

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

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## **1. Timing of introduction of allergenic foods and risk of AID – summary of interventions and 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 5 intervention studies which reported the association between timing of introduction of allergenic food(s) and risk of AID. Of these, 4 were randomised control trials, and 1 quasi randomised controlled trial. No studies used a multifaceted intervention.

### **1.2. Populations**

The majority of studies (n=4) were carried out either largely, or exclusively, in European populations; one study was undertaken in North America. Overall ~2800 participants were allocated to intervention arms, and ~2800 participants to control arms.

### **1.3. Interventions and comparators**

Cow's milk was used in the intervention group in one study, as a short-term early intervention in the first days of life. Gluten was the intervention in the other 4 studies – in 3 cases from 6 months of age, in one case from 4 months of age.

### **1.4. Outcome assessment methods used**

Type 1 Diabetes Mellitus (T1DM) was evaluated in 2 studies – in one study diagnosis was based on clinical assessment, and in one study using American Diabetes Association criteria. Coeliac disease was evaluated in 4 studies – in two using just serological markers, and in two using serology and/or biopsy to support the diagnosis.

### **1.5. Risk of bias assessment**

Overall risk of bias was considered high in 1 study (20%) due to high attrition rate. Only 1 study had low overall risk of bias, in the other three risk of bias was unclear. Four studies were considered as having low risk of conflict of interest.

## **1.6. Key findings**

- i. Data were limited to cow's milk and TIDM, gluten and TIDM or coeliac disease, and the interaction between breastfeeding status and gluten introduction on coeliac disease.
- ii. We did not find evidence for significant associations. Early gluten introduction may lead to earlier onset of coeliac disease, but there is no evidence that it influences disease risk.

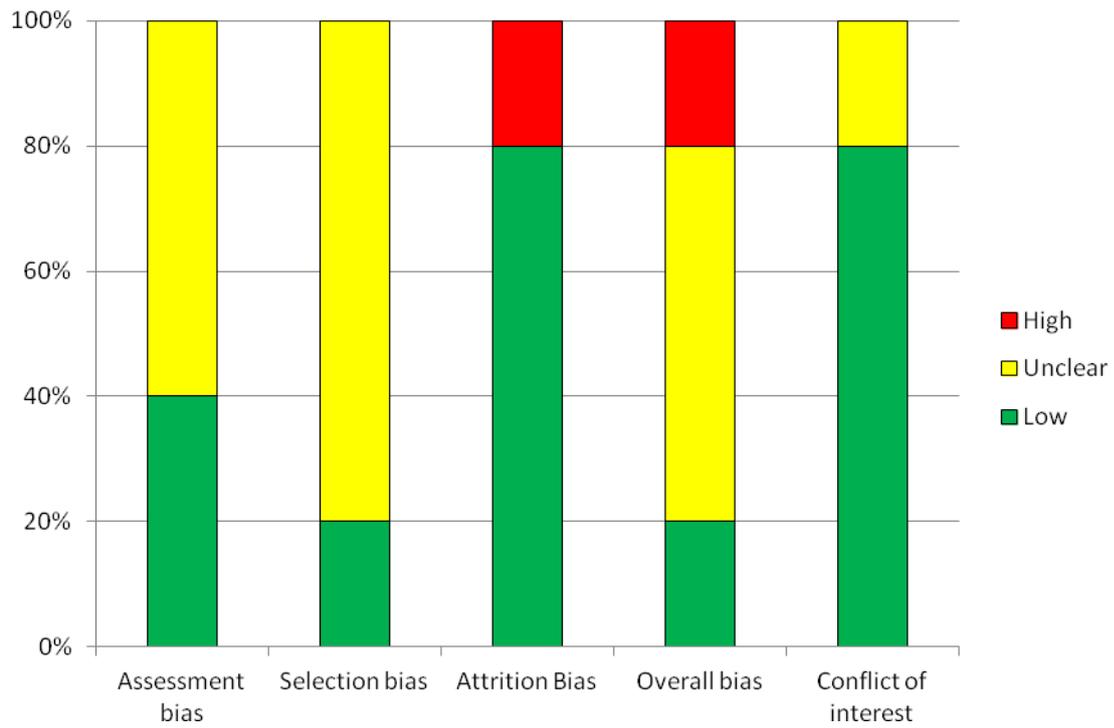
**Table 1 Characteristics of intervention trials evaluating timing of allergenic food introduction in infants and AID**

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Beyerlein, 2014 (1); Hummel 2011 (2)	RCT	77/ 73	Introduction of gluten into diet at 6 months, versus delay to 12 months	BABYDIET Study. Infants < 2 months with at least one first-degree relative with type 1 diabetes, no gluten in diet yet, and one of five specific type 1 diabetes-associated HLA genotypes	Germany	High	8	tTG antibody positive in $\geq 2$ samples; taken at 6, 12, 16, 24, 30, 36 months then annually.  T1DM by American Diabetes Association Expert Committee criteria
Lionetti, 2014 (3)	RCT	416/ 416	Introduction of food containing gluten (pasta, semolina, and biscuits) at 6 months, versus delay to 12 months.	SIGENP Study. Newborns with at least one first-degree relative with coeliac disease.	Italy	High	7.9	Coeliac disease autoimmunity and Marsh 2 or 3 at small-bowel biopsy.

