TIMING OF INTRODUCTION OF ALLERGENIC FOODS IN INFANTS, AND RISK OF OTHER AUTOIMMUNE DISEASE (AID)

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1. Timing of introduction of allergenic foods and risk of AID – summary of findings

Key information about each study is shown in the Table of Study Characteristics (Table 1), and summarised below.

1.1. Studies identified

We identified 2 high quality systematic reviews and a further 13 observational studies not included in those reviews, which reported the association between timing of introduction of allergenic food(s) and risk of AID. Of the original studies, 4 were prospective cohort studies, 1 nested case control and 8 case-control studies.

1.2. Populations

The majority of studies (n=9) were carried out in European populations. Other studies were from North America (n=2), Asia Pacific region (n=1), and unclear (n=1).

1.3. Exposure assessment

We identified 5 studies which assessed cow's milk introduction and AID, and 8 studies of gluten or cereal introduction. Questionnaire was the most common method to collect data (n=7), followed by interview (n=4) and records (n=1), unclear in 3 studies, not mutually exclusive because more than one method was used in several studies. In most studies there was no information on whether the dietary questionnaire used had been validated or piloted. One study used a validated food frequency questionnaire (FFQ) (Jansen 2014).

1.4. Outcome assessment methods used

For coeliac disease (CD) 9 studies evaluated clinical disease; 3 studies only reported the outcome serological CD ie tissue Transglutaminase (tTG), and in 1 case the method of outcome assessment was unclear. One study reported Crohn's disease, one ulcerative colitis, one both together as inflammatory bowel disease, and two juvenile idiopathic arthritis (JIA).

1.5. Risk of bias assessment

Among 14 original studies reviewed, overall bias was considered to be low in 2 (14%), unclear in 7 (50%), and high in 5 (36%) of studies. The risk of bias was most commonly considered high due to lack of adjustment for potential confounders, or selection bias. Conflict of interest was judged to be low or unclear in all studies.

1.6. Key findings

i. Full meta-analysis of all studies was not undertaken for timing of gluten introduction and coeliac disease, due to the presence of a high quality recent systematic review of this area.
ii. One systematic review (Pinto-Sanchez 2016) reported one meta-analysis of unadjusted data showing increased risk of CD with introduction of gluten at ≥7 months, but this was not confirmed in other analyses, nor in those original studies of gluten introduction and CD which were not captured by the recent systematic reviews.
iii. One systematic review (Pinto-Sanchez 2016) found retrospective data suggested a relationship between continued breastfeeding during gluten introduction, and reduced CD; but this was not confirmed in prospective studies.
iv. For the original studies not covered by the systematic review, risk of bias was high in one third of studies, and data were sparse so that meta-analysis was not possible.
v. We found no evidence that timing of introduction of allergenic food to the infant diet is associated with risk of CD, inflammatory bowel disease or JIA.
vi. Overall we found no evidence to suggest that different timing of introduction of allergenic foods influences risk of AID. Ranges of timing evaluated were greater or less than 3-4 months for cow's milk and CD, 12 months for cow's milk and JIA, 1 to 6 months for gluten and CD, and 6 months for gluten and inflammatory bowel disease.

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Table 1 Characteristics of included studies evaluating timing of allergenic food introduction in infants and auto-immune diseases (AID)

