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Association between the age of solid food introduction and eczema; a systematic review and a meta-analysis

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Abstract

Introduction

Eczema is a common childhood ailment responsible for a considerable disease burden. Both timing of introduction to solid food and allergenic food are believed to be related to childhood eczema. Despite the growing body of evidence, the relationship between timing of any solid food introduction (allergenic and/or non-allergenic) and development of eczema has not previously been systematically reviewed.

Methods

PubMed and EMBASE databases were searched using food and eczema terms. Two authors selected papers according to the inclusion criteria and extracted information on study characteristics and measures of association. Meta-analyses were performed after grouping studies according to the age and type of exposure.

Results

A total of 17 papers met the inclusion criteria, reporting results from 16 study populations. Of these, 11 were cohort studies, two case controls, one cross sectional study and, 2 randomised controlled trials. Limited meta-analyses were performed due to heterogeneity between

studies. Timing of solid food introduction was not associated with eczema. One randomized controlled trial provided weak evidence of an association between early allergenic (around 4 months) food introduction and reduced risk of eczema.

Conclusions

The available evidence is currently insufficient to determine whether the timing of introduction of any solid food influences the risk of eczema.

(Word count 198)

Key Words

Solid food, allergenic food, timing/introduction, eczema, dermatitis.

1. Introduction

Eczema is the most common skin disease in childhood [1] and it causes a considerable amount of distress to both children and parents [2]. The prevalence of eczema varies globally but is higher in developed countries [2]. Timing of introduction to complementary food for infants has recently received increased interest [3], as this may impact on the child's immune system [4], and risk of developing eczema.

Complementary feeding describes the provision of nutrition other than breast milk [5]. It may be either in liquid form, typically formula feeding, or in solid form, with introduction of solid food to the infant's diet. Introduction of liquid and solid complementary foods generally occur at different times, responding to different needs. Formula or substitute milk feeding is introduced as a breast milk substitute until the child can be weaned onto solid foods. Solid food introduction is the start of transition to an adult diet and relies also on developmental readiness.

Prolonged exclusive breastfeeding, which is intimately related to the timing of solid food introduction, is widely advocated as a preventive measure for childhood allergic disorders, although there is little clear evidence to support this claim [6]. Guidelines for the timing of allergenic food introduction also differ, with some authorities recommending introduction between four to six months, and others before 12 months of age [12, 13]. Currently, there is no consensus concerning the timing of introduction to solid foods with the aim of preventing eczema. The World Health Organization (WHO) guidelines recommend exclusive breastfeeding for six months, prior to complementary food introduction [5]. The food introduced at this time may be solid and/or liquid but the expectation is that solids will be introduced. The ASCIA (Australian Society of Clinical Immunology and Allergy) guidelines recommend complementary feeding around six months and allergenic food within the first year of life [7]. All other national and international organizations recommend timing complementary feeding around the age of six months and not before the age of four months [8-10].

A recently published systematic review, based on 17 trials and 37 observational studies, investigated the association between allergenic food introduction and eczema, including both liquid and solid allergenic foods.[11] They found no clear evidence for an association between timing of introduction of any allergenic food and eczema. However, they did not report on the associations between a) timing of introduction of only solid foods, or b) the exposure to specific allergenic foods (apart from cows' milk) and the outcome of eczema. Furthermore, the review included multifaceted intervention trials, where the effect of timing of introduction of individual foods could not be determined (14). Therefore, the literature concerning timing of introduction to solid foods not specifically focussing on allergenic food and the risk of eczema has not yet been systematically synthesised. Understanding this relationship may help inform infant feeding guidelines.

The aim of this paper is to appraise all available literature on the association between timing of solid food introduction and the risk of eczema. For the purpose of this review, we have excluded exposure to cows' milk, as it is commonly given as liquid formula before the introduction of complementary solids.

2. Methods

PubMed and EMBASE electronic data bases were systematically searched using both key words and MeSH terms for both solid food, complementary and allergenic food introduction and eczema. We also reviewed the reference lists of all included articles. Additionally we searched trial registries (Australian and New Zealand, European, Japanese) and created citation alerts to screen for the most current publications. We included all relevant English-language human studies. Further details of the search terms are provided in the online supplement (S1). The review was prospectively registered in the PROSPERO systematic review registry (CRD42016033473). The final search was performed on the 18th of February 2017. Following the final search data base alerts were established to keep the authors updated on new publications.

2.1 Inclusion and exclusion criteria

Inclusion criteria

- Types of studies – We included all cohort studies, case control studies, cross sectional studies and randomised controlled trials based on general population or high risk population groups.
- Published in English.
- Study participants - Human.
- Exposures - The exposure of interest was timing of solid food introduction to the child (solid food may be allergenic or non-allergenic). Both the exact age in months and interval cut-offs were considered as suitable for the analysis.
- Outcomes – Diagnosis of eczema (any definition).
- Peer reviewed publications (conference papers, abstracts and letters to the editor) that did not contain original data were excluded from the review.

2.2 Selection of studies

Two authors independently reviewed the titles and abstracts (NW and GB). Any disagreements were resolved by consulting a third reviewer (CL) who made the final

decision. The list of excluded studies after the full text review is provided in the online supplement (S2).

2.3 Data extraction

Two authors independently performed the data extraction (NW and GB). Details of the studies were extracted into a standard table. The fields included: first author, year published, exposure and its definition, outcome and its definition, study design, sample size, confounding and moderating factors considered, measures taken to control for reverse causation, and effect estimates.

2.4 Effect estimates

Associations with the dichotomous outcome of eczema versus no eczema were extracted from each paper. Associations were reported as odds ratios/risk ratios or hazard ratios.

2.5 Quality assessment and risk of bias

Two authors were independently involved in assessing the study quality (NW and GB). Study quality was assessed by using Newcastle-Ottawa scale (NOS) for individual studies. The cohort and case control studies were graded as very good (9-10), good (7-8), satisfactory (5-6) and unsatisfactory (0-4). The Cochrane Review Quality assessment scale was used for quality assessment of Randomised Controlled Trials.

