

## **TIMING OF INTRODUCTION OF ALLERGENIC FOODS IN INFANTS, AND RISK OF TYPE 1 DIABETES**

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## **1. Timing of introduction of allergenic foods and risk of T1DM – 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 35 observational studies which reported the association between timing of introduction of allergenic food(s) and risk of T1DM. Of these, 8 were prospective cohort studies, some with separate reports of a nested case control analysis, 1 nested case control and 26 were case control studies.

### **1.2. Populations**

The majority of studies (n=23) were carried out in European populations. Other studies were from North America (n=3), Asia Pacific region (n=5), Latin America (n=3) and Africa (n=1).

### **1.3. Exposure assessment**

We identified 33 studies which assessed cow's milk introduction and T1DM, 2 studies of soya, 6 studies of egg, 2 studies of fish, no studies of nut introduction, and 10 studies of cereal introduction. We did not identify any studies of the interaction between allergenic food introduction and breastfeeding status, and T1DM. Questionnaire was the most common method to collect data (n=29), followed by interview (n=9), food diary (n=2) and records (n=1), not mutually exclusive because more than one method was used in several studies. Twenty-four studies used only questionnaire. It was unclear whether any study used a validated or piloted dietary questionnaire.

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

In 28 studies outcome assessment relied on physician assessment (eg using WHO criteria), and in 7 T1DM assessment was serological (ie islet autoimmunity). Analyses were not stratified by age of assessment for T1DM or other autoimmune outcomes.

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

Among 35 studies, overall bias was considered to be low in 12 (34%), unclear in 7 (20%), and high in 16 (46%). The risk of bias was most commonly considered high due to lack of adjustment for potential confounders.

### **1.6. Key findings**

- i. Risk of bias was mixed, with over 40% of studies considered at high risk of bias, often due to poor methods of exposure assessment and/or failure to adjust for potential confounding variables in analysis.
- ii. We found significant statistical heterogeneity in some analyses, for unclear reasons. For some analyses retrospective studies found associations between early allergenic food introduction and increased TIDM risk, but for the same exposure/outcome, prospective studies did not confirm the association.
- iii. We found no evidence that timing of cow's milk introduction is associated with TIDM risk.
- iv. We found no evidence that the timing of egg, soya, fish or cereal introduction is associated with TIDM risk, although data were sparse. No data were identified for timing of peanut or tree nut introduction.

**Table 1 Characteristics of included studies evaluating timing of allergenic food introduction in infants and type 1 diabetes mellitus**

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Chmiel, 2015 (1)	PC	2291	Germany	Population from 2 prospective cohort, offspring or siblings of patients with T1DM. DABYDIAB 1989-2000 and BABYDIET 2000-2006	Cereal, Q/I	25	Islet autoimmunity (IAA, GADA and IA2A)
Couper, 1999 (2); Couper, 2009 (3)	PC	548	Australia	Australian BABYDIAB: Birth cohort of newborns with a first-degree relative with type 1 diabetes were recruited during the pregnancy in Victoria and South Australia, Australia in 1993	Cow's milk, cereal, D/Q	2.4, 1.7	Islet autoimmunity (IAA, GADA and IA2A)
Holmberg, 2007 (4); Karlen, 2012 (5); Wahlberg, 2005 (6); Wahlberg, 2006 (7)	PC	8715	Sweden	ABIS: Population based birth cohort of children born in Southeast Sweden between 1997 and 1999	Cow's milk, cereal Q	1, 2, 5.5	Islet autoimmunity (GADA, IAA and/or IA2A)
Ludvigsson, 2003 (8)	PC	186	Sweden	Children with one or more family members with atopy	Cow's milk, cereal, Q	0.5, 5	Islet autoimmunity (GADA, IAA OR IA2A)
Virtanen, 1998 (9)	PC	697	Finland	Childhood Diabetes in Finland Study: Unaffected siblings of index children newly diagnosed with T1DM aged between 3 and 19 years old	Cow's milk, Q	<25	Islet autoimmunity (ICA, IAA, GADA, IA2A)
Ziegler, 2003 (10)	PC	1282	Germany	German BABYDIAB: Birth cohort of newborns with a first-degree relative with type 1 diabetes were recruited during the pregnancy in Germany between 1989 and 2000	Cow's milk, cereal, Q	4, 5	Islet autoimmunity (IAA, GADA or IA2)
Frederiksen, 2012/3 (11, 12); Lamb, 2008/13 (13, 14); Norris, 1996/03 (15, 16)	PC, NCC	1886	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 T1DM	Cereal, cow's milk, egg, Q	4, 7, 9	DD, Islet autoimmunity (GADA and/or IA2A and/or IAA)