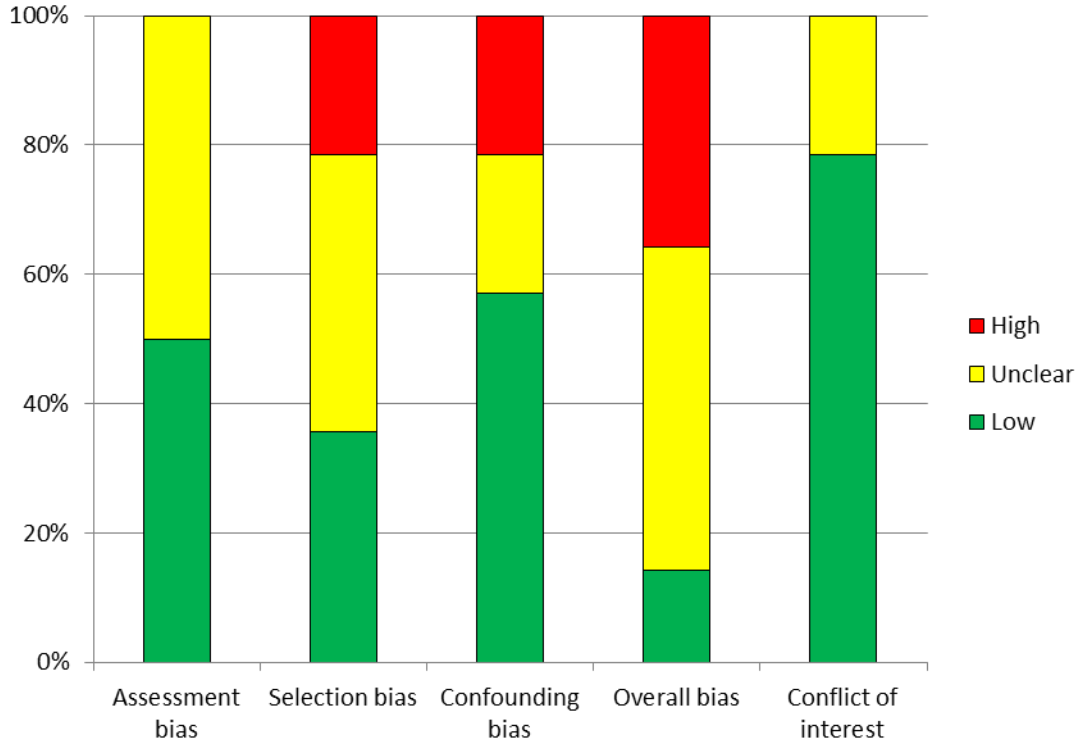
Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Szajeweska 2012 (1)	SR	266, 728	-	Infants at population risk or increased risk of developing Coeliac disease (defined by HLA status, first-degree relative with celiac disease or type 1 diabetes mellitus)	Gluten	Any	Coeliac disease – clinical or serological
Pinto-Sanchez 2016 (2)	SR	429,069	-	Intervention and observational studies evaluating timing of gluten introduction) to the infants' diet, and gluten consumption (quantity)	Gluten	Any	Coeliac disease - clinical or serological in high risk or normal risk populations
Chmiel, 2015 (4)	PC	2401	Germany	Population from 2 prospective cohort, offspring or siblings of patients with T1DM. DABYDIAB 1989-2000 and BABYDIET 2000-2006	Cereal, I/Q	25	Antibodies to transglutaminase C
Hummel, 2007 (5) ; Ziegler, 2003 (6)	PC	1219; 1460	Germany	BABYDIAB: Birth cohort of newborns with a first-degree relative with type 1 diabetes recruited during the pregnancy between 1989 and 2000	Cow's milk, Q	5,8	Coeliac disease: IgA-tTG
Jansen, 2014 (7)	PC	8305	Netherlands	Generation R study: Population based cohort study. This analysis involved those at risk of Coeliac disease based on HLA type.	Cereal, Q	6	Coeliac disease: tTG antibody positive

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Norris, 2005 (8)	PC	1560	USA	DAISY: Prospective birth cohort of children at increased risk for T1DM (relative with T1DM via registries and hospital records) recruited from 1993 to 2004 in Denver, Colorado US were screened for human leukocyte antigen (HLA) genotype associated with celiac disease and TIDM	Cow's milk, I,Q	<5, <10	Coeliac disease: Positive IgA-tTG on 2 consecutive visits or a positive small bowel biopsy after only a single tTG-positive visit.
Aronson, 2016 (10)	NCC	146/436	Sweden	**TEDDYstudy**. Swedish participants in a prospective birth cohort study of infants with a high risk HLA-type, recruited between 2004 and 2010.	Cereal, R	1 to 8 (median 3.2 years)	Coeliac disease: tTG plus biopsy-confirmed (Marsh 2 or greater) coeliac disease versus tTG negative controls without coeliac disease, matched for HLADR3-DQ2 and sex
Ascher, 1997 (11)	CC	81	Sweden	Cases were diagnosed with coeliac disease between 1970-91 at the East University Hospital, Göteborg: controls were older siblings of cases without coeliac disease.	Cow's milk, I	<18	Coeliac disease: Biopsy, ESPGHAN criteria
Myleus, 2012 (16)	CC	954	Sweden	Cases were included from the Swedish National Childhood Celiac Disease Register with matched controls selected randomly from the National Population Register	Cereal, Q	< 2	Coeliac disease: Biopsy, ESPGAN criteria
Pacilio, 2010 (17)	CC	278	Not known	Cases were children 0.5-2 years old with age matched healthy controls	Cereal, unknown	2	Coeliac disease: Unclear