2.6 Data analysis

Studies that provided the age of exposure and a numerically measured outcome as a risk ratio or odds ratio with 95% confidence interval were included in the meta-analysis. The I^2 was used to assess the heterogeneity of the pooled estimate (>75% was considered to be high statistical heterogeneity). We performed random effect meta-analysis and studies were grouped according to exposure time in age and also the food groups the child was exposed to. Although early introduction of solids was considered to be when a child was introduced to solids below the age of four months, during the analysis we considered different levels of exposure as provided by the included studies. Studies that were not included in the meta-analysis were included in a narrative synthesis.

All analyses were performed using STATA 14 statistical package.

159 3. Results

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161 Electronic searches identified 1414 records (figure 1). Following removal of duplicates, 1092
162 articles underwent title and abstract screening, of these, 987 were excluded. The remaining
163 105 papers underwent full text review, and 89 articles were excluded, leaving 17 articles for
164 inclusion. Two studies were added after screening trial registries (Australian and New
165 Zealand trial registry).

166 Figure 1- The PRISMA flow diagram for selection of studies for the review.

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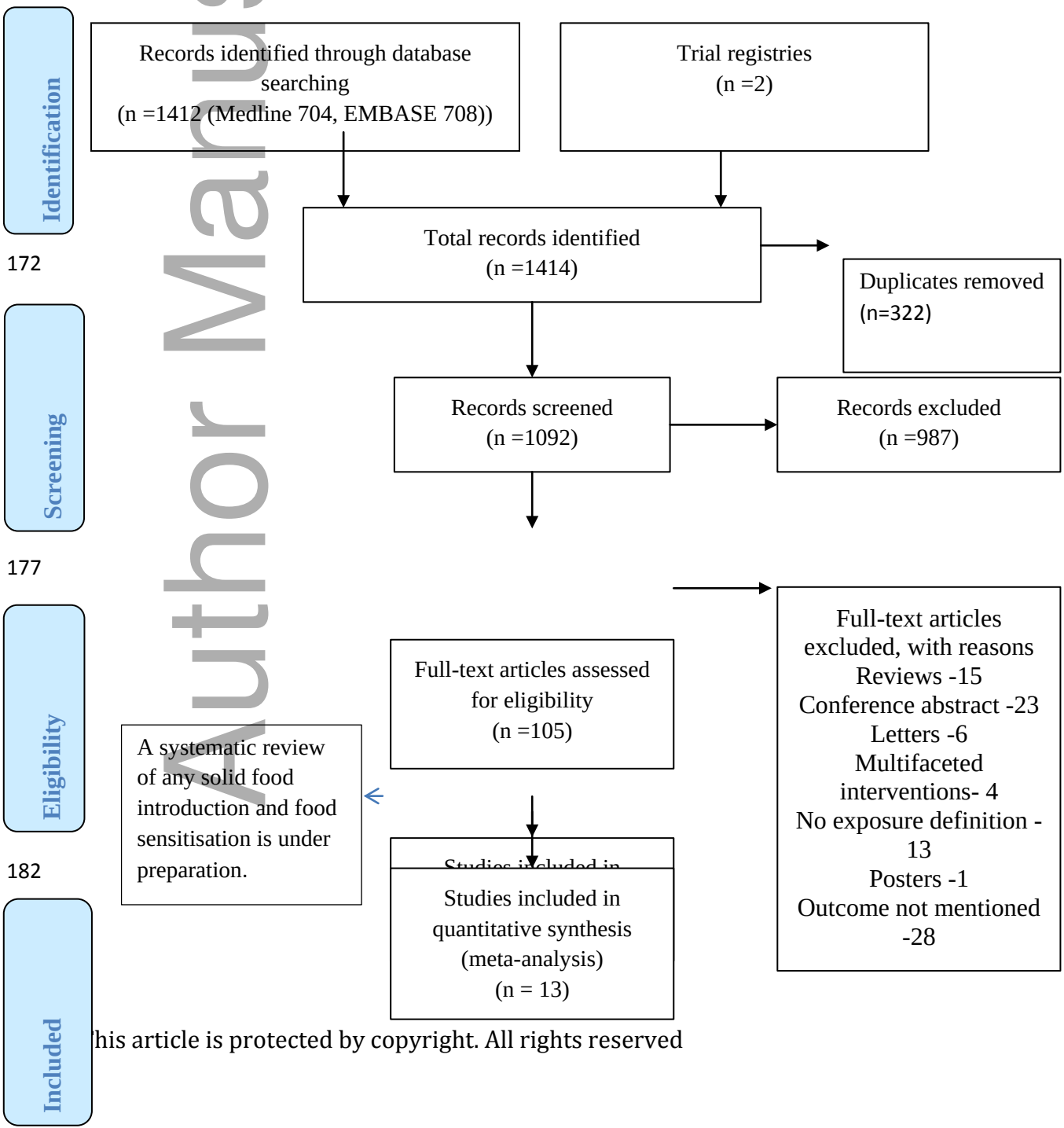

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Of the 17 papers included in the review, 11 were birth cohort studies [3, 4, 12-21]. As the LISA birth cohort study generated two publications [17, 18], the number of papers exceeds the number of study populations. There was one cross sectional study [22], two case control studies [23, 24] and two randomised controlled trials [25, 26]. Among the birth cohort studies, one was a high-risk birth cohort [13]. The exposure differed considerably among the studies. In some it was any solid food [12, 13, 15, 17, 18, 21] whilst in others the exact food item was mentioned [3, 4, 14, 16, 20, 27] (Table 1). The age of eczema outcome was also different between studies (1- 6 years). Also, the definition used for diagnosis of eczema differed between studies. Some used questionnaire based diagnosis (the questionnaire identifies whether child had eczema or not) [15] and in others a clinician diagnosed the condition [12, 17, 18]. Some studies adjusted for potential confounding factors such as parental and sibling atopy and type of breastfeeding [12, 13] while others did not [20]. Further details of the selected studies are given in Tables 1 to 4.