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Vaarala, 1999 (17); Virtanen, 2006/11 (18, 19); Kimpimäki, 2001 (20); Lempainen, 2012 (21)	PC, NCC	5619	Finland	DIPP: Prospective birth cohort of children at high risk of T1DM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland	Cow's milk, cereal, egg, Q, I	<2, <10, <4, <19	Isle autoimmunity (GADA and/or IAA and/or IA2A)
Savilahti, 2009 (22)	NCC	6209	Finland	Cases and controls taken from the NHI database, Finland	Cow's milk, cereal, R/D	11.5	DD
Alves, 2012 (23)	CC	246	Brazil	Cases with T1DM were sourced from hospital paediatric endocrinology clinics after diagnosis and controls were unaffected siblings	Cow's milk, cereal, I	6.7, 9	DD WHO criteria
Baruah, 2011 (24)	CC	86	India	Cases were T1DM treated on an endocrinology ward & matched controls were recruited from other wards or among family members of medical professionals	Cow's milk, I	<18	DD: History of diabetic keto acidosis or documentation of spontaneous ketonuria
Bodington, 1994 (25)	CC	393	UK	UK study of T1DM cases diagnosed 1980-90 and matched controls from a Population Register in Leicestershire.	Cow's milk, Q	<15	DD
Esfarjani, 2001(26)	CC	104	Iran	Case children selected from an endocrine clinic in Tehran, with controls selected from a paediatric outpatient department	Cow's milk, Q	<14	DD
EURODIAB, 2002 (27)	CC	2226	Austria, Latvia, Lithuania, Luxembourg and UK	EURODIAB (Austria, Latvia, Lithuania, Luxembourg & UK): Cases with T1DM were selected from a population-based register and controls from population registers, schools & polyclinics	Cow's milk, I/Q	<15	DD
Gimeno, 1997 (28)	CC	626	Brazil	Cases with T1DM were identified through a social/education program for young diabetics or through the Hospital Sao Paulo. Controls were matched non-diabetic children.	Cow's milk, Q	<18	DD

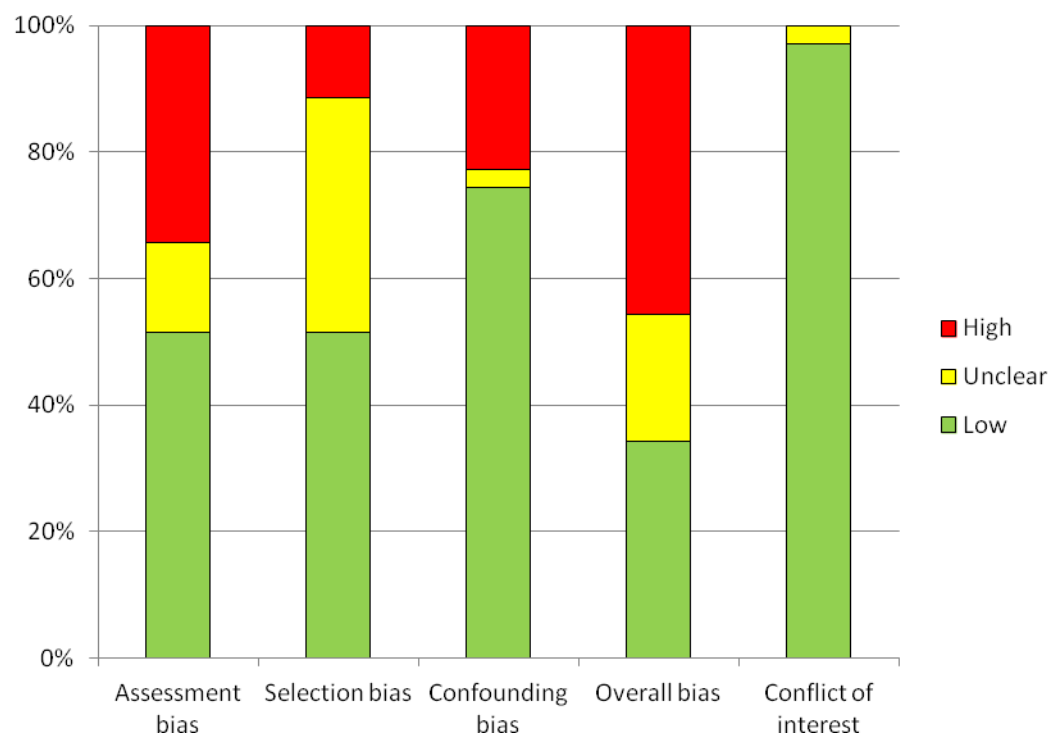
Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Hypponen, 1999 (29); Virtanen, 1992 (30); Virtanen, 1993 (31)	CC	1380	Finland	Finnish children <14years diagnosed between 1986-1989, with matched controls selected from the Finnish Population Registry	Cow's milk, Q	8.2, 7-14	DD
Kostraba, 1992 (32)	CC	372	Pittsburgh, USA	Cases were selected from hospital IDDM registers and controls were the non-diabetic siblings of subjects: Pittsburgh, USA. All black population.	Cow's milk, Q	8.6, 10.1	DD
Kostraba, 1993 (33)	CC	306	Colorado, USA	Cases were found through the IDDM Registry & controls recruited from licensed motor vehicle register, both in Colorado, USA	Cow's milk, Q	<18	DD
Malcova, 2006 (34)	CC	2334	Czech Republic	Cases were identified from the Czech Childhood Diabetes Register, with unrelated aged-match controls selected from among the schoolmates of cases	Cow's milk, Q	<15	DD
Marshall, 2004 (35)	CC	577	UK	Cases were T1 diabetics registered at a Paediatric Diabetes Clinic, Lancashire, UK, 1998. Controls were children, without chronic disease, selected from the local Health Authority Register	Cow's milk, I	<16	DD
Meloni, 1997 (36)	CC	200	Sardinia	Cases were diabetic children followed up by the Paediatric Department of the University of Sassari, Sardinia, with controls selected from children also admitted to the same hospital but with no personal or family history of IDDM	Cow's milk, Q	<17	DD
Perez-Bravo, 1996 (37); Perez-Bravo, 2003 (38)	CC	250	Chile	Cases were T1DMs selected from the Santiago de Chile registry and controls were randomly recruited from several schools	Cow's milk, I/Q	<15. 8	DD, WHO criteria
Rami, 1999 (39)	CC	609	Austria	EURODIAB: cases were from the Austrian diabetes register, diagnosed between 1989-94 in Vienna and matched controls were randomly selected from schools in Vienna: Austria.	Cow's milk, Q	<15	DD

