that infants with food allergy
278 (double-blind placebo-controlled food challenge) at age 2 years had a 3.42-fold increased
279 odds of food allergy if complementary solids had been introduced before compared to after
280 the age of 16 weeks.

281

282 **Specific allergenic foods**

283 **Egg**

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

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

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

293 Nwaru et al., (2010),²⁰ found that egg introduced later than age 10.5 months compared to
294 <8.1 months was associated with a 2-fold increased odds of egg sensitization at age 5
295 years.

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

301

302 **Fish**

303 Three studies (6,472 participants) investigated fish exposure and fish allergy or sensitization
304 outcomes. Hesselmar et al.¹⁷ found that later introduction of fish (median age 13 months vs
305 9 months) was associated with a reduced risk of fish allergy but not fish sensitization at
306 age 18 months. However, Kull et al.¹⁹ found that early introduction of fish (<8 months) was
307 associated with a reduced risk of fish sensitization at age 4 years which became non-
308 significant when children who developed eczema or wheeze during the first year of life were
309 excluded. Nwaru et al.²⁸ found that the early introduction of fish (< 6 months and between 6
310 and 9 months vs >9 months) was associated with a reduced risk of sensitization to wheat,
311 eggs and milk at age 5 years.

312

313 **Peanut** –

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

319

320 **Cereal** –

321 Poole et al.²⁹ examined age at first exposure to cereal grain or rice cereal and wheat allergy
322 (1612 participants). They found that delaying the age of cereal grain exposure to ≥ 7 months,
323 compared to <7 months, was associated with a near 4-fold increased risk of wheat allergy at
324 age 4 years. However, exposure to rice cereal at ≥ 7 months was not associated with wheat
325 allergy at age 4 years. Major limitations were the poor objectivity of the definition of wheat
326 allergy which was based on parent report (16 subjects) supported by physician diagnosis (4
327 subjects, 3 with elevated wheat specific IgE), and the small numbers of events, rendering the
328 study conclusion suspect.

329

330 **Meta-analyses –**

331 Of the 16 cohort studies in Tables 1, ten^{17, 19, 20, 22-24, 26, 28, 29, 32} were not considered for meta-
332 analysis due to reporting the outcome as a mean or median age at introduction^{17, 26} or
333 because the age at exposure to complementary solids did not fit with the research
334 question^{20, 24, 28, 29} or the complementary food exposure did not fit with our definition of
335 complementary solid food.^{19, 22, 23} One excluded study formed the first part of a later, more
336 complete study.³² The single case-control study³⁴ was not considered for meta-analysis
337 among the cohort studies.

338 Meta-analyses of the remaining six cohort studies^{18, 25, 27, 30, 31, 33} were then planned where
339 the age at exposure to complementary solids and the comparison age were ≥ 4 months and
340 < 4 months and the outcome was either food allergy or food sensitization. However, four
341 studies^{18, 25, 30, 33} presented results for age at complementary solids exposure in one or more
342 age bands (4, 5, 6 and > 6 months), each compared to exposure at < 4 months. Within each
343 study, we meta-analysed these age-band results to give a pooled estimate of the effect of
344 exposure to complementary solids at age ≥ 4 months or more compared to < 4 months.
345 These pooled estimates were then used in meta-analyses where food allergy or food
346 sensitization was the outcome.

347 **Food allergy**

348 From 3 studies, there was no evidence of association between exposure to complementary
349 solids at age ≥ 4 months compared to < 4 months and later food allergy (OR, 1.22; 95%CI
350 0.76 – 1.96; $I^2=57.0\%$) (Figure 2). Sensitivity analysis performed by omitting the study by
351 Luccioli (where food allergy was not assessed by food challenge) reduced the I^2 statistic to
352 28.2% without any change in the pooled estimate (not shown).

353 Similarly, there was no evidence of association between exposure to complementary solids
354 at age 4-6 months compared to < 4 months and later food allergy from 2 studies (OR, 1.01;
355 95%CI 0.64-1.60, $I^2= 9.5\%$) (Figure 3).