Table 1- The Association between the Timing of First Food (allergenic)Introduction and Eczema (Randomised Controlled Trials included in the review)

Author, year, Study name, country and the sample size	Exposure definition	Outcome definition	Confounding factors considered during the analysis	Results					Main findings
Tan et al 2016 [26] BEAT Australia N=319 infants were randomized, 165 to egg and 154 to placebo	Intervention with egg powder or rice powder between 4-8 months of age 350mg egg protein daily from 4-8 months	Modified Hanifin and Raijka criteria 1 year	-	Time point ITA* 4 months Intervention started 8 months Intervention completed 12 months	Eczema evident on examination in Placebo group (n, %) 45/154(29%) 41/131(31%) 48/124(39%)	Eczema evident on examination in Egg group (n, %) 37/164(23%) 46/133(35%) 45/129(35%)	RR(95%CI) 0.77(0.53,1.12) 1.10(0.78,1.56) 0.90(0.65,1.24)		The prevalence of eczema is the same between the egg exposed and placebo groups
Palmer et al 2016 [25] STEP Australia N=820 infants with atopic mothers were randomised into two groups, egg powder (n = 407) or a color-matched rice powder (n = 413). (excluded infants who had a history of allergic disease or any previous known direct ingestion of egg)	The intervention (egg powder 0.4g per day), mixed with carrot, pineapple, and rice powders; the control (egg-free), only carrot, pineapple, and rice powders were given to infants (starting from age 4 to 6 months) to 10 months.	Doctor diagnosed 1 year	City, infant sex, breast-feeding status, and paternal history of allergic disease.	ITA* Eczema Atopic eczema	Allergenic food group 40 of 374 (10.7%) 10 of 372 (2.07%)	Control group 45 of 378 (11.9%) 20 of 379 (5.3%)	aRR and 95%CI 0.84 (0.57-1.23) 0.53 (0.26-1.09)	P value 0.37 0.09	The prevalence of eczema is the same between the egg exposed and egg-free groups

*ITA-Intention to treat analysis

Table 2 –The Association between the Timing of First food introduction and eczema (Cohort Studies included in the review)

Author & year, Study name, Country, type of population and sample size n/N- (analysed sample/total sample)	Exposure definition Age How measured	Outcome (Eczema) definition Age How measured	Confounders /selection bias, stratification and reverse causation	Results	Main finding
Cohort Studies					
Chuang et al 2011 [15] Taiwan Birth Cohort Study Taiwan Population based n/N=18773/24208	Any solid food and age first solid introduced 6-18 months Measured at six 6 & 18 months Interviewer administered questionnaire	Parent report of Doctor diagnosis 6-18 months Questionnaires	Adjusted for: infants' gender, birth order, birth weight, and gestational age, parents' age, education, allergic history, place of residence, maternal smoking or passive smoking during pregnancy, mould spots, carpet, and pets. Considering reverse causality, 2399 children with eczema in the first 6 months were excluded from the analysis	Introduction of solids and eczema from 6 to 18 months Time of solid introduction / Yes / No / aOR (95%CI) / P value < 4 months / 41 / 806 / 1 4-6 months / 906 / 15139 / 1.11 (0.80, 1.53) / 0.593 >6 months / 103 / 1778 / 1.08 (0.74, 1.57) / 0.698	No association between early /late introduction of solid food and eczema from 6-18 months
Snijders et al 2008 [12] KOALA birth cohort Netherlands Population based n/N=2434/2558	First food products ingested, measured at 3, 7, 12, and 24 months by self-administered questionnaire	1. Parent reported eczema at 3, 7, 12 and 24 months 2. Eczema defined at the age of 2 years using UK working party criteria 24 months	Adjusted for: duration of breastfeeding, gender of infant, recruitment group (conventional, alternative lifestyle), maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery (in years), maternal education, presence of parental allergic disease, and (older) siblings' atopic history. Exclusion of infants with early symptoms of eczema (to avoid reverse causation) did not essentially change results .	Introduction of solid food and infants' Eczema Age at solid introduction / Parent reported eczema (birth-24 months) aOR(95%CI) / Eczema at 24 months defined using UK working party criteria aOR(95%CI) 3 / 1.00 / 1.00 4-6 / 1.28 (0.91–1.81) / 2.67 (0.80–8.97) >7 / 2.10 (1.17–3.76) / 9.46 (2.05–43.61) P for trend / 0.02 / <0.001	Delayed introduction of solids associated with increased risk of eczema
Zutavern et al 2008	Six months,	Parent reported	Adjusted for: study centre, parental allergy, gender,	Introduction of solids and eczema at 6 years of age	No association

[18] LISA birth cohort Germany Population based n/N=2073/3097	parents reported age of first solid introduction from 1st to the 6th months of age (1st/2nd month, 3rd/4th month, 5th/6th month) reported by mother	Doctor diagnosed eczema 6 years	parental education and breastfeeding type. Early life atopic status or parental history of allergy did not alter the association between age of solid food introduction and eczema at 6 years	Timing of solid introduction Ref(0-4 months) 5-6 months >6 months	OR(95%CI) 1 0.92(0.61,1.39) 0.82(0.49,1.40	between introduction of solids beyond 4 or 6 months and eczema at the age of 6 years
Mihrshahi et al 2007 [13] CAPS birth cohort Australia High risk population n/N=516/616	Solids given regularly by the age of three months by interviewer administered questionnaire at three months	By Observation eczema at age 5 years by a research nurse/ parent reportedcombined with seeking medical care/use of steroid cream for eczema 5 years	Adjusted for: intervention or control group allocation, mothers and fathers history of asthma, maternal smoking during pregnancy and the gender of the child. -	Association between introduction of solids and eczema at age 5 years Age at solid food introduction By 3 months Yes compared to no	aOR(95%CI) 0.59(0.33,1.04)	No association between the timing of solid introduction and eczema.
Zutavern et al 2006 [17] LISA birth cohort Germany	Solids introduced age obtained by a self-administered questionnaire at six, 12, 18 and 24 months	Parent reported doctor diagnosed eczema 2 years	Adjusted for: study centre, parental atopy, child's gender, parental education, birth weight, and breastfeeding type. Infants with early skin or allergic symptoms had increased risk of symptomatic eczema (not doctor diagnosed) when exposed to delayed introduction of solids	Association between the introduction of solids and eczema from 0 to 24 months Timing of solid introduction Ref(0-4 months) 5-6 months >6 months	OR(95%CI) 1 1.02(0.64,1.62) 0.96(0.53,1.74)	No association between delayed introduction of solids beyond the 6 month and prevention of