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Rosenbauer, 2007 (40); Rosenbauer, 2008 (41)	CC	2631	Germany	EURODIAB: Cases are newly diagnosed diabetics registered by nationwide active hospital-based surveillance system ESPED and controls from acquaintances of cases.	Cow's milk, Q	<5	DD
Sadauskaite-Kuehne, 2004 (42)	CC	517	Sweden, Lithuania	DEBS Study: cases were newly diagnosed between 1995-2000 in South East Sweden and aged <15	Cow's milk, Q	7	DD
Sipetic, 2005 (43)	CC	315	Serbia	Cases were children hospitalised with new diagnosis of T1DM in Belgrade, with controls selected from a population of children treated for skin disease as outpatients	Cow's milk, I	<16	DD WHO criteria
Skrodeniene, 2010 (44)	CC	1099	Lithuania	DEBS: cases were hospitalized new diagnoses of T1DM 1996-2000 and matched controls randomly selected from outpatient departments	Egg, Q	10	DD WHO criteria
Soltesz, 1994 (45)	CC	305	Hungary	Hungarian Childhood Diabetes Epidemiology Study Group (part of EUROBIAB/DIAMOND): Cases were newly diagnosed T1DM as per the incidence register for 1990 and matched controls were selected by case families	Cow's milk, Q	<14	DD
Strotmeyer, 2004 (46)	CC	690	China	WHO Multinational Project for Childhood Diabetes (DiaMond): cases selected from T1DM incidence registries 1985-98 and matched controls from locally resident populations (>95%)	Cow's milk, cereal, egg, fish, soya, Q	9.7	DD WHO criteria
Svensson, 2005 (47)	CC	1186	Denmark	Cases taken from the National Register, diagnosed between 1996-99, and controls from the Population Register	Cow's milk, Q	8.4	DD
Telahun 1994 (48)	CC	129	Ethiopia	Cases selected from attendees of a diabetic clinic and controls from their non-diabetic siblings	Cow's milk, Q	<15	DD
Thorsdottir, 2000 (49)	CC	220	Iceland	Cases were children with IDDM and controls were children selected by Statistical Bureau of Iceland.	Cow's milk, I	12	DD

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Verge, 1994 (50)	CC	475	Australia	Cases taken from an incidence register and controls from school registers in New South Wales	Cow's milk, soya, Q	≤14	DD
Visalli, 2003 (51)	CC	900	Italy	EURODIAB Italy: Cases with T1DM selected from within the EURODIAB ACE study, born 1977-89, with controls selected from school records for the same period	Cow's milk, egg, fish, Q	6-18	DD WHO criteria
Wadsworth, 1997 (52)	CC	639	UK	Cases were newly diagnosed with IDDM <5y in 1992 reported through BPASU and controls were selected from District Health Authority Immunisation Register	Cow's milk, Q	<5	DD

PC prospective cohort, NCC nested case-control, CC case-control, D food diary, GADA glutamic acid decarboxylase antibodies, IAA insulin autoantibodies, IA2A insulinoma-2-associated autoantibodies, Q questionnaire, Physician assessment refers to assessment by a study physician, DD doctor diagnosis, I interview, R records