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Strisciuglio, 2016 (18)	CC	264, 434	Italy	Cases were children age 1-18 with inflammatory bowel disease; controls were healthy siblings or age- and sex- matched healthy controls.	Gluten, unknown	<18	Crohn's disease or ulcerative colitis: Unclear
Roman, 2010 (20)	CC	1488	Spain	Prospective observational study and nationwide registry in Spain (REPAC), including all new CD cases in children (<15years), from 06–2006 until the 05–2007. Participating centres have a well-established health area and population. Presentation patterns at diagnosis were recorded. Case/control 1:1 study with children paired for age and sex.	Gluten, unknown	15	Coeliac disease: DD
Baron, 2005 (21)	CC	444	France	Cases were identified from the EPIMAD registry with matched controls from the same area identified by random digit dialling	Cereal, I	<17	Crohn's disease, Ulcerative colitis: DD
Rosenberg, 1996 (22)	CC	419	Canada	Cases were recruited from the Pediatric Rheumatic Disease Clinic, University of Saskatchewan, and matched controls were identified by the parents of cases.	Cow's milk, Q	<18	JRA: DD American College of Rheumatology criteria
Ellis, 2012 (23)	CC	655	Australia	CLARITY: cases were recruited during a clinic visit to Royal Children's Hospital, with diagnosed JIA using ILAR criteria: controls were patients in for elective surgery	Cow's milk, Q	18	DD ILAR criteria

PC prospective cohort, CC case-control, D food diary, Q questionnaire, Physician assessment refers to assessment by a study physician, DD doctor diagnosis, I interview, R records, T1DM type 1 diabetes mellitus, ESPGAN European Society for Paediatric Gastroenterology, JRA juvenile rheumatoid arthritis, ILAR League of Associations for Rheumatology, tTG tissue Transglutaminase; IBD inflammatory bowel disease

Figure 1 Risk of bias in observational studies of timing of allergenic food introduction and risk of AID



2. Timing of cow's milk introduction and risk of AID

Figures 2 and 3 show the outcomes of 2 eligible observational studies reporting OR for timing of cow's milk introduction and CD (1 prospective study) or JIA (1 retrospective study). The data show no significant association between timing of cow's milk introduction to the infant diet and CD or JIA. Three further studies were included but did not contribute to meta-analysis. **Norris 2005** reported no significant difference in hazard of CD for cow's milk introduction at 1-3 months (HR 1.37 95% CI 0.57, 3.31) or at ≥7 months (HR 1.74 95% CI 0.89, 4.42) compared with introduction at 4-6 months in unadjusted analysis; adjusted analysis also showed no significant relationship. **Ellis 2012** reported mean time of cow's milk introduction 16.4 weeks (sd 17.5) in controls without JIA, and 18.3 (sd 20.1) in cases with JIA, and this difference was not statistically significant in adjusted analysis. **Ascher 1997** reported median time of cow's milk introduction 3 months (range 0-9) in controls without CD, and 4 months (range 1.5-6) in cases with CD which was not statistically significant, and did not present an adjusted analysis.

Figure 2: Cow's milk introduction ≤3-4 months and CD

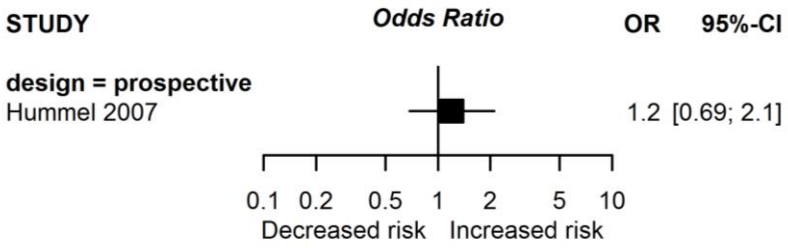
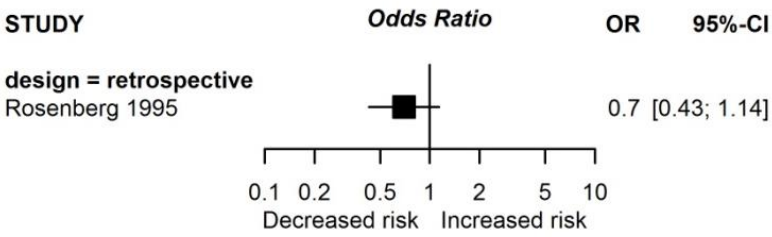