Population based n/N=2612/3097									eczema by 2 years of age
Filipak et al 2007 [21] Birth cohort study Germany Began as RCT investigating hydrolyzed vs cows milk formulae An intervention group n=2252 and a non-intervention group n=3739	Solids introduced age obtained by a self-administered questionnaire at the age of 12 months 4 years	Doctor diagnosed eczema	Adjusted for: family history of eczema and atopy, type of milk feeding such as breast feeding or formula feeding,	Timing of solid introduction 0-4 months 5-6 months > 6 months	Non-intervention group (any solid) Doctor diagnosed eczema aOR(95%CI) 1 0.86(0.66-1.12) 1(0.72-1.40)	Symptomatic eczema aOR(95%CI) 1 0.95(0.73-1.23) 1.07(0.77,1.50)	Intervention group(any solid) Doctor diagnosed eczema aOR(95%CI) 1 0.95(0.69-1.31) 1.00(0.72,1.39)	Symptomatic eczema aOR(95%CI 1 1.14(0.81-1.59) 1.28(0.91,1.81)	No association between delay in any solid food introduction and eczema.
Niinivirta et al 2014 [20] Probiotic intervention birth cohort Finland high-risk cohort n/N=256/256	Details of solids given to the child until the age of one year by a self-administered food diary 4 years	Doctor diagnosed atopic eczema	Child's gender, parental perception of child's possible reactions and study group -	Timing introduction Fish ≥ 7 months Cereal ≥ 7 months	HR (95%CI) 1.73(0.75,3.99) 1.43(0.73,2.80)				No association between delayed introduction and eczema.
Nwaru et al 2013 [19] DIPP birth cohort	Self-administered questionnaire at 3, 6 and 12 months of age	Parent reported doctor diagnosed ever eczema	Adjusted for: sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1	Timing of Cereal Introduction < 4.5 months 4.5-5.5 months 5.5 months	OR(95%CI) 1.47(1.10,1.97) 1.17(0.88,1.56) ref				Introduction of cereal <4.5 months associated with

Finland high-risk cohort n/N=3109/3789		5 years	year of age, mode of delivery, and birth weight Interaction tests for eczema by 6 months and parental allergic history were performed to evaluate the potential for reverse causality .					increased risk of eczema
Tromp et al 2011 (3) Generation R cohort study Netherlands Population based n/N=6300/6905	Food frequency questionnaire administered at 6 and 12 month	Parent reported physician diagnosed eczema (ISAAC definition) At the ages of 2, 3 and 4 years	Adjusted for: sex, mother's socioeconomic status, race/ethnicity, smoking during pregnancy, gestational age, birth weight, parity, breastfeeding, parental history of atopy and any of the following from 12 to 24 months: antibiotics day care attendance, gastroenteritis, respiratory tract infections, over weight A history of cow's milk allergy in the first year of life increased the risk of eczema Parental history of allergy increased the risk of eczema	Introduction of allergenic foods and eczema at ages 2, 3, and 4 years				No association between delayed introduction of allergenic foods after 6 months and prevention of eczema
				Food group introduced ≤ 6 months	OR(95%CI)	OR(95%CI)	OR(95%CI)	
				Hen's egg	1.10 (0.51-2.32)	0.87 (0.69-1.10)	1.05(0.81,1.35)	
				Peanut	1.11 (0.34-3.61)	0.99 (0.72-1.36)	0.87(0.65,1.16)	
				Tree nuts	1.54 (0.35-6.69)	1.16 (0.76-1.76)	1.06(0.72,1.56)	
				Soy	1.33 (0.72-2.44)	0.95 (0.75-1.19)	0.97(0.80,1.17)	
				Gluten	0.90 (0.71-1.14)	0.90 (0.76-1.06)	1.02(0.81,1.27)	
Hesselmar et al 2010 [3] Allergy Flora birth cohort Sweden Population based n/N=184/256	Food diaries maintained by the mother at the ages of 0-6 and 6-12 months	`	Adjusted for: maternal and paternal history of allergy, as well as ongoing breastfeeding at 6 months of age After controlling for reverse causation (eczema ever in the first 6 months) there was no change in results -	Introduction of different food items, in relation to a diagnosis of 'eczema at 18 months of age				Early fish introduction protective against eczema
				Food type	Median age and the IQR at which the food items were introduced Eczema			
					yes	no	P	
				Fruit	5(4,5)	5(4,5)	0.859	
				Solids†	4(4,5)	4(4,4.6)	0.971	
				Fish	11(8,13)	8(6,11)	0.004	
				Egg	13(10,13)	11(9,13)	0.070	
				†Solids- potatoes, root vegetables and meat Delayed introduction of fish for every 2 moths associated with 16% increased prevalence				

				of eczema (OR 1.16 (95% CI 1.02–1.33),			
Alm et al 2009 [14] Birth cohort Western Sweden Population based n/N=4941/8176	Food introduction by a self-administered questionnaire bi-annually 1 year	Parent reported ever eczema	Maternal eczema, sibling with eczema, bird in the home and cow's milk allergy	Introduction of solids and eczema at 1 year of age Age at introduction of fish Before 9 months	OR(95%CI) 0.76(0.62,0.94)	P value 0.009	Early introduction of fish has a protective effect on eczema
Mihrshahi et al 2007 [13] CAPS birth cohort Australia High risk n/N=516/616	Allergenic food(arbitrarily defined as cow's milk, eggs, nuts or fish) introduction By 9 months by a by interviewer administered questionnaire at one, three, six, nine and 12 months	Dr diagnosed 5 years	Intervention or control group allocation, mothers and fathers history of asthma, maternal smoking during pregnancy and the gender of the child -	Allergenic food introduction By 9 months Yes compared to no	aOR(95%CI) 0.96(0.60,1.54)		Late introduction of Allergenic solids not associated with risk of eczema