**Figure 1 Risk of bias in observational studies of timing of allergenic food introduction and risk of type 1 diabetes**



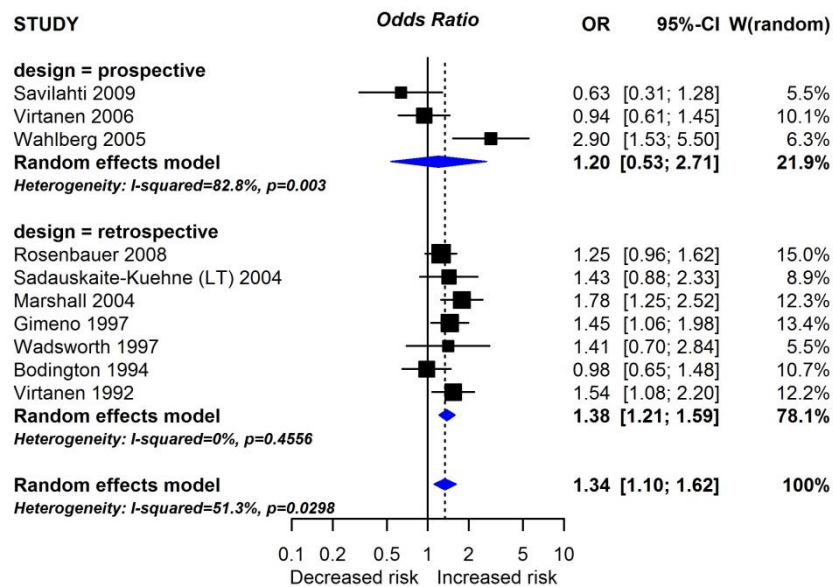
## **2. Timing of cow's milk introduction and risk of TIDM**

### **2.1. Timing of cow's milk introduction and risk of TIDM**

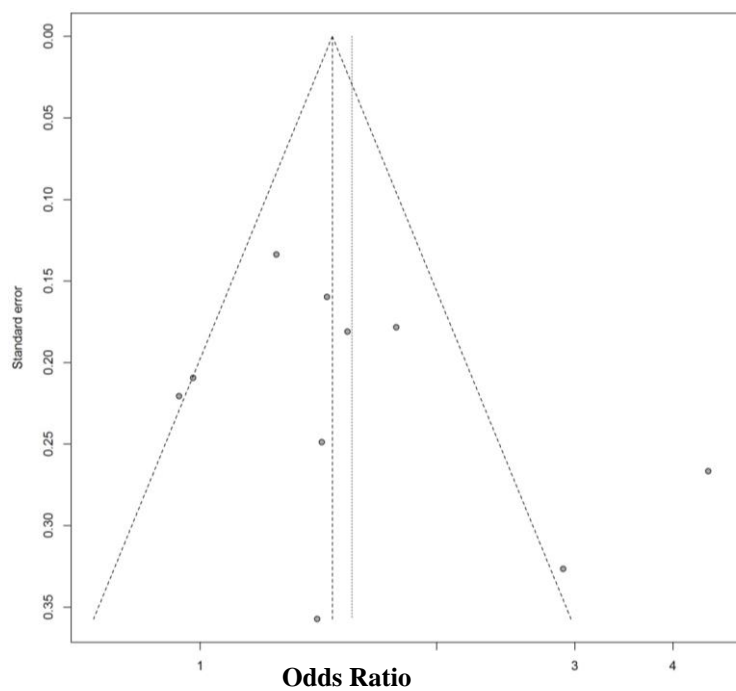
Figures 2 to 7 show the outcomes of 28 eligible observational studies reporting OR for TIDM. Figure 2 shows extreme statistical heterogeneity in prospective studies, and evidence for increased TIDM risk with early cow's milk introduction in the retrospective studies, with no statistical heterogeneity. Of the prospective studies, Savilahti 2009 assessed clinical TIDM, and the other 2 studies assessed serological TIDM, in a representative population (Wahlberg 2005) and in a population at increased genetic risk of TIDM (Virtanen 2006). These differences may account for some of the statistical heterogeneity. A funnel plot showed no evidence of publication bias (Figure 3). Subgroup analyses (Table 2) show a significant difference between the prospective study of Virtanen 2006 in a high risk population, with no association seen, and other studies in low/normal risk populations, where an association was seen. Figure 4 shows no evidence of association in prospective studies, all of which assessed serological TIDM, but evidence of association between early cow's milk introduction and increased TIDM in retrospective studies, albeit with moderate statistical heterogeneity. A funnel plot showed no evidence of publication bias (Figure 5). Subgroup analyses (Table 3) showed a statistically significant difference in findings in Figure 4 between the retrospective studies, which used clinical TIDM diagnosis, and the prospective studies, which used serological diagnosis. Figures 6 and 7 reveal no consistent evidence of association between early cow's milk introduction and TIDM risk, using different cut-offs to categorise timing of cow's milk introduction. Two prospective studies found significantly increased TIDM with cow's milk introduction before 5-7 months (Figure 6) with no statistical heterogeneity. However, other data from one of these cohorts (DAISY – Norris 2003) suggest no relationship between timing of cow's milk introduction and TIDM risk (Figure 4), and retrospective studies of cow's milk introduction at 5-7 months also found no association. Figure 8 shows a pooled analysis of mean difference in time of introduction of cow's milk in 5 retrospective case control studies and one prospective study. Pooled data from retrospective studies show a significant association, but all data are unadjusted. Adjusted analyses in the study of Alves 2012 showed no significant difference, and the other studies did not report adjusted analyses. The prospective study

(Savilahti 2009) found no difference in unadjusted analysis, and a second prospective study (Couper 1999) found no significant association in an adjusted regression analysis - HR 1.0 for single T1DM-associated antibody, 0.9 for detection of  $\geq 2$  antibodies but could not be included in the meta-analysis since no 95% CI or P value was reported.