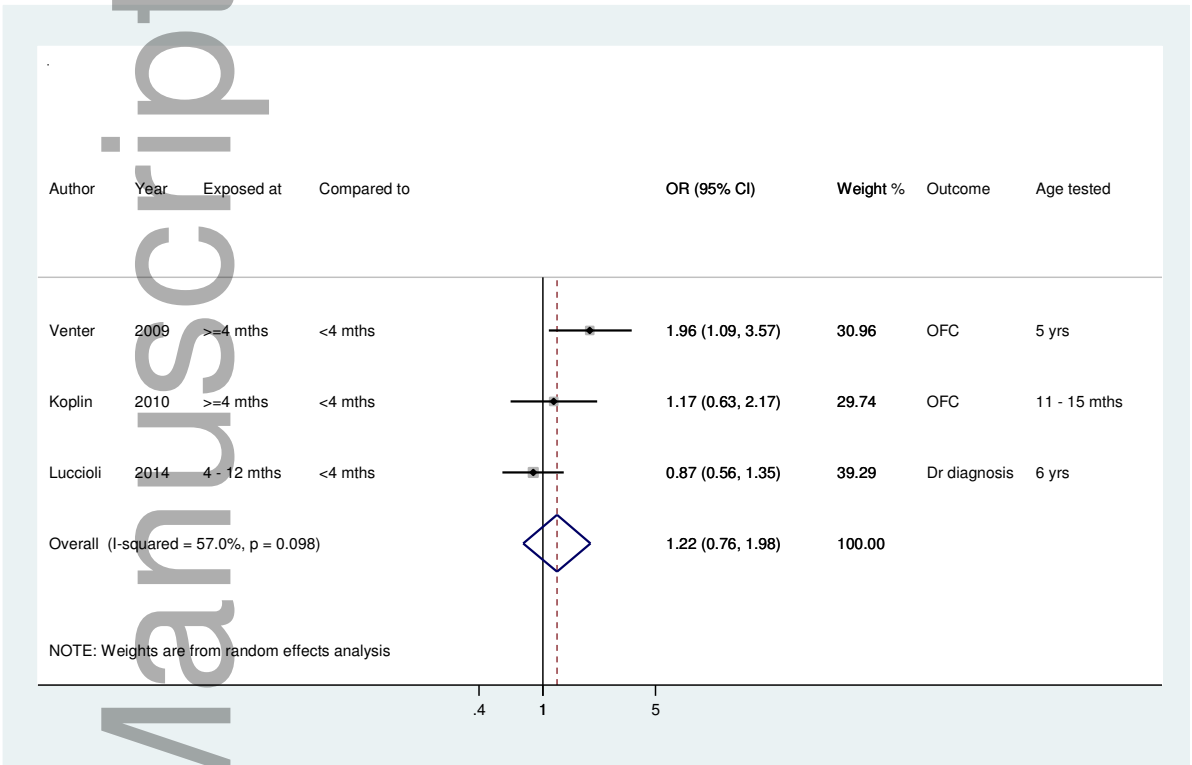
357 **Food sensitization**

358 Exposure to complementary solids at age ≥ 4 months compared with < 4 months was
359 associated with an increased risk of food sensitization from 3 studies (OR, 1.93; 95%CI
360 1.57-2.38, $I^2= 0\%$) (Figure 4). To minimize heterogeneity, this meta-analysis excluded Venter
361 et al. which did not consider confounding. However, a sensitivity analysis with Venter et al
362 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, I²= 2.2%) (Figure 5).