Kull et al 2006 [4] BAMSE birth cohort Sweden Population based n/N=2614/4089	Parent reported timing of fish introduction to the child at 1, 2 and 4 years	Doctor diagnosed eczema at 4 years 4 years	Adjusted for: parental allergic disease, maternal age, maternal smoking and breastfeeding. After excluding infants had eczema during the 1st year of life showed significant association with fish in diet during first 12 months and eczema at 4 years.	Association introduction of fish during the first 12 months of age and eczema at age 4 years Reported fish in diet (first 12 months) — aOR and 95%CI Never Once a month — 0.72 0.51–1.00 Two to three times a month — 0.71 0.53–0.95 Once a week — 0.54 0.41–0.70 ≥Once a week — 0.57 0.43–0.76 P trend — <0.001 After excluding children with eczema during the first year of life , the association of fish consumption ≥2–3 per month compared to ≤ 1 per month during the first 12 months associated with increased risk of eczema at 4 years aOR 0.76 (95% CI 0.60–0.98)	Fish in diet during the first year of life is associated with reduced risk of eczema
Cross sectional studies					
Horwitz et al 2009 [22] United States Children current age of 5 to 18 years and a diagnosis of eczema N=177	Solid food introduction by both medical record reviewing and parental questioning during the health care visit	Doctor diagnosed At the 5 years children were divided into 2 groups; persistent eczema and non-persistent eczema (in remission)		Type of atopic dermatitis at the age of 5 years Age at solid food introduction — Persistent (not in remission) — Non-persistent (in remission — OR(95%CI) < 6 months — 34 — 14 — ref ≥ 6 months — 40 — 15 — 1.10(0.47,2.60) Reference group – children without persistent eczema at the age of 5 years	No association between timing of solid food introduction and persistence of eczema
Case control studies					

Sahakyan et al 2006 [23] Armania N=85 cases and 155 controls	Cases: children aged 1–7 years and diagnosed with eczema by a paediatrician Controls: children aged 1-7 years who have never been diagnosed with eczema Information regarding age of first solid food introduction collected using a telephone interviews with mother of the child	UK working party's criteria 1 year	Adjusted for: birth weight, gestational age, presence of atopic diseases (eczema, asthma, wheeze, urticaria, allergic reactions to food, contact rashes, and hay fever) in the parents, surroundings of child's home and antibiotic use in the first year of life	Age of solid introduction Solid food introduction before 4 months vs after 4 months	aOR(95%CI) 3.1(1.4,6.9)	P value 0.006	Solid food introduction before 4 months increased eczema risk

Sariachvili et al 2010 [24] PIPO cohort Belgium N=252 cases and 305 controls	Cases: children with one or more episodes of parent-reported eczema during the first 4 years of life Controls: children without parent-reported eczema up to 4 years of age Parents provided information about introduction of solid foods when the child was 12 months old	Parent reported eczema using ISAAC definition Ever eczema up to 4 years	Adjusted for: child's gender, birth weight and birth order, maternal age, parental allergy and educational level, smoking in pregnancy, passive smoking up to 4 years and breastfeeding. Early introduction of solids reduced eczema significantly among children with parents with allergy	Age of solid introduction Solid food introduction before 4 months vs after 4 months	aOR(95%CI) 0.49(0.32,0.74)	Early solid introduction has a protective effect towards eczema

Synthesis of study findings

Overview of the included studies

The two randomised controlled trials of egg introduction did not find evidence that early introduction of egg was protective against eczema [25, 26] (ORs: 0.90(0.65,1.24) and, 0.84(0.57,1.23) respectively). Both studies performed the intervention on children less than one year of age. Both trials presented the results of the intention to treat analysis but only one study adjusted for baseline disparities [25]. The diagnosis of eczema in both studies was made by a clinician and the outcome was assessed during early childhood (1 year).

There were 11 birth cohort studies. Six of these investigated the association between any solid food introduction and eczema [3, 4, 12-21]. All six assessed the outcome of eczema in early childhood (below the age of six years). Except for the CAPS study (10) all were population based cohorts. Only one study found that delayed introduction of any solids increased the risk of eczema [12]. Seven birth cohort studies investigated the introduction of specific allergenic foods such as cereal, fish, eggs or fruits [3, 4, 13, 14, 16, 19, 20]. From the three studies investigating the association between only fish introduction (rather than a multi-food exposure including fish (20) and eczema, early versus late introduction of fish was found to have consistent evidence of protection [3, 14, 20]. Early fruit or cereal introduction did not show evidence of protection for eczema [3, 20].

The cross-sectional study did not show any significant association [22]. The results from the case control studies were conflicting [23, 24]. One study found solid introduction before four months increased the risk of eczema [23] while the other found a protective effect [24].

Study quality

The quality of the cohort studies was generally within the range of satisfactory (a minimum score of five) to very good (a maximum score of ten), while the cross sectional and case control studies all achieved a score of more than six (Online repository tables 1-4). The common area of weakness was how the researchers assessed the exposure and dealt with the possibility of reverse causation in terms of early signs of allergic disease in the children. Most studies did not account for reverse causation based on family history of allergy and

breastfeeding. However, even among the studies which accounted for reverse causation the evidence was inconclusive.

Studies that were not included in the meta-analyses

There were three observational studies that we could not include in the meta-analysis as risk ratios were not provided [3, 4, 20]. Details of these studies are presented in Table 2.

Hesselmar et al found that introduction of many food items including allergenic as well as non-allergenic food was delayed among children who had eczema compared to the no-eczema group [3]. Kull et al investigated the association between the timing of introduction of fish and eczema finding that later exposure to fish increased the risk of eczema at 1 year of age [4]. The other study which investigated early fish exposure and eczema observed a protective effect HR:1.73(0.75,3.99).

Studies Included in the Meta-analyses

A. Evidence based on RCTs

Introduction to egg

There were two randomised controlled trials which investigated the effect of timing of introduction of egg and the risk of eczema (pooled OR:0.87, 95%CI:0.68,1.12, I^2 0.0%) (figure 2). In one trial the prevalence of eczema among children exposed to egg from 4-8 months was not different from the placebo group (RR:0.90,95%CI:0.65,1.24) (24). The second trial also found no protective effect in the egg group compared to placebo (0.84 (0.57-1.23)) (23), however when the children with eczema were stratified by atopic status, there was some evidence for a reduction of atopic eczema in the intervention group (p=0.09).