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Sellitto, 2012 (4)	RCT	17/ 13	Daily purified wheat gluten versus daily cornstarch from 6 months to 12 months age, at 3-5g daily.	Infants of first-degree relatives with biopsy proven CD, and positive for HLA DQ2 and/or HLA DQ8 genotypes, eBF to 6 months.	USA	High	1	Tissue transglutaminase (tTG) antibodies $\geq 7$ AU and subsequent positive endomysial IgA antibodies.
Vriezinga, 2014 (5)	RCT	483/ 480	200 mg wheat gluten with 1.8 g of lactose (equivalent to 100 mg of immunologically active gluten) versus 2g lactose daily from 16-24 weeks age.	PreventCD Study. Infants aged 0-3 months with $\geq$ first degree relative with biopsy-proven coeliac disease, and HLA-DQ2, HLA-DQ8 or DQB1*02 genotype	Croatia, Germany, Hungary, Israel, Italy, the Netherlands, Poland and Spain	High	4	Serological (tTG IgA or IgG antibodies) or biopsy (1990 ESPGHAN criteria) diagnosis.
Savilahti, 2009 (6)	qRCT	1789 / 1859	Cow's milk formula versus pasteurised human milk from birth for mean 4 days.	Term infants in Helsinki fed formula milk before hospital discharge.	Finland	normal	11.5	TIDM Clinical Diagnosis

BF breastfeeding; eBF exclusive breastfeeding; RCT randomised clinical trial, qRCT quasi-randomised controlled trial: ESPGHAN European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; tTG tissue transglutaminase; Marsh stage 0 is normal, stage 1 has increased intraepithelial lymphocytes, stage 2 involves proliferation of the crypts of Lieberkühn, stage 3 involves partial or complete villous atrophy and crypt hypertrophy.

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

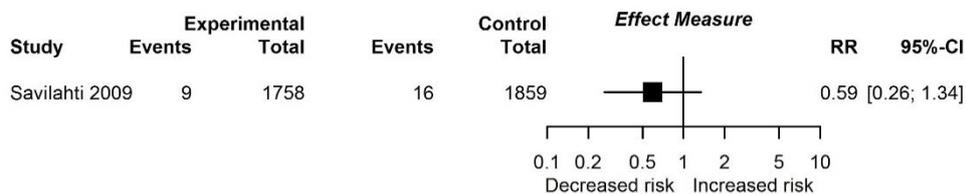


## 2. Timing of allergenic food introduction and risk of AID

### 2.1. Short term early cow's milk introduction and risk of TIDM

Figure 2 shows data from a study of short term early cow's milk introduction (where the intervention period was limited to the first week of life, and did not extend beyond this) and risk of TIDM. Data are sparse due to the small number of cases, and there is no statistically significant association seen.

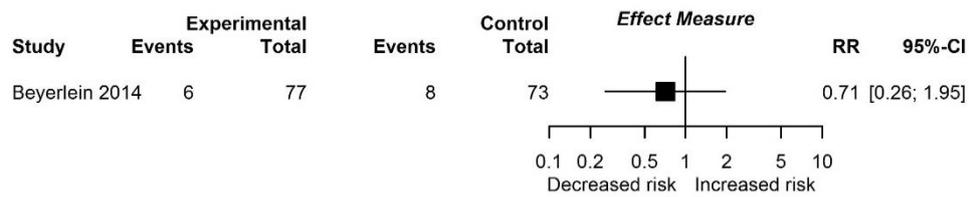
**Figure 2 Short term early cow's milk introduction and risk of TIDM**



## 2.2. Early gluten introduction and risk of T1DM

Figure 3 shows data from a study of timing of gluten introduction at 6 months versus 12 months and risk of T1DM. No significant association is seen.