365

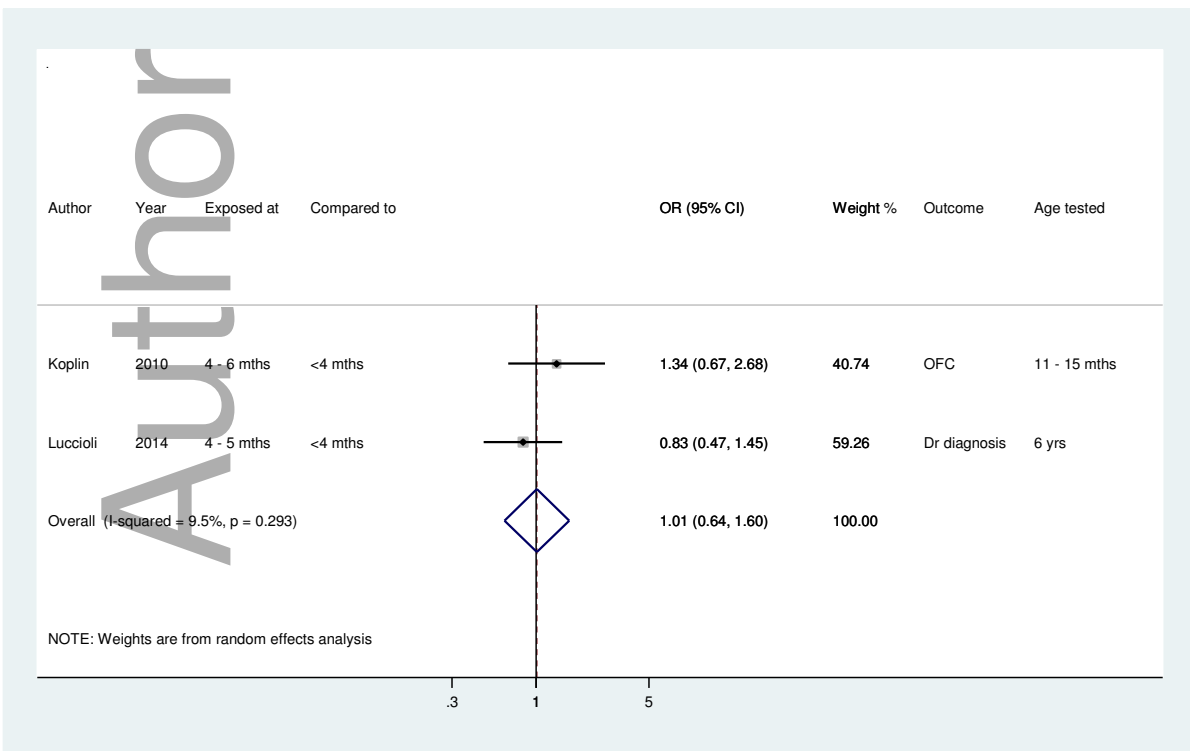
366 **Forest plots – Cohort studies .**



367

Figure 2

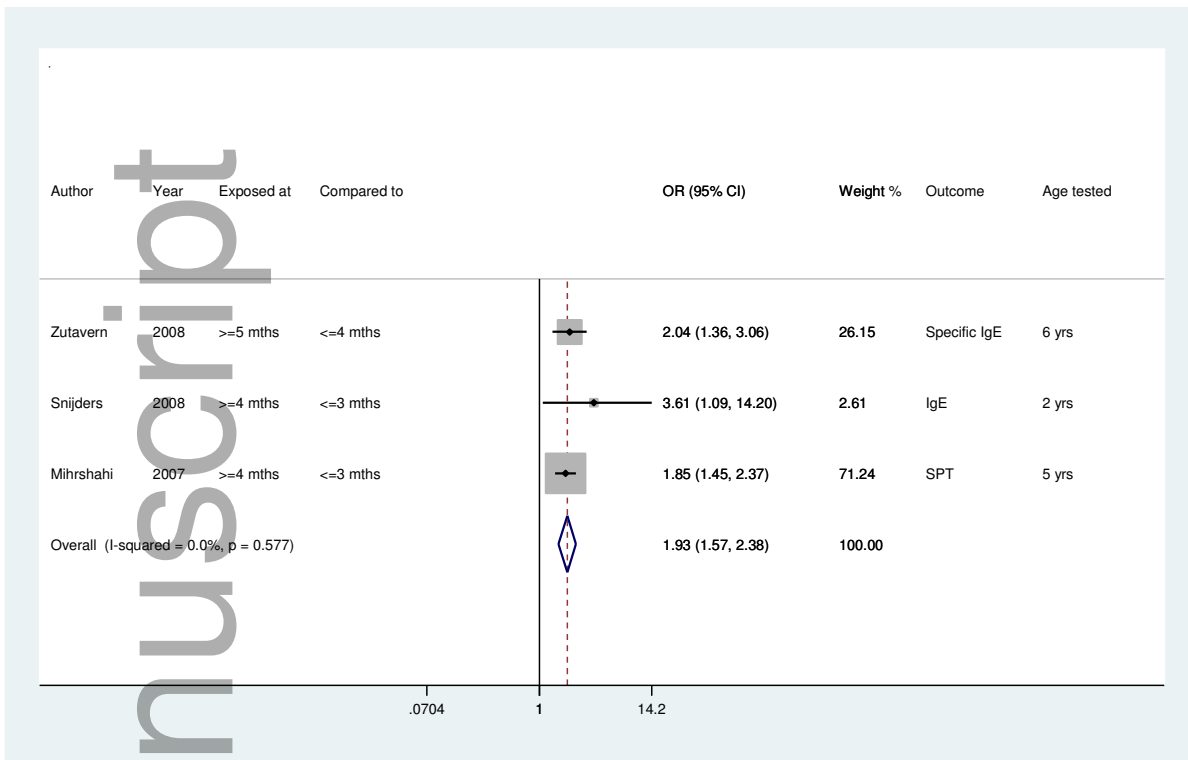
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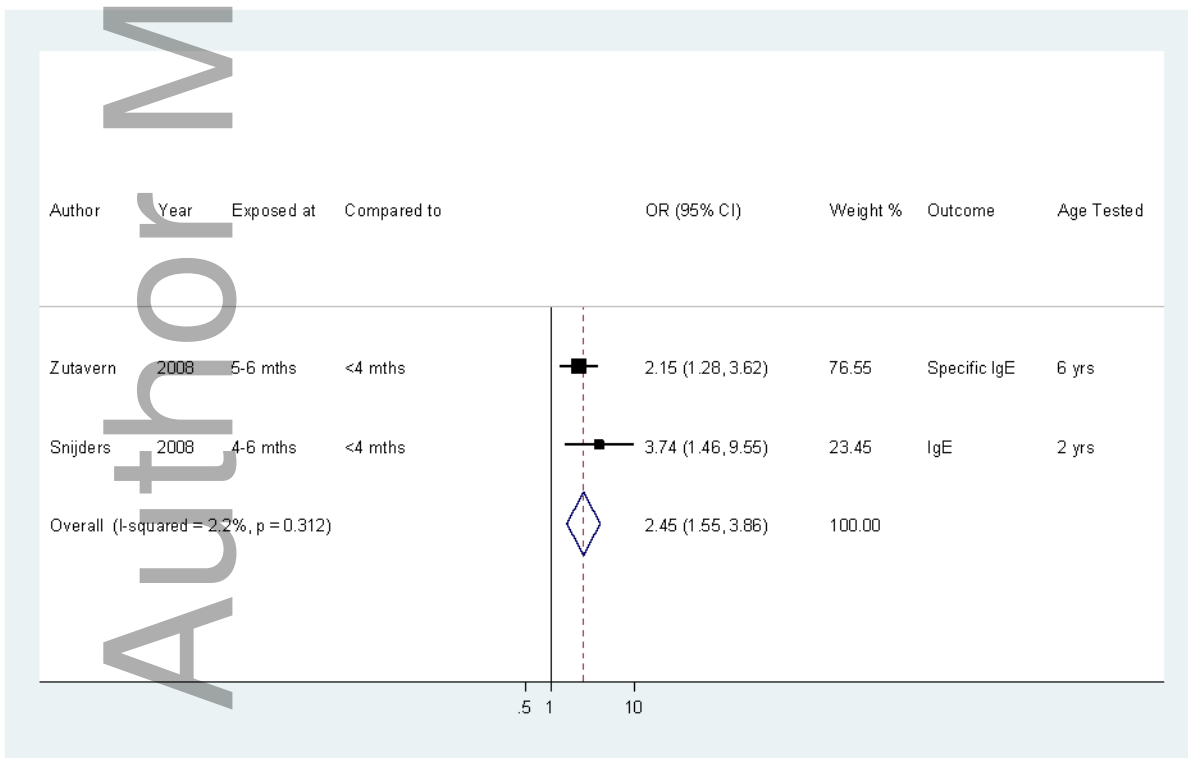
Figure 3



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Figure 4

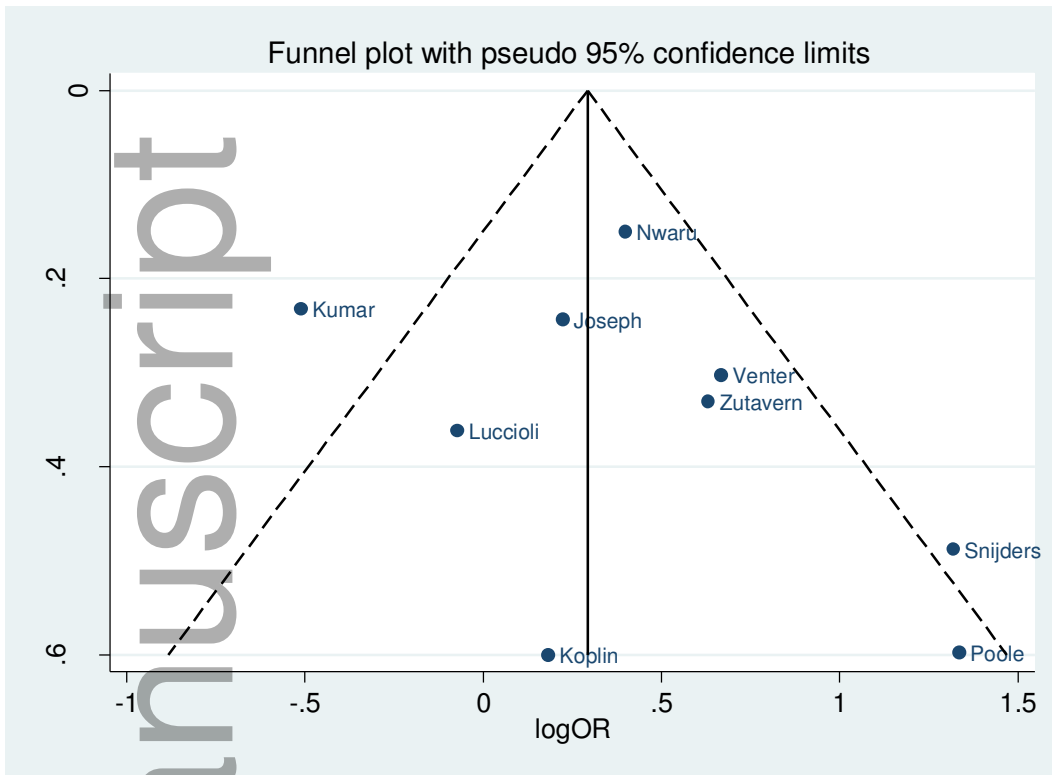


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Figure 5

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Figure 6

379 A statistical test to evaluate small study bias was not presented as the number of included
380 studies was small.^{36, 37}

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395 **Randomized controlled trials**

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

398 There were 8 RCTs that examined early versus late introduction of specific allergenic foods
399 as the intervention.^{1, 3-6, 16, 38, 39} Of these, six^{3-6, 16, 38, 39} examined egg, one examined peanut¹
400 and one examined a group of 6 allergenic foods⁶ (Table S2 and Figures S1-S3). A detailed
401 summary of the RCTs is included in the supplement.