Figure 3: Cow's milk introduction ≤8-12 months and JIA



3. Timing of cereal introduction and risk of AID

Evidence from existing systematic reviews

Table 2 summarises the findings of the systematic review by **Szajeweska 2012** which met our criteria for extraction of data (R-AMSTAR scores 35 and 36). Szajeweska identified 3 prospective cohort studies and 4 case control studies assessing the relationship between timing of gluten introduction to the infant diet, and CD. Meta-analysis was not undertaken by Szajeweska because of a lack of data suitable for meta-analysis. Overall Szajeweska 2012 did not find evidence of an association. When analysed according to breastfeeding status, the authors reported mixed findings. In the case-control studies of Falth-Magnusson 1996 (OR 0.35 95%CI 0.17, 0.66), Ivarsson 2002 (OR 0.50 95% CI 0.40, 0.64) and Peters 2001 (OR 0.46 95%CI 0.27, 0.78) there were reduced odds of CD in infants who were breastfed at the time of gluten introduction. However, the case control study of Ascher 1997 (OR 1.54 95%CI 0.27, 10.56), and the cohort study of Norris 2005 (HR 1.32 95% CI 0.76, 2.28), found no evidence for such an effect. The systematic review of **Pinto Sanchez 2016** also met our inclusion criteria (R-AMSTAR scores 32 and 40). Pinto-Sanchez reported results from 2 intervention trials – their analysis of these 2 trials is not included, since our own search identified 4 trials with a much larger numbers of participants (see report- *Autoimmune – Intervention*). Pinto-Sanchez analysed observational studies of gluten intake and CD – findings from their meta-analyses are summarised in Table 3. They found no association between timing of gluten introduction and CD in most analyses, but in one meta-analysis of unadjusted data from 5 observational studies they reported increased CD with later gluten introduction compared with introduction at 4-6 months RR 1.25 95%CI 1.08, 1.45. A third systematic review by Silano 2016 (3) did not meet our criteria for extraction of data for this report (R-AMSTAR scores 25 and 30). The authors analysed eleven observational studies (2 retrospective and 9 prospective) and concluded that there is no evidence for association between age of first exposure to gluten and risk of CD.

Table 2. **Relationship between timing of gluten introduction and celiac disease -** data from the systematic review of Szajeweska et al 2012 (1)

Study	Comparison	Outcome	Interpretation
Falth-Magnusson 1996	Age of gluten introduction	Mean 6 months CD, 6 months control	No significant difference
Ivarsson 2002	Gluten introduction at 1-4; 5-6; 7-12 months	5-6 months OR 1.4 (0.9, 2.4) 7-12 months OR 0.8 (0.4, 1.4) Compared with 1-4 months	No significant difference
Norris 2005	Gluten introduction at 1-3; 4-6; ≥7 months	1-3 months HR 2.94 (0.83, 10.40) ≥7 months HR 1.78 (0.92, 3.42) Compared with 4-6 months	Increased risk of CD serology with early or late gluten introduction
Peters 2001	Gluten introduction at <4; 4 months, 5 months, >5 months	4 months aOR 0.52 (0.18, 1.44) 5 months aOR 1.21 (0.40, 3.68) >5 months aOR 0.72 (0.28, 1.85) Compared with <4 months	No significant difference
Welander 2010	Gluten introduction at 0-2; 3-4; 5-6; 7-8; 9-10; 11-12 months	3-4 months HR 1.0 (0.3, 3.3) 7-8 months HR 1.1 (0.6, 2.0) Compared with 5-6 months	No significant difference
Ziegler 2003	Gluten introduction at ≤3; 3.1-6; >6 months	≤3 months HR 2.3 (0.3, 18.2) >6 months HR 0.7 (0.3, 1.8) Compared with 3.1-6 months	No significant difference

aOR adjusted odds ratio; CD coeliac disease; HR hazard ratio; OR odds ratio

Table 3. **Relationship between timing of gluten introduction and celiac disease -** data from the systematic review of Pinto-Sanchez et al 2016 (2)