**Figure 2: Cow's milk introduction  $\leq 0$ -2 months and T1DM**



**Figure 3: Funnel plot for studies of cow's milk introduction  $\leq 0$ -2 months and TIDM**

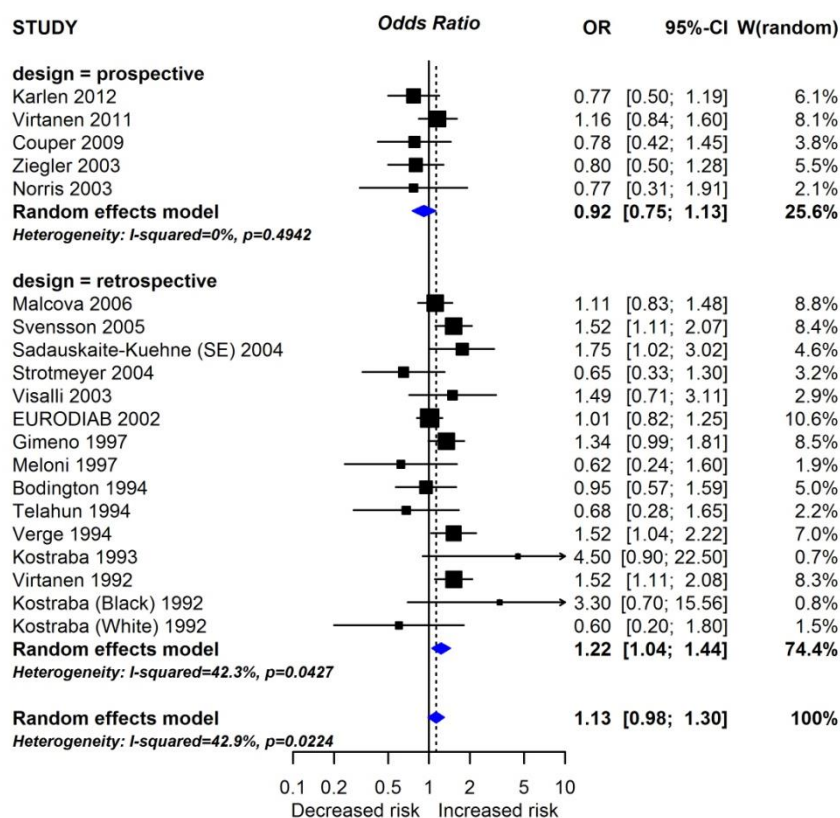


Egger's test for asymmetry P=0.26

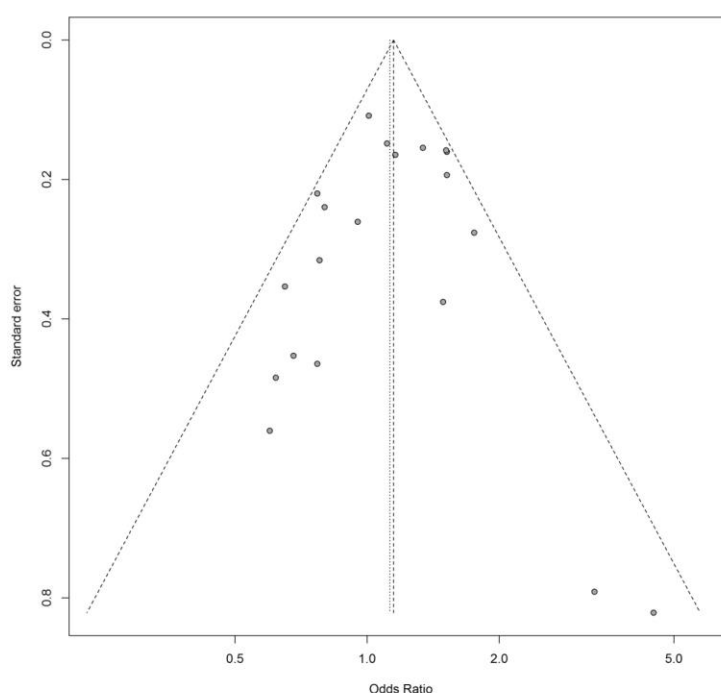
**Table 2 Stratified and subgroup analyses of association between cow's milk introduction at ≤0-2 months and risk of TIDM**

	Number of studies	OR [95% CI]	I <sup>2</sup> (%)	P-value for between groups difference
Risk of disease – High	1	0.94 [0.61-1.45]	-	0.028
Risk of disease – Normal	9	1.65 [1.28-2.13]	70.9	
Overall risk of bias – Low	3	1.27 [0.91-1.77]	35	0.20
Overall risk of bias – High/Unclear	7	1.71 [1.24-2.36]	78.2	
Method of diagnosis – clinical	8	1.57 [1.21-2.02]	70.3	0.96
Method of diagnosis – serological (single or combination of antibodies)	2	1.61 [0.53-4.85]	87.8	