402

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

409

410 Two trials of early exposure to peanut or allergenic food containing peanut (Figure S3)
411 showed good evidence of a protective effect of early peanut exposure (starting at an age of
412 3 months⁶ or from 4-11 months¹) against peanut allergy measured at 12 – 36 months or 60
413 months [OR 0.28; 95%CI (0.14-0.57)]. These results were nearly identical to those
414 presented in a recently published systematic review⁷ with differences being explained by our
415 review including the STEP study⁵ and not including published abstracts.

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431 **Discussion**

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

435 Cohort studies and food sensitization – We found evidence from a meta-analysis of another
436 3 cohort studies that the introduction of complementary solid food after the age of 4 months
437 compared to less than 4 months appeared to increase the risk of food sensitization.

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

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

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

460

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

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

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

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

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

486

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

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

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

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

504 ± physician-diagnosis of wheat allergy.²⁹ In these instances, the food allergy outcome must
505 be regarded as not objectively verified, and form an important limitation to this systematic
506 review. However, the authors of these four studies have acknowledged this definition
507 limitation, and only one of the 4 studies appeared in a meta-analysis (Figure 2). A sensitivity
508 analysis done by omitting that study²⁵ did not change the pooled estimate and we believe
509 that the inclusion of these four studies in the systematic review is justified.

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

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

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

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

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

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

545

546 Author contributions –

547 Dr John Burgess performed the literature search, played a significant role in the
548 development of the summary tables, performed the meta-analyses and wrote the
549 manuscript.

550 Professor Shyamali Dharmage assisted in the design of the study, provided intellectual input
551 to the manuscript and critically evaluated the evidence and the statistical results.

552 Professor Katrina Allen developed and obtained funding for the Centre for Research
553 Excellence, assisted in the design of the study, provided intellectual input to the manuscript
554 and critically evaluated the evidence and the statistical results.

555 Dr Jennifer Koplin provided intellectual input to the manuscript and critically evaluated the
556 evidence and the statistical results.

557 Dr Vanessa Garcia-Larsen provided intellectual input to the manuscript and critically
558 evaluated the evidence and the statistical results.

559 Professor Robert Boyle provided intellectual input to the manuscript and critically evaluated
560 the evidence and the statistical results.

561 Dr Nilakshi Waidyatillake performed the literature search, played a major role in the
562 development of the summary tables, provided intellectual input to the manuscript and
563 critically evaluated the evidence and the statistical results.

564 Dr Caroline J. Lodge assisted in the design of the study, resolved disagreements concerning
565 the inclusion or exclusion of certain studies, provided intellectual input to the manuscript and
566 critically evaluated the evidence and the statistical results.

567

568 Conflict of interest –

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

570

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578 **References**

- 579 1. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at
580 risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-13.
- 581 2. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema:
582 A randomized controlled trial. *J Allergy Clin Immunol*. 2013;132(2):387-92 e1.
- 583 3. Wei-Liang Tan J, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4
584 months of age in infants at risk for egg allergy. *J Allergy Clin Immunol*. 2017;139(5):1621-8 e8.
- 585 4. Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg
586 consumption for primary prevention in infants. *J Allergy Clin Immunol*. 2017;139(5):1591-9 e2.
- 587 5. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of
588 early regular egg intake to prevent egg allergy. *J Allergy Clin Immunol*. 2017;139(5):1600-7 e2.
- 589 6. Perkin MR, Logan K, Tseng A, et al. Randomized Trial of Introduction of Allergenic Foods in
590 Breast-Fed Infants. *N Engl J Med*. 2016;374(18):1733-43.
- 591 7. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of Allergenic Food Introduction to
592 the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis.
593 *JAMA*. 2016;316(11):1181-92.
- 594 8. Arden MA. Conflicting influences on UK mothers' decisions to introduce solid foods to their
595 infants. *Matern Child Nutr*. 2010;6(2):159-73.
- 596 9. Broilo MC, Louzada ML, Drachler Mde L, Stenzel LM, Vitolo MR. Maternal perception and
597 attitudes regarding healthcare professionals' guidelines on feeding practices in the child's first year
598 of life. *J Pediatr (Rio J)*. 2013;89(5):485-91.
- 599 10. Koplin JJ, Allen KJ. Optimal timing for solids introduction - why are the guidelines always
600 changing? *Clin Exp Allergy*. 2013;43(8):826-34.
- 601 11. WHO. Infant and Young Child Nutrition. *World Health Organisation, 2002 (WHA5525)*.
- 602 12. Fiocchi A, Assa'ad A, Bahna S. Food allergy and the introduction of solid foods to infants: A
603 consensus document. *Annals of Allergy, Asthma and Immunology*. 2006;97(1):10-21.
- 604 13. ASCIA Guidelines for infant feeding and allergy prevention: Australian Society for Clinical
605 Immunology and Allergy 2016. Available from [http://www.allergy.org.au/health-
606 professionals/papers/ascia-guidelines-for-infant-feeding-and-allergy-prevention](http://www.allergy.org.au/health-professionals/papers/ascia-guidelines-for-infant-feeding-and-allergy-prevention). Accessed October
607 18, 2016.
- 608 14. Netting MJ, Campbell DE, Koplin JJ, et al. An Australian Consensus on Infant Feeding
609 Guidelines to Prevent Food Allergy: Outcomes From the Australian Infant Feeding Summit. *J Allergy
610 Clin Immunol Pract*. 2017;5(6):1617-24.
- 611 15. Fewtrell MS, Lucas A, Morgan JB. Factors associated with weaning in full term and preterm
612 infants. *Arch Dis Child Fetal Neonatal Ed*. 2003;88(4):F296-301.
- 613 16. Halpern SR, Sellars WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of
614 childhood allergy in infants fed breast, soy, or cow milk. *J Allergy Clin Immunol*. 1973;51(3):139-51.
- 615 17. Hesselmar B, Saalman R, Rudin A, Adlerberth I, Wold A. Early fish introduction is associated
616 with less eczema, but not sensitization, in infants. *Acta Paediatr*. 2010;99(12):1861-7.
- 617 18. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in
618 infants? A population-based study. *J Allergy Clin Immunol*. 2010;126(4):807-13.
- 619 19. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year
620 of life and development of allergic diseases during childhood. *Allergy*. 2006;61(8):1009-15.
- 621 20. Nwaru BI, Erkkola M, Ahonen S, et al. Age at the introduction of solid foods during the first
622 year and allergic sensitization at age 5 years. *Pediatrics*. 2010;125(1):50-9.
- 623 21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa
624 Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses.
- 625 22. Bedolla Barajas M, Alcalá-Padilla G, Morales Romero J, Camacho Fregoso J, Rivera Mejía V.
626 Peanut allergy in Mexican children: what is the effect of age at first consumption? *Iran J Allergy
627 Asthma Immunol*. 2016;15(1):53-61.
- 628 23. Joseph CL, Ownby DR, Havstad SL, et al. Early complementary feeding and risk of food
629 sensitization in a birth cohort. *J Allergy Clin Immunol*. 2011;127(5):1203-10 e5.