Study	Comparison	Outcome	Interpretation
Meta-analyses of Cohort Studies			
4 studies (50,351 participants)	Introduction of gluten at <4 vs >6 months	RR 1.08 (0.76, 1.54) I^2=0%	No significant difference
	Introduction of gluten at <4 vs 4-6 months	RR 1.27; (0.86, 1.86) I^2=3%	No significant difference
5 studies (100,224 participants)	Introduction of gluten at >6 vs 4-6 months	RR 1.25 (1.08-1.45) I^2=0%	Increased risk with later introduction of gluten
4 studies (774 participants)	Difference in timing of gluten introduction in CD versus controls	MD (months) -0.10 (-0.27, 0.07) I^2= 12%	No significant difference
5 studies (48,845 participants)	Breastfeeding at the time of gluten introduction	OR 0.70 (0.45, 1.10) I^2=78%*	No significant difference

Other data from the systematic review of Pinto-Sanchez, which overall included data from 13 observational studies (5 cohort studies) did not identify evidence for a relationship between timing of gluten introduction and risk of CD.

* Within this analysis the prospective cohort studies of Stordal 2013 and Norris 2005 showed no evidence for association; but 3 of 4 case control studies found significantly reduced breastfeeding at the time of gluten introduction in CD compared with controls.

Evidence from original observational studies not included in other recent systematic reviews

i. Timing of gluten introduction and CD

Two further cohort studies, one nested case-control studies, and two case-control studies reported this association but were not included in the previous systematic reviews. The prospective cohort study of **Chmiel 2015**, and the case control study of **Myleus 2012** found no significant association between gluten containing cereal introduction at less than 3 and less than 1 month respectively, and odds of CD. The prospective cohort study of **Jansen 2014** found no association between cereal introduction at <6 months and CD. The nested case-control study of **Aronsson 2016** reported that age at first introduction to gluten (median 22 weeks in each group) did not differ between cases and tTG-negative controls. The case control study of **Pacilio 2010** reported that gluten was introduced either before 4 or after 6 months age in 1 of 139 (0.8%) controls without CD, compared with 36 of 139 (26.3%) cases with CD (P<0.001).

ii. Breastfeeding at the time of gluten introduction, and CD

Two further case control studies reported this association but were not included in the previous systematic reviews. **Myleus 2012** reported significantly less breastfeeding at the time of gluten introduction in CD versus controls (OR 0.55 95% CI 0.39, 0.78). **Roman 2010** in an abstract publication reported a statistically significant association between gluten introduction during breastfeeding, and reduced CD in univariate analysis, and in one multivariate analysis. These findings are consistent with the findings of the retrospective studies included in the systematic review of Pinto-Sanchez, where prospective studies failed to confirm the association.

iii. Timing of gluten introduction and inflammatory bowel disease

Two case control studies evaluated this association. **Baron 2005** reported no significant difference between cases with Crohn's disease or ulcerative colitis, and controls without either condition, in timing of gluten introduction to the infant diet – no numerical data were presented, but analyses were adjusted for relevant potential confounders. **Strisciuglio 2016** in an abstract publication reported that introduction of gluten before 6 months was more frequent in cases with Crohn's disease or ulcerative colitis than in

healthy age and sex matched controls without inflammatory bowel disease (P<0.001). It is unclear whether these data were adjusted, the source of controls is not clear, and 10 other statistically significant differences (all P values <0.02) were reported between cases and controls

3.1. Conclusions: timing of allergenic food introduction and AID

Overall 5 studies reported the association between timing of cow's milk introduction and CD or JIA, and found no significant association either alone or in the single meta-analysis. Two systematic reviews and a further 6 original studies reported the association between timing of cereal introduction and/or breastfeeding status at the time of cereal introduction and CD, and two studies reported timing of cereal introduction and Crohn's disease or ulcerative colitis. The two systematic reviews found no consistent evidence for an association between timing of gluten introduction and risk of CD. One analysis of unadjusted data which focussed on a specific time period (4-6 months) for gluten introduction reported increased CD risk for later introduction, however other data did not support an association between late gluten introduction and CD. One case control study presented as an abstract (Strisciuglio 2016) found increased gluten introduction at <6 months in cases with inflammatory bowel disease; this was not confirmed in a separate case control study presenting adjusted data (Baron 2005).

Overall we found no evidence that timing of cow's milk or gluten introduction influences risk of CD or JIA, or that timing of gluten introduction influences risk of Crohn's disease or ulcerative colitis. Ranges evaluated for comparison of timing were more or less than 3-4 months for cow's milk and CD, 12 months for cow's milk and JIA, 1 to 6 months for gluten and CD, and 6 months for gluten and inflammatory bowel disease.

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