**Figure 4: Cow's milk introduction  $\leq 3$ -4 months and TIDM**



**Figure 5: Funnel plot for studies of cow's milk introduction  $\leq 3$ -4 months and TIDM**

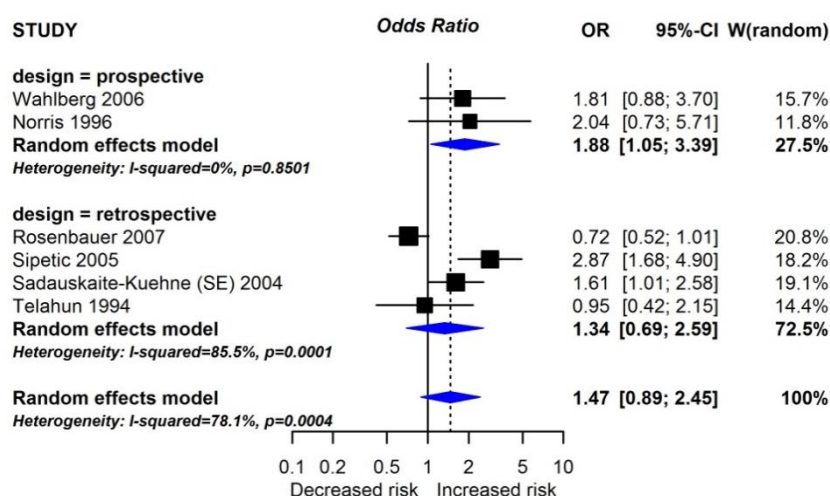


Egger's test for asymmetry P=0.59

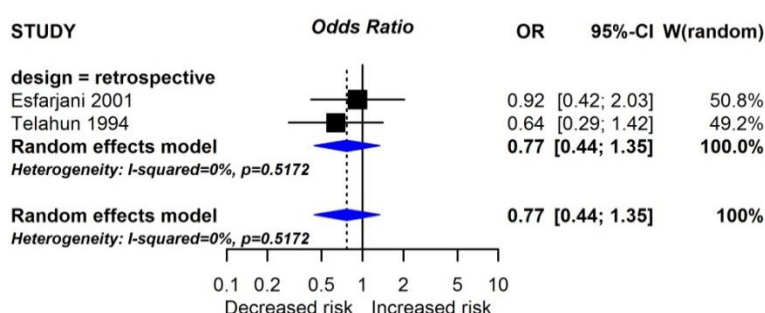
**Table 3 Stratified and subgroup analyses of association between cow's milk introduction at  $\leq 3$ -4 months and risk of TIDM**

	Number of studies	OR [95% CI]	I <sup>2</sup> (%)	P-value for between groups difference
Risk of disease – High	4	0.97 [0.77-1.23]	0	0.18
Risk of disease – Low/Normal	16	1.18 [1.00-1.39]	47.1	
Overall risk of bias – Low	8	1.20 [0.98-1.47]	47	0.41
Overall risk of bias – High/Unclear	12	1.06 [0.86-1.31]	44	
Method of diagnosis – clinical	15	1.22 [1.04-1.44]	42.3	0.033
Method of diagnosis – serological (single or combination of antibodies)	5	0.92 [0.75-1.13]	0	

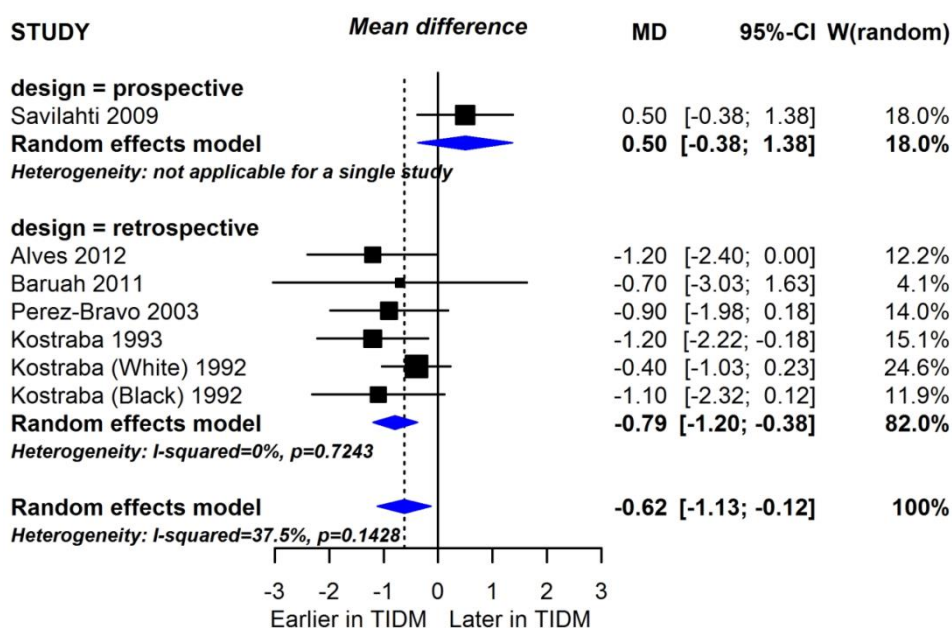
**Figure 6: Cow's milk introduction  $\leq 5-7$  months and TIDM**