Figure 2- Meta-analysis: The association between introduction to egg and eczema.

B. Evidence from observational studies

Introduction to first solids

Introduction to solids after seven months of age compared to early introduction (less than four months)

Pooling four birth cohort studies, we found no evidence for an association between increased risk of eczema for late introduction to solids (>7months) compared to early introduction (<3-4 months) (OR: 1.04 95%CI: 0.77, 1.41) (figure 3 I^2 =54.5%).

Figure 3- Meta-analysis: The association between introduction to solids after seven months of age and the risk of eczema.

Introduction to solids after four months of age compared to early introduction (less than four months)

Pooling 2 case-control studies and one cross-sectional study, infants who were exposed to solids after four months of age compared to before four months demonstrated no evidence of association with eczema risk (OR:1.14 95%CI:0.37,3.58) (Figure 4). The reliability of this estimate is undermined by the high heterogeneity of the pooled studies (I^2 =88.1%).

Figure 4- Meta-analysis: The association between introduction to solids after four months of age and eczema.

Introduction to solids between four to six months of age compared to early introduction (less than four months)

Meta-analysing four birth cohort studies with introduction of solids between four to six months of age showed no association with risk of eczema (OR:0.91 95%CI:0.78,1.07) when compared with those who had solids introduced before four months (online repository figure 5, I^2 = 0.0%).

Figure 5 - Meta-analysis: The association between introduction to solids between four to six months of age compared with earlier introduction and eczema.

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290 Introduction to allergenic foods (evidence from birth cohort studies)

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292 Introduction to specific allergenic solids (early versus late) and the risk of eczema
293 Pooling results from three birth cohorts (one high-risk) which had data on earlier (<9 or <6
294 months) compared to later (>6- >9 months) introduction of specific allergenic food (fish and
295 egg) showed a non-significant trend towards increased risk of eczema when allergenic food
296 was introduced later (OR:1.13 95% CI:0.91,1.42) (online repository figure 1), with an I^2 of
297 45.04%.

298 **Online repository figure 1- Meta-analysis: The association between introduction of**
299 **allergenic food and risk of eczema.**

300

301 Introduction to allergenic food (plant based) other than fish (early versus late) and the risk of
302 eczema
303 We confined the meta-analysis to age of exposure to plant based allergens and, using two
304 birth cohort studies, found no association (OR: 0.82 95%CI: 0.58,1.18) (Online repository
305 figure 2), with an I^2 of 74.2%.

306 **Online repository figure 2- Meta-analysis: The association between introduction to**
307 **plant based allergens (gluten or cereal) and the risk of eczema.**

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318 4. Discussion

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320 Overall, we found no strong evidence that early introduction of solid food was associated
321 with less risk of childhood eczema. There was limited evidence of an association for
322 introduction to specific allergenic foods. The evidence from RCTs of egg introduction was
323 limited to two trials, one of which reported failure to achieve their desired sample size
324 (pooled OR;0.87,95%CI;0.68,1.12). The observational studies (three studies) which
325 investigated the association between fish introduction and eczema suggested a protective
326 effect with early introduction. We found no evidence that early introduction of cereal or fruit
327 reduced the risk of eczema.

328 Although, our review focussed on the timing of introduction of any solid food as opposed to
329 allergenic food introduction as in the published systematic review by Ierodiakonou et al
330 [11]our results are similar to their findings, despite a different research question and the
331 inclusion of several different studies [11]. Our review addresses primarily the association
332 between first solids (both allergenic and non-allergenic) and the risk of eczema. Our findings
333 suggest that the associations are similar between timing of introduction of non-allergenic and
334 allergenic foods to infants and eczema.

335 In 2008, Prescott et al described a critical window for development of maximum immune
336 tolerance, which could have an impact on overall allergic disease outcomes of the child. It
337 has been suggested that this critical window may span from four to six months of age, but this
338 is controversial [28]. This critical window is important as introduction of solids during this
339 period and onset of eczema and persistent eczema may predict the other allergic outcomes
340 such as asthma and allergic rhinitis in later childhood [29]. With the increasing global
341 prevalence of food allergy, introduction of allergenic food to infants has recently received
342 much interest [17]. Allergenic food introduction may have an impact on the child's immune
343 system and this may be modified by other predisposing factors such as pre-existing allergic
344 disease of the child and family history of allergy [17, 18].

Part of the difficulty in assessing the relationship between solid food introduction and eczema is that there may be multiple forms of eczema or phenotypes, with common physical appearances, but different aetiological risk factors. In support of this concept, was the stronger relationship between age of introduction to egg for atopic eczema, as opposed to non-atopic eczema. Additionally there are many other factors that may be related to introduction of food that could also influence the risk of eczema [17, 25], which may be potentially confounding or modifying the associations seen. Duration of exclusive breastfeeding, duration of total breastfeeding, formula introduction and the type of formula introduced prior to solid food introduction are some of the factors which are intimately related to solid food introduction and could also have an impact on the immune system and the risk of eczema [30]. Not all the studies have commented on these factors. Other factors, such as family history of allergic disease and cultural beliefs are important, as these could have an impact on the feeding behaviour of the parents and influence risk of allergic disease in the child [31]. Moreover, early symptoms of allergic disorders during infancy may influence the timing of solid food introduction [32] as there is a belief in some communities that extended duration of exclusive breastfeeding (thus delaying the introduction of solid foods) is protective against childhood allergic disorders. As this belief may influence allergic families to delay solid introduction, it could lead to an association through reverse causation. Failure to account for this reverse causation will bias the association between later solid introduction and eczema. Therefore, the methodological quality of the studies in assessment of potentially confounding and modifying factors and reverse causality will be important in interpreting the study findings. Among the studies included in this review, only a few have looked at reverse causation with respect to duration of breastfeeding and allergic diseases (family history and childhood allergies) [12, 15, 17, 18] and these studies did not find evidence for reverse causation. All these factors have contributed to a significant amount of heterogeneity. Furthermore, we could not comment about the quantity of food introduced or any allergic reaction which occurred following food introduction as these data were not available.