- 630 24. Kumar R, Caruso DM, Arguelles L, et al. Early Life Eczema, Food Introduction, and Risk of
631 Food Allergy in Children. *Pediatr Allergy Immunol Pulmonol*. 2010;23(3):175-82.
- 632 25. Luccioli S, Zhang Y, Verrill L, Ramos-Valle M, Kwegyir-Afful E. Infant feeding practices and
633 reported food allergies at 6 years of age. *Pediatrics*. 2014;134 Suppl 1:S21-8.
- 634 26. McGowan EC, Bloomberg GR, Gergen PJ, et al. Influence of early-life exposures on food
635 sensitization and food allergy in an inner-city birth cohort. *J Allergy Clin Immunol*. 2015;135(1):171-8.
- 636 27. Mührshahi S, Ampon R, Webb K, et al. The association between infant feeding practices and
637 subsequent atopy among children with a family history of asthma. *Clin Exp Allergy*. 2007;37(5):671-
638 9.
- 639 28. Nwaru BI, Takkinen HM, Niemela O, et al. Introduction of complementary foods in infancy
640 and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort.
641 *Allergy*. 2013;68(4):507-16.
- 642 29. Poole JA, Barriga K, Leung DY, et al. Timing of initial exposure to cereal grains and the risk of
643 wheat allergy. *Pediatrics*. 2006;117(6):2175-82.
- 644 30. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk
645 products and other food products in relation to infant atopic manifestations in the first 2 years of
646 life: the KOALA Birth Cohort Study. *Pediatrics*. 2008;122(1):e115-22.
- 647 31. Venter C, Pereira B, Voigt K, et al. Factors associated with maternal dietary intake, feeding
648 and weaning practices, and the development of food hypersensitivity in the infant. *Pediatr Allergy
649 Immunol*. 2009;20(4):320-7.
- 650 32. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic
651 dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics*.
652 2006;117(2):401-11.
- 653 33. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to
654 eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results
655 from the prospective birth cohort study LISA. *Pediatrics*. 2008;121(1):e44-52.
- 656 34. Grimshaw KE, Maskell J, Oliver EM, et al. Introduction of complementary foods and the
657 relationship to food allergy. *Pediatrics*. 2013;132(6):e1529-38.
- 658 35. McBride D, Keil T, Grabenhenrich L, et al. The EuroPrevall birth cohort study on food allergy:
659 baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr
660 Allergy Immunol*. 2012;23(3):230-9.
- 661 36. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational
662 studies. *BMJ*. 1998;316(7125):140-4.
- 663 37. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of
664 statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53(11):1119-29.
- 665 38. Natsume O, Kabashima S, Nakazato J, et al. Two-step egg introduction for prevention of egg
666 allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial.
667 *Lancet*. 2017;389(10066):276-86.
- 668 39. Palmer DJ, Sullivan T, Gold MS, et al. Randomized controlled trial of fish oil supplementation
669 in pregnancy on childhood allergies. *Allergy*. 2013;68(11):1370-6.
- 670 40. Pediatric Nutrition. 7th ed. Kleinman RE GF, editor. Elk Grove Village, IL: American Academy
671 of Pediatrics; 2014.
- 672 41. Peters RL, Koplin JJ, Allen KJ, et al. The Prevalence of Food Sensitization Appears Not to Have
673 Changed between 2 Melbourne Cohorts of High-Risk Infants Recruited 15 Years Apart. *J Allergy Clin
674 Immunol Pract*. 2017.
- 675 42. Muraro A, Halcken S, Arshad SH, et al. EAACI food allergy and anaphylaxis guidelines. Primary
676 prevention of food allergy. *Allergy*. 2014;69(5):590-601.
- 677 43. Daniels L, Mallan KM, Fildes A, Wilson J. The timing of solid introduction in an 'obesogenic'
678 environment: a narrative review of the evidence and methodological issues. *Aust N Z J Public Health*.
679 2015;39(4):366-73.
- 680 44. Przyrembel H. Timing of introduction of complementary food: short- and long-term health
681 consequences. *Ann Nutr Metab*. 2012;60 Suppl 2:8-20.

682 45. Beyerlein A, Chmiel R, Hummel S, Winkler C, Bonifacio E, Ziegler AG. Timing of gluten
683 introduction and islet autoimmunity in young children: updated results from the BABYDIET study.
684 *Diabetes Care*. 2014;37(9):e194-5.
685 46. Lionetti E, Castellaneta S, Francavilla R, et al. Introduction of gluten, HLA status, and the risk
686 of celiac disease in children. *N Engl J Med*. 2014;371(14):1295-303.
687 47. Grimshaw KEC, Maskell J, Oliver EM, et al. Introduction of complementary foods and the
688 relationship to food allergy. *Pediatrics*. 2013;132(6):e1529-e38.