**Figure 7: Cow's milk introduction  $\leq 8-12$  months and TIDM**



**Figure 8: Mean time of cow's milk introduction and TIDM**



## **2.2. Studies of cow's milk introduction and TIDM which could not be included in meta-analysis**

Five further studies reported the relationship between timing of cow's milk introduction to the infant diet, and risk of TIDM. In 4 there was no association reported, in 1 there were mixed findings – association with 1 autoantibody, not with another. The findings from each study are summarised below:

**Soltesz 1994** reported no difference in median age of cow's milk introduction in infants with and without TIDM. **Thorsdottir 2000** reported no difference in timing of cow's milk introduction in infants with and without TIDM. **Ludvigsson 2003** found increased level of GADA (glutamic acid decarboxylase antibodies) but not IA2A (insulinoma-2-associated autoantibodies), with early cow's milk introduction. **Virtanen 1998** found no significant relationship between timing of introduction of cow's milk and serological TIDM, in a prospective cohort study of siblings of TIDM cases. **Rami 1999** reported no difference in median age of cow's milk introduction in infants with and without TIDM.

## **2.3. Conclusions: cow's milk introduction and TIDM**

Overall 33 studies reported this association – 8 prospective studies, and 25 case control studies. Statistical heterogeneity was high in some analyses, for reasons that are unclear. Analyses of retrospective studies and unadjusted data showed significantly earlier cow's milk introduction in cases than controls, but this was not supported by prospective or adjusted data. Overall there was no evidence to suggest a relationship between timing of introduction of cow's milk to the infant diet, and TIDM. We did not identify any systematic reviews in this area which met our quality criteria. One systematic review (53) identified just seven case-control studies (total 2007 cases, 8455 controls) and reported that in 6 of 7 studies there was no difference in TIDM risk with cow's milk introduction before 3, 5, 7 or 11 months. Data were not pooled in meta-analysis. Our findings are consistent with their conclusions that there is no evidence for an association between timing of cow's milk introduction and risk of TIDM.

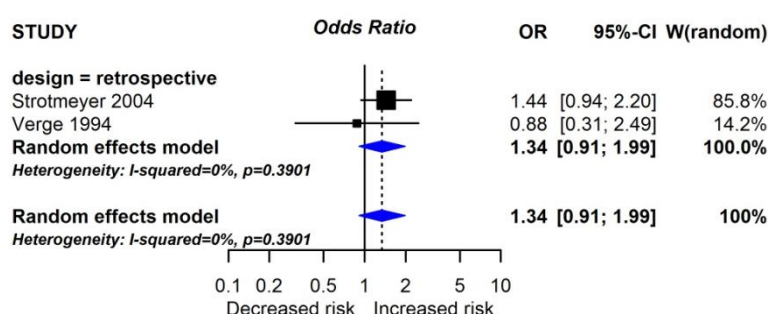
**Overall we found no evidence that timing of cow's milk introduction influences risk of TIDM.**

### 3. Timing of other allergenic food introduction and risk of TIDM

Figures 9 to 13 show the outcomes of 10 eligible observational studies reporting OR for TIDM. The pooled data show no significant association between timing of soya, fish or cereal introduction to the infant diet and TIDM. One case-control study found egg introduction prior to 5 months of age was more common in cases compared with controls in adjusted analysis; a separate case control study evaluating egg introduction prior to 3 months found no significant difference between cases and controls, in unadjusted analysis (Figures 10 and 11). A larger prospective study evaluating hazard of TIDM for egg introduction  $\leq$  8-12 months found increased TIDM with earlier egg introduction, but the difference did not reach statistical significance.

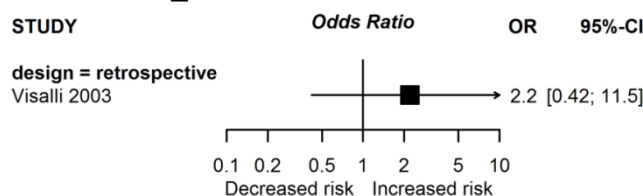
#### 3.1. Timing of soya introduction and risk of TIDM

**Figure 9: Soya introduction  $\leq$ 3-4 months and TIDM**

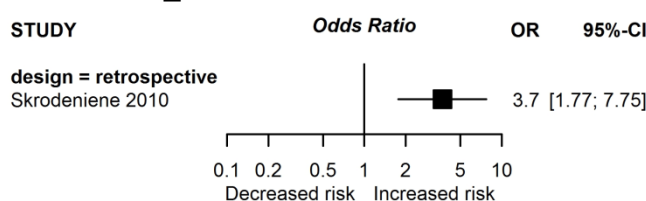


#### 3.2. Timing of egg introduction and risk of TIDM

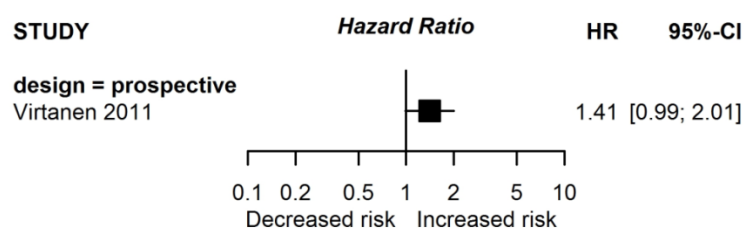
**Figure 10: Egg introduction  $\leq$ 3-4 months and TIDM**