We have limited evidence to comment on early life egg exposure and the risk of eczema. There was weak evidence from one RCT that early introduction of egg may reduce the risk of atopic eczema [25].Two studies [14, 20] based in Scandinavian countries identified that earlier introduction of fish might be associated with reduced risk of eczema. Unfortunately, we do not have adequate details on the type of fish and the quantity introduced. Therefore, we

are unable to comment in terms of n-3 fatty acids which have been postulated to reduce the risk of allergic disease. It is possible that n-3 fatty acids, which are rich in some fish, might cause such an effect. Despite the biologic plausibility that n-3 fatty acids may modulate the immune response, there is currently no consistent evidence that n3-fatty acids reduce the risk of allergic disease. A number of observational studies have investigated breast milk PUFA (poly unsaturated fatty acids) and their association with eczema in infants, but findings have not been consistent. Some studies showed a protective effect [33] associated with increased n-3 fatty acid levels in breast milk while others did not [34].

In terms of "best evidence", if you had to choose between one RCT or a meta-analysis of birth cohort studies, the guidelines pertaining to hierarchy of evidence would suggest that the RCT carries more weight. Evaluation of this conundrum is not always straightforward. It would depend upon objective measures of the individual studies contributing evidence, including size, quality, and risk of bias. The RCT involved may be small., non-representative of the target population and have extensive loss to follow-up introducing bias and lack of external validity, whereas the birth cohort studies may be relatively free from bias except from unknown confounders. The conclusion of this paper was based on evidence from both RCTs and birth cohort studies. An overall assessment of the "quality of evidence" for any meta-analysis could be estimated in a more objective manner using the GRADE criteria; [35]however it is difficult to know how you would then compare this to the quality of evidence contributed by one RCT.

Based on this review we do not have adequate statistical evidence to say that solid food introduction at four months is better compared to introduction at 6 months or whether the timing of allergenic food introduction protects against development of eczema. Also, there is no consistency of results among the studies suggesting an unaccounted source of heterogeneity between the studies/study populations. As eczema is a disease which is closely related to other allergic diseases there might be a strong genetic component[36] which could mask the true association with solid food introduction.

Strengths and limitations of this review-

This review contains all available peer reviewed papers up to the final search date on food introduction and its association with eczema. Mostly, the evidence in this paper comes from birth cohort studies which are the strongest observational study design in which to assess potential causation as these studies use prospectively collected data and are therefore not

affected by recall bias. Although different outcome definitions were used by the included studies, all of them were standard definitions developed by the researcher or clinicians. Creating different forest plots according to different age exposure categories has enabled us to get an overview of the available studies on timing of solid food introduction and allergic disease outcomes. All the studies in the review are of reasonably good quality according to the Newcastle Ottawa scale. The disadvantage of different definitions was that we could not combine the outcome of atopic eczema with the other outcomes. Furthermore, multifaceted intervention studies were not included in the review as there were multiple exposures. Not all studies adjusted for important confounding factors, such as family history of allergic disease, gender, and allergic disease of the child or looked for reverse causation. Also, we were unable to comment on the quantity of the food introduced to the child or any adverse reactions to that food. Furthermore, we have not included studies which investigated infant foods and exacerbations of existing eczema. The majority of the evidence we found was based on observational studies. Therefore, we are unable to comment on inherent biases and unknown confounding factors which may have influenced outcomes. While the evidence from well-conducted randomised controlled trials is robust, there is currently limited evidence.

Future directions based on our findings-

The available evidence is currently insufficient to determine whether the timing of solid food introduction influences the risk of eczema. Our review indicates that findings from RCTs and well-conducted observational studies are similar. Large observational cohorts can complement the evidence from RCTs as they are more likely to be representative of the target population for a universal population exposure such as introduction of solids. Future directions for individual studies may include better characterization of exposures in terms of quantities, better characterization of outcomes in terms of phenotyping eczema, and a way to measure the cultural and familial reasons for the individual differences in timing of solid food introduction.

Conclusion

The available evidence is inconclusive regarding the association between timing of any solid food introduction and the risk of eczema. There is currently no clear evidence to determine

whether weaning at 4 months, between 4-6 months or after 6 months of age is better in terms of eczema risk. There is no impetus to alter current guidelines. All of which support the introduction of complementary food around or at six months of age with a spectrum of food items and the introduction of allergenic foods by one year with the aim of prevention of allergic diseases.