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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.

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

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

Table 1
Cohort Studies from general populations

Study	Exposure	Outcome	Outcome age	Confounders	Results				Conclusions																													
<u>Koplin</u> 2010 Australia Population-based cohort (N=2161) Ref. ¹⁸	Interviewer questionnaire	Egg allergy- Part-blinded oral egg challenge if preliminary egg SPT +ve	11-15 mths	Yes.	<table border="1"> <thead> <tr> <th>Age (mths) egg introduced</th> <th>Egg allergy *aOR (95% CI)</th> <th colspan="2">P trend</th> </tr> </thead> <tbody> <tr> <td>4-6</td> <td>1</td> <td colspan="2"><0.001</td> </tr> <tr> <td>7-9</td> <td>1.3 (0.8,2.1)</td> <td colspan="2"></td> </tr> <tr> <td>10-12</td> <td>1.6 (1.0,2.6)</td> <td colspan="2"></td> </tr> <tr> <td>>12</td> <td>3.4 (1.8,6.5)</td> <td colspan="2"></td> </tr> </tbody> </table>				Age (mths) egg introduced	Egg allergy *aOR (95% CI)	P trend		4-6	1	<0.001		7-9	1.3 (0.8,2.1)			10-12	1.6 (1.0,2.6)			>12	3.4 (1.8,6.5)			Egg at ≥10 mths c/w 4-6 mths increased later egg allergy									
					Age (mths) egg introduced	Egg allergy *aOR (95% CI)	P trend																															
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*Adjusted for FH allergy, infant eczema, parent-reported infant reaction to ≥1 food																																						
<u>Luccioli</u> 2014 USA Birth cohort (N=1363) Ref. ²⁵	Parent questionnaire	Food allergy Physician diagnosed food allergy.	6 yrs	Yes	<table border="1"> <thead> <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> </thead> <tbody> <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> </tbody> </table>				Age (mths) solids started.	Food allergy present at 6 yrs.		Food allergy present at 6 yrs & not before 1yr.		†aOR	95% CI	†aOR	95% CI	1-3	1		1		4-5	0.83	0.47,1.45	0.98	0.53,1.80	6-12	0.93	0.45,1.86	0.87	0.37,1.89	‡NR	0.64	0.21,1.60	0.84	0.28,2.29	No association between age at solid food introduction & physician-diagnosed food allergy at 6 yrs
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†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.																																						
<u>Zutavern</u> 2008 Germany Birth cohort (N=1123) Ref. ³³	Parent questionnaire	Food sensitization Specific IgE ≥ 0.35 kU/L	6 yrs	Yes	<table border="1"> <thead> <tr> <th colspan="2">Food sensitisation *aOR (95%CI)</th> </tr> </thead> <tbody> <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> </tbody> </table>				Food sensitisation *aOR (95%CI)		Any solids 0-4 months	Ref	Any solids 5-6 months	2.15 (1.28,3.62)	Any solids > 6 months	1.88 (0.98,3.58)	Delaying solids to > 4 c/w ≤ 4 mths was associated with food sensitization at 6 yrs																					
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<u>Zutavern</u>	Parent	Food	2 yrs	Yes	Food sensitisation				Delaying																													