**Figure 11: Egg introduction  $\leq$ 5-7 months and TIDM**

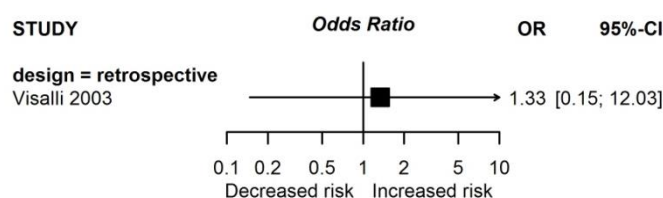


**Figure 12: Egg introduction  $\leq 8-12$  months and TIDM**



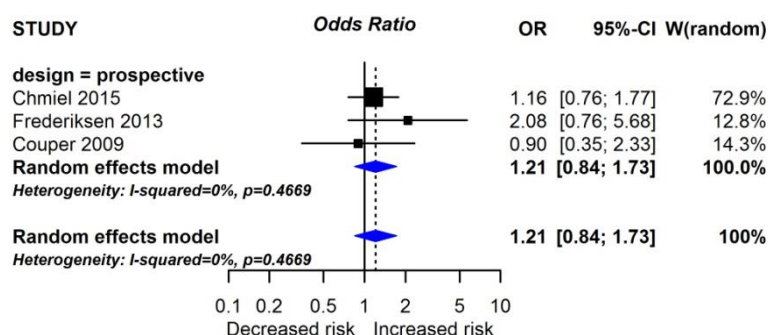
### 3.3. Timing of fish introduction and risk of TIDM

**Figure 13: Fish introduction  $\leq 3-4$  months and TIDM**

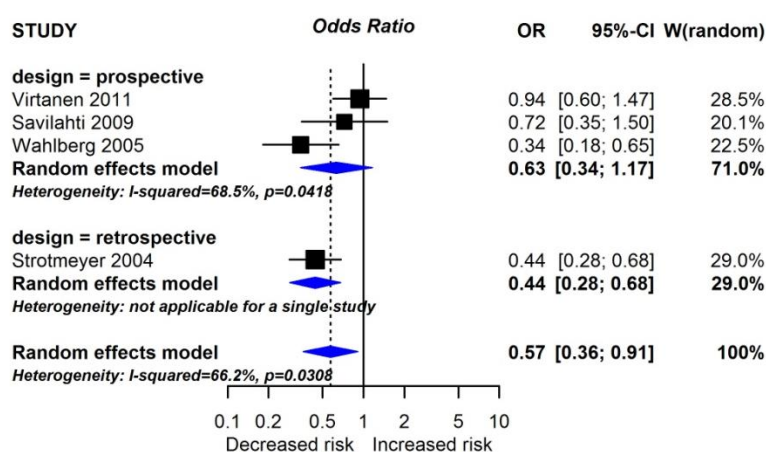


### 3.4. Timing of cereal introduction and risk of TIDM

**Figure 14: Cereal introduction  $\leq 3-4$  months and TIDM**



**Figure 15: Cereal introduction  $\leq 5-7$  months and TIDM**



### **3.5. Studies of other allergenic food introduction and TIDM which could not be included in meta-analysis**

Five further studies reported the relationship between timing of other allergenic food introduction to the infant diet, and risk of TIDM. In 4 there was no association reported, in 1 study findings were mixed. The findings from each study are summarised below:

**Ludvigsson 2003** found no significant association between timing of gluten introduction and any of 3 TIDM-associated antibodies GADA, IA2A or IAA in a prospective cohort study. **Zeigler 2003** found significantly increased risk of positive TIDM-associated antibodies with gluten introduction before 3 months, but not when categorised as before or after 6 months, in a prospective cohort study. **Alves 2012** reported mean time of introduction of cereal to the infant diet as 3.2 months (sd 2.5) for cases, and 3.7 months (sd 2.4) in controls but the difference was not statistically significant ( $P=0.082$ ).

**Strotmeyer 2004** reported no significant difference between cases and controls in timing of introduction of egg or fish, using adjusted analyses in a case control study design.

**Lamb 2013** reported unadjusted data from a nested case control analysis of the DAISY cohort, showing no significant association between timing of egg introduction and serological TIDM.

### **3.6. Conclusions: other allergenic food introduction and TIDM**

Overall 15 studies reported this association – 8 cohort studies, 1 nested case control study and 6 case control studies. Statistical heterogeneity was high in some analyses, for reasons that are unclear. A single retrospective study found early egg introduction to be associated with TIDM in a logistic regression model - this was not supported by analysis of two other retrospective studies or two prospective studies, although one of the prospective studies found increased TIDM-associated beta-cell autoimmunity associated with early egg introduction which was almost statistically significant. We found no evidence that timing of introduction of soya, fish or cereal is associated with TIDM, and there were no data for nuts.

**We found no evidence that timing of soya, egg, fish or cereal introduction to the infant diet is associated with TIDM.**

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