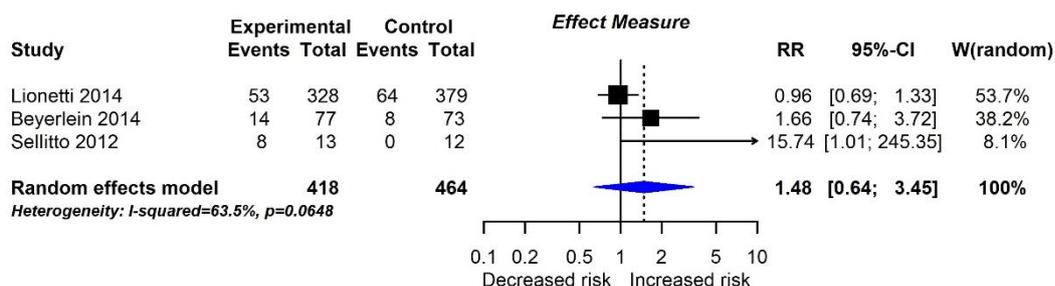
**Figure 3 Early gluten introduction and risk of T1DM**



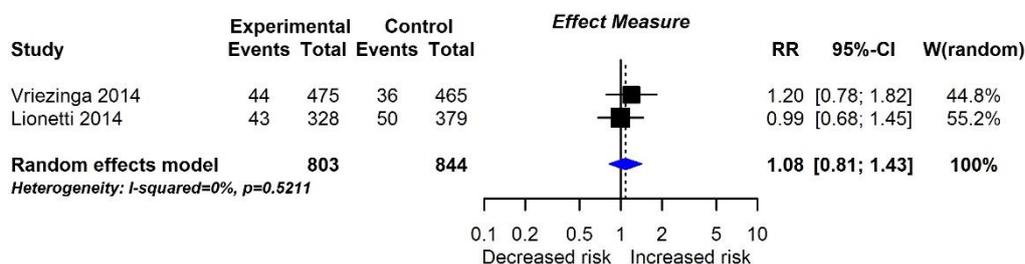
### 2.3. Early gluten introduction and risk of coeliac disease

Figures 4 to 6 show pooled data for timing of gluten introduction and risk of serological, clinical or ‘any’ coeliac disease. No association is seen, with significant statistical heterogeneity seen in those meta-analyses which included the study of Sellitto 2012. Sellitto reported significantly increased serological coeliac disease at age 1 with early gluten introduction. However, this study suffered from high attrition bias, and perhaps more importantly they measured coeliac disease at the end of the intervention period, at which stage only the intervention group had received gluten so the control group could not yet manifest serological coeliac disease. The subsequent trial of Lionetti 2014, which assessed coeliac disease at a later timepoint, has shown that early gluten introduction leads to earlier development of coeliac disease, but does not overall lead to increased disease risk. Vriezinga 2014 reported no significant interaction between early gluten introduction and duration of exclusive (P=0.70) or total (P=0.83) breastfeeding; Lionetti reported no association between breastfeeding status at the time of gluten introduction and coeliac disease (HR for breastfed at gluten introduction 1.5 95% CI 0.70, 3.0).

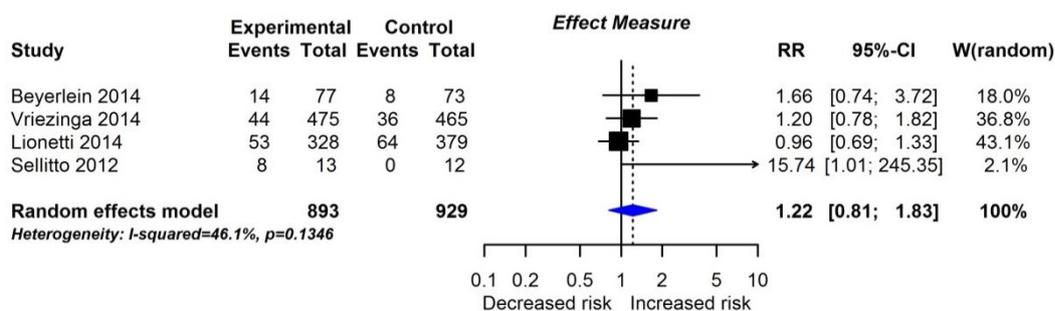
**Figure 4 Early gluten introduction and risk of serological coeliac disease**



**Figure 5 Early gluten introduction and risk of clinical coeliac disease**



**Figure 6 Early gluten introduction and risk of clinical or serological coeliac disease**



**2.4. Conclusions: timing of allergenic food introduction and AID**

Overall we found no evidence that introduction of cow’s milk for the first 4 days of life, or gluten at 4-6 months influences the development of AID, and no evidence for an interaction with breastfeeding status in the case of gluten introduction and coeliac disease. However, data were limited to very early CM and to gluten as exposures, and to coeliac disease and TIDM as outcomes.

**Overall we found no evidence that brief early cow’s milk exposure, or gluten introduction at age 4-6 months influences risk of AID, or that there is an interaction between breastfeeding status and gluten introduction on disease risk. Introduction of gluten at 6 months may lead to earlier development of coeliac disease than introduction at 12 months, but does not influence overall disease risk.**

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