2006 Germany Birth cohort (N= 2612) Ref. ³²	questionnaire	<u>sensitization</u> Specific IgE ≥ 0.35 kU/L			<table border="1" style="width: 100%;"> <thead> <tr> <th colspan="2">aOR (95%CI)</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>*Adjusted for study centre, gender, parental education, parental atopy, birth weight and breastfeeding type</p>	aOR (95%CI)		Any solids 0-4 months	Ref	Any solids 5-6 months	1.04 (0.71,1.53)	Any solids > 6 months	0.83 (0.49,1.41)	solids to 5-6 mths or >6 mths c/w ≤4mths not associated with food sensitisation at 2 yrs.																									
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Kull 2006 Sweden Birth cohort (N=2614) Ref. ¹⁹	Parent questionnaire	<u>Food sensitisation</u> Specific IgE ≥ 0.35 kU/L. (Few had specific IgE ≥ 0.35 kU/L)	4 yrs	Yes	<table border="1" style="width: 100%;"> <thead> <tr> <th></th> <th>Fish sensitization aOR (95%CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2"><i>All children</i></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 colspan="2"><i>Excluding eczema or wheeze</i></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> </tbody> </table> <p>astfeeding, maternal age and smoking</p>		Fish sensitization aOR (95%CI)	<i>All children</i>		Fish at ≥ 8 months	1	Fish at < 8 months	0.17 (0.04,0.64)	<i>Excluding eczema or wheeze</i>		Fish at ≥ 8 months	1	Fish at < 8 months	0.27 (0.04-1.47)	*Adjusted for parent allergy, breastfeeding Introducing fish at <8 mths protected against fish sensitization at 4 yrs.																			
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Nwaru 2013 Finland Population-based cohort (N=3674) Ref. ²⁸	Parent questionnaire	<u>Food sensitisation</u> Specific IgE ≥ 0.35 kU/L.	5 yrs	Yes	<table border="1" style="width: 100%;"> <thead> <tr> <th></th> <th>Any food</th> <th>Wheat</th> </tr> <tr> <th>Egg</th> <th>*aOR (95% CI)</th> <th>*aOR (95% CI)</th> </tr> </thead> <tbody> <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> <tr> <th>Fish</th> <th>*aOR (95% CI)</th> <td></td> </tr> <tr> <td><6 mths</td> <td>0.67 (0.50,0.90)</td> <td></td> </tr> <tr> <td>6-9 mths</td> <td>0.60 (0.48,0.75)</td> <td></td> </tr> <tr> <td>>9 mths</td> <td>1</td> <td></td> </tr> <tr> <td>p-value</td> <td><0.001</td> <td></td> </tr> </tbody> </table> <p>*Adjusted - sex, sib number, parent asthma/AR, birth hospital, mother smoking, age/education, birth season, gestation (wks), pets, delivery mode, birth wt.</p>		Any food	Wheat	Egg	*aOR (95% CI)	*aOR (95% CI)	<8 mths	0.78 (0.60,1.03)	0.71 (0.42,1.17)	8-11 mths	0.74 (0.56,0.96)	0.40 (0.26,0.63)	>11 mths	1	1	p-value	0.031	<0.001	Fish	*aOR (95% CI)		<6 mths	0.67 (0.50,0.90)		6-9 mths	0.60 (0.48,0.75)		>9 mths	1		p-value	<0.001		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.
	Any food	Wheat																																					
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<p>Nwaru 2010 Finland Population-based cohort (N=994) Ref.²⁰</p>	<p>Parent questionnaire</p>	<p>Food sensitisation Specific IgE ≥ 0.35 kU/L.</p>	<p>5 yrs</p>	<p>Yes</p>	<table border="1"> <thead> <tr> <th>Age (mths)</th> <th>Any food sensitisation</th> <th>Egg sensitisation</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>*Adjusted for sex, number of sibs, parent asthma/AR, maternal age/education/smoking, delivery mode, pets at home, ponderal index</p>	Age (mths)	Any food sensitisation	Egg sensitisation	Egg introduction	*aOR (95%CI) -	*aOR (95%CI) -	<8.10	1.00	1.00	8.10-10.50	1.01 (0.58,1.76)	1.02 (0.47,2.22)	>10.50	1.87 (1.13,3.10)	2.16 (1.08,4.31)	p-value (overall)	0.008	0.017	<p>Egg introduction at >10.5 mths associated with any food sensitisation and egg sensitisation at age 5 yrs.</p>										
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<p>Joseph 2011 USA Birth cohort (N=594) Ref.²³</p>	<p>Interviewer questionnaire</p>	<p>Food sensitisation Specific IgE ≥ 0.35 kU/L.</p>	<p>2-3 yrs</p>	<p>Yes</p>	<table border="1"> <thead> <tr> <th colspan="5">Complementary food (solids &/or cow's milk) at <4 mths.</th> </tr> <tr> <th rowspan="3">§Sensitization at 2-3 yrs</th> <th colspan="4">Parental history of asthma and allergy</th> </tr> <tr> <th colspan="2">Yes</th> <th colspan="2">No</th> </tr> <tr> <th>aOR (95%CI)</th> <th>p-value</th> <th>aOR (95%CI)</th> <th>p-value</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>§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</p>	Complementary food (solids &/or cow's milk) at <4 mths.					§Sensitization at 2-3 yrs	Parental history of asthma and allergy				Yes		No		aOR (95%CI)	p-value	aOR (95%CI)	p-value	IgE egg/milk	*0.8 (0.5,1.3)	0.375	‡1.5 (0.9,2.6)	0.147	IgE peanut	†0.2 (0.1,0.7)	0.007	**1.3 (0.6,2.7)	0.544	<p>For children with FH of asthma or allergy, introduction of solids &/or cow's milk at <4mths reduced peanut sensitization at 2-3 yrs.</p>
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<p>Venter 2009 UK Birth cohort (N=969) Ref.³¹</p>	<p>Interviewer questionnaire</p>	<p>Food sensitisation SPT Food hypersensitivity (FHS) OFC & SPT</p>	<p>1 & 3 yrs</p>	<p>No</p>	<table border="1"> <thead> <tr> <th></th> <th>OR (95% CI)</th> <th></th> <th>OR (95% CI)</th> </tr> </thead> <tbody> <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> </tbody> </table>		OR (95% CI)		OR (95% CI)	At 1 year SPT+ve	0.25 (0.05-0.94)	At 3 years SPT +ve	0.33 (0.11-0.85)	SPT -ve	ref	SPT -ve	ref	FHS yes	0.41 (0.28-0.89)	FHS yes	0.51 (0.28-0.92)	FHS no	ref	FHS no	ref	<p>Weaning before 16 wks lessens food sensitization & FHS at 1 & 3 yrs</p>								
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<p>Snijders</p>	<p>Parent</p>	<p>Food</p>	<p>2 yrs</p>	<p>Yes</p>	<table border="1"> <thead> <tr> <th>Solids at (mths)</th> <th>Any food sensitisation</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	Solids at (mths)	Any food sensitisation			<p>Delaying</p>																								
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2008 Netherlands Birth cohort (N=2343) Ref. ³⁰	questionnaire	<u>Sensitisation</u> IgE ≥ 0.35 kU/L.			<table border="1" data-bbox="1030 183 1550 370"> <thead> <tr> <th></th> <th>*aOR (95%CI)</th> </tr> </thead> <tbody> <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> </tbody> </table> <p data-bbox="1030 370 1550 466">*Adjusted for breastfeeding, gender, maternal smoking/education/age, infant ETS exposure, family allergy.</p>		*aOR (95%CI)	3	1.00	4-6	3.74 (1.46,9.55)	>7	3.94 (1.09,14.2)	P for trend	0.01	solids to age >3 mths increases “any food sensitisation” at 2 yrs.
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Poole 2006 USA Birth cohort (N=1612) Ref. ²⁹	Interviewer questionnaire (3 mthly to 15 mths then annually).	<u>Wheat allergy-</u> Parent report or physician diagnosis.	4 yrs	Yes	<table border="1" data-bbox="922 561 1736 758"> <thead> <tr> <th colspan="2">Wheat allergy</th> </tr> <tr> <th>Age exposed to cereal grain</th> <th>*aOR (95%CI)</th> </tr> </thead> <tbody> <tr> <td><7 months</td> <td>1.00</td> </tr> <tr> <td>≥7 months</td> <td>3.8 (1.18,12.28)</td> </tr> </tbody> </table> <p data-bbox="922 694 1736 758">*Adjusted for FH allergy, duration of breast feeding, age at exposure to rice cereal, any food allergy before age 6 mths.</p>	Wheat allergy		Age exposed to cereal grain	*aOR (95%CI)	<7 months	1.00	≥7 months	3.8 (1.18,12.28)	Delaying cereal grain to ≥7 mths increased wheat allergy at 4 yrs.		
Wheat allergy																
Age exposed to cereal grain	*aOR (95%CI)															
<7 months	1.00															
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Cohort Studies from high-risk populations

<p>Hesselmar 2010 Sweden</p> <p>Birth cohort (high risk) (N=184) Ref. ¹⁷</p>	<p>Food diaries</p>	<p>Food allergy Symptoms & OFC &/or SPT or specific IgE >0.35 kU/L. Food sensitisation SPT +ve</p>	<p>18 mths</p>	<p>Yes.</p>	<table border="1"> <thead> <tr> <th rowspan="3"></th> <th colspan="6">Median age (mths) (IQR) when food introduced</th> </tr> <tr> <th colspan="3">Allergy</th> <th colspan="3">Sensitisation</th> </tr> <tr> <th>Yes</th> <th>No</th> <th>P</th> <th>Yes</th> <th>No</th> <th>P</th> </tr> </thead> <tbody> <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> </tbody> </table>		Median age (mths) (IQR) when food introduced						Allergy			Sensitisation			Yes	No	P	Yes	No	P	Fish	13 (9.8-13)	9 (6-12)	0.01	9.5 (6-13)	9 (6-12)	0.28	<p>Age at fish introduction influenced fish allergy but not fish sensitization at 18 mths.</p>
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	Allergy			Sensitisation																												
	Yes	No	P	Yes	No	P																										
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<p>Kumar 2010 Nth America</p> <p>High risk cohort (N=960) Ref. ²⁴</p>	<p>Interviewer questionnaire</p>	<p>Food allergy- Observed food allergy symptoms + SPT +ve or Specific IgE >0.35 kU/L</p>	<p>36 mths</p>	<p>Yes (stratified by eczema Y/N).</p>	<p>Food allergy (one or more foods) at 3 yrs*</p> <table border="1"> <thead> <tr> <th>Timing and food type in those <u>without</u> eczema</th> <th>†aOR (95%CI)</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>†Adjusted for age, gender, race, caesarean section, pets in 1st year, parent education & income, atopy, FH atopy, first born, breast-feeding, day care.</p>	Timing and food type in those <u>without</u> eczema	†aOR (95%CI)	Rice, wheat and cereal		< 6 mths	1.0	> 6 mths	0.6 (0.3,1.0)	Egg, peanut, tree nut, shell fish, fish, sesame		< 1 year	1.0	> 1 year	0.5 (0.3,0.95)	<p>Later introduction of solids protective against food allergy at 3 yrs only in children without eczema.</p>												
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<p>McGowan 2015 USA</p> <p>High risk birth cohort (N=609, Atopic=560) Ref. ²⁶</p>	<p>Physician- administered questionnaire</p>	<p>Food allergy- Allergist clinical diagnosis Sensitization Food specific IgE ≥0.35ku/l</p>	<p>5 yrs</p>	<p>Yes</p>	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="3">Food allergy at age 5 yrs.</th> </tr> <tr> <th>Allergic</th> <th>Non-allergic</th> <th>p-value</th> </tr> </thead> <tbody> <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> <th rowspan="2"></th> <th colspan="3">Food sensitization at 5 yrs.</th> </tr> <tr> <th>Sensitized</th> <th>Non-sensitized</th> <th>p-value</th> </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> </tbody> </table>		Food allergy at age 5 yrs.			Allergic	Non-allergic	p-value	Age solids introduced (wks, mean ± SD)	13.9 (7.4)	15.1 (8.9)	0.27		Food sensitization at 5 yrs.			Sensitized	Non-sensitized	p-value	Age solids introduced (wks, mean ± SD)	14.8 (8.5)	15.2 (8.6)	0.63	<p>No association between timing of solid food introduction and food allergy or sensitization at age 5 yrs.</p>				
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<p>Mihrshahi 2007 Australia</p>	<p>Interviewer questionnaire</p>	<p>Atopy- SPT+ve to food or</p>	<p>5 yrs</p>	<p>Yes</p>	<table border="1"> <tbody> <tr> <td>Atopy *aOR (95%CI)</td> </tr> </tbody> </table>	Atopy *aOR (95%CI)	<p>Early introduction of solids</p>																									
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High risk birth cohort (N=516) Ref. ²⁷		inhalant allergen or HDM.			<table border="1"> <tr> <td>Solids by 3 mths - Yes</td> <td>0.54 (0.33,0.87)</td> </tr> <tr> <td>- No</td> <td>Ref</td> </tr> <tr> <td>†Allergenic foods by 9 mths - Yes</td> <td>0.67 (0.45,1.02)</td> </tr> <tr> <td>- No</td> <td>Ref</td> </tr> </table> <p>* Adjusted for intervention or control group allocation, parental history of asthma, mother smoking in pregnancy and gender. † Cow's milk, egg, nuts or fish</p>	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	(≤3mths) and allergenic food (≤9mths) protected against atopy at 5 yrs
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- No	Ref													
†Allergenic foods by 9 mths - Yes	0.67 (0.45,1.02)													
- No	Ref													
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	<table border="1"> <tr> <th colspan="2">Peanut allergy</th> </tr> <tr> <th>First peanut exposure</th> <th>*aOR (95%CI)</th> </tr> <tr> <td>At age < 2yrs</td> <td>Ref.</td> </tr> <tr> <td>At age ≥ 2yrs</td> <td>8.0 (1.3-50.0)</td> </tr> </table> <p>*Adjusted for age, sex and breast-feeding history.</p>	Peanut allergy		First peanut exposure	*aOR (95%CI)	At age < 2yrs	Ref.	At age ≥ 2yrs	8.0 (1.3-50.0)	Later peanut introduction increased peanut allergy risk
Peanut allergy														
First peanut exposure	*aOR (95%CI)													
At age < 2yrs	Ref.													
At age ≥ 2yrs	8.0 (1.3-50.0)													

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	<table border="1"> <tr> <th>Exposure</th> <th>Food allergy aOR (95%CI)</th> </tr> <tr> <td>Solids at ≤16 weeks</td> <td>*3.42 (1.16 – 10.10)</td> </tr> <tr> <td>Solids at ≤16 weeks</td> <td>†3.58 (1.03 – 12.50)</td> </tr> <tr> <td>Solids at ≥17 weeks</td> <td>Ref.</td> </tr> </table> <p>*Adjusted for breast feeding, cow's milk protein, †Additionally adjusted for sex, single child, pets, maternal age/education/asthma & allergy,</p>	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.	Early introduction of solids (≤16 weeks) associated with food allergy.
Exposure	Food allergy aOR (95%CI)													
Solids at ≤16 weeks	*3.42 (1.16 – 10.10)													
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