Conflict of interest

None

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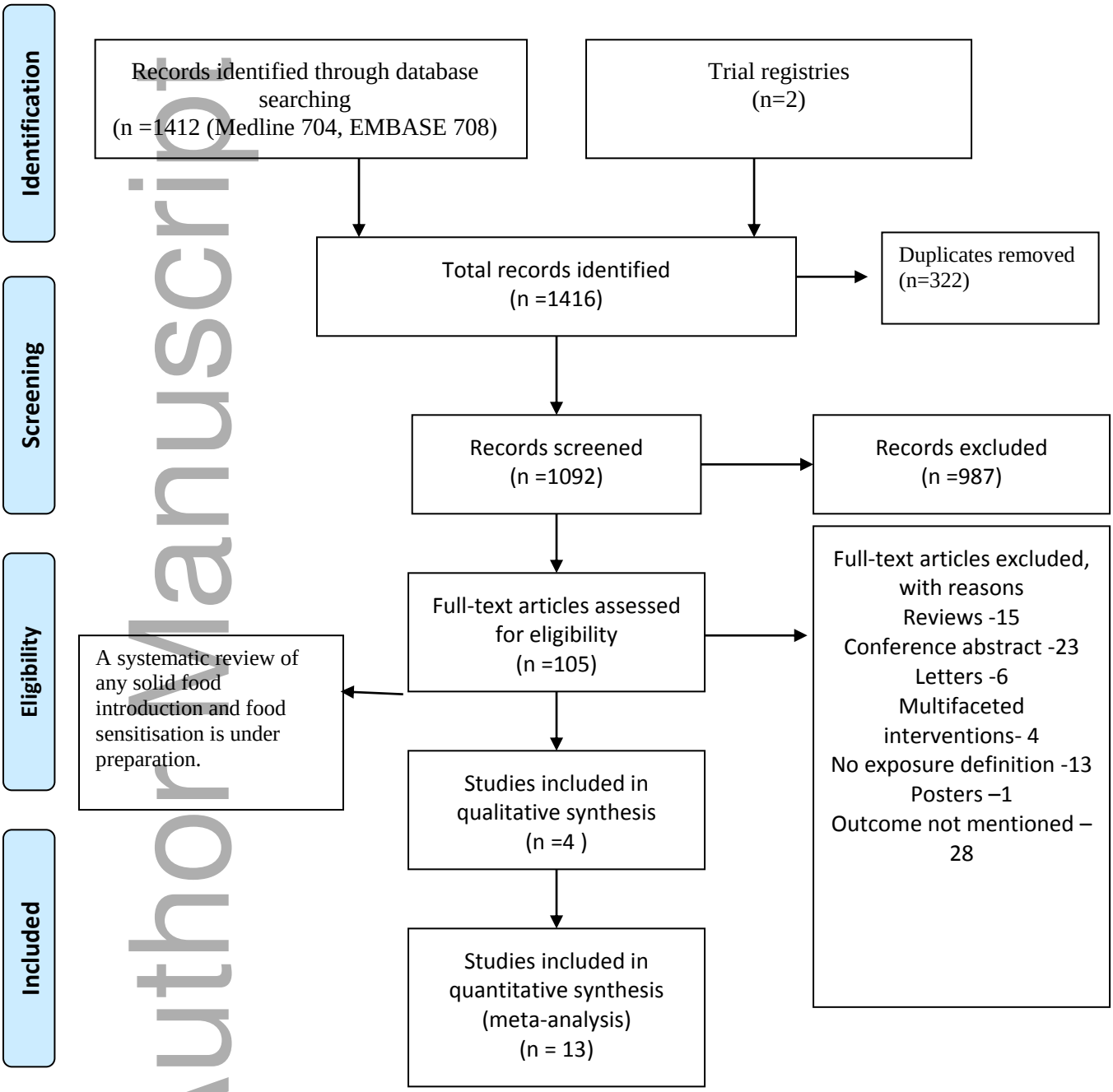


Figure 2- Meta-analysis: The association between introduction to eggs and eczema.

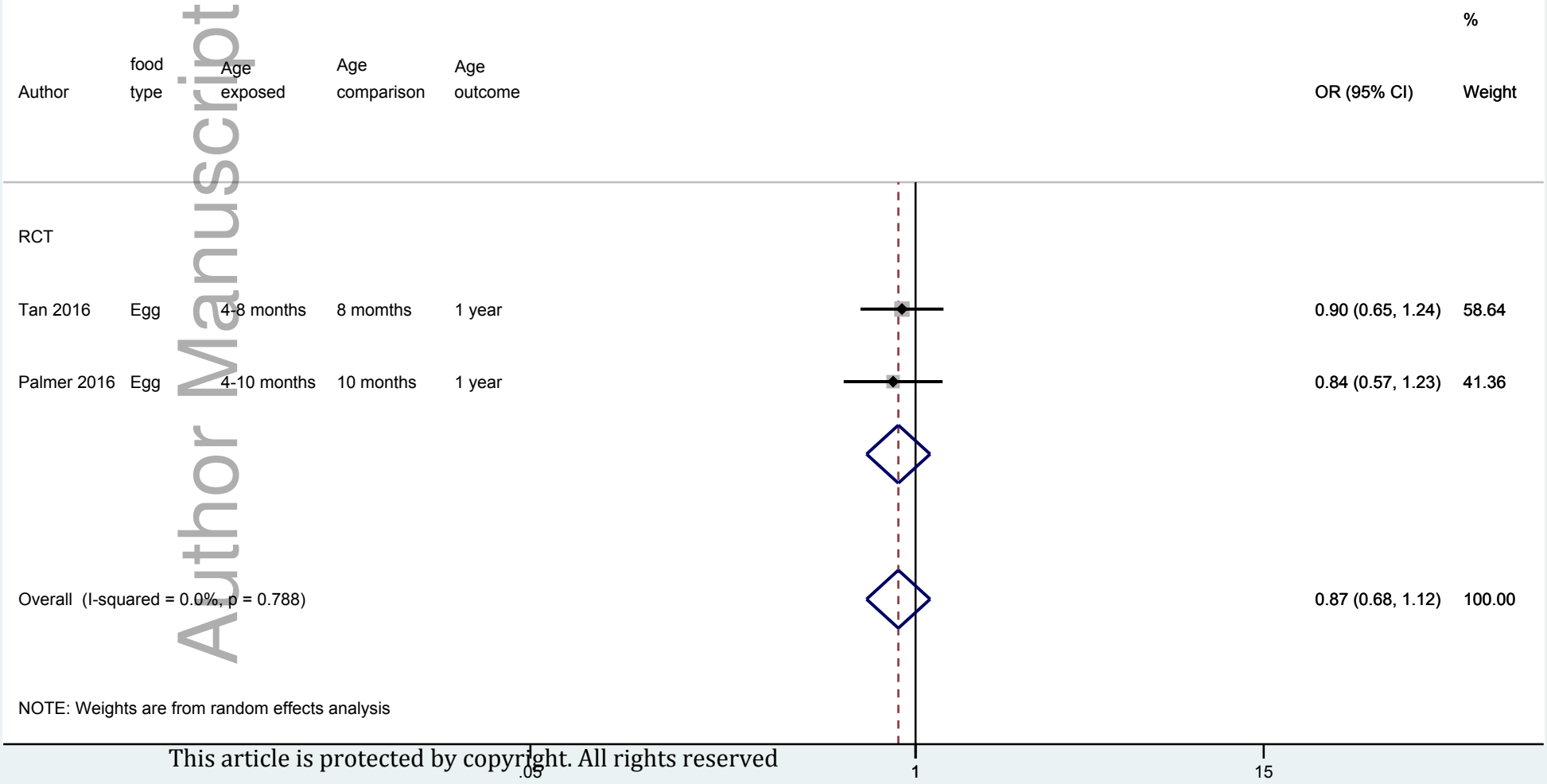


Figure 3-Meta-analysis: The association between introduction of solids after seven months of age and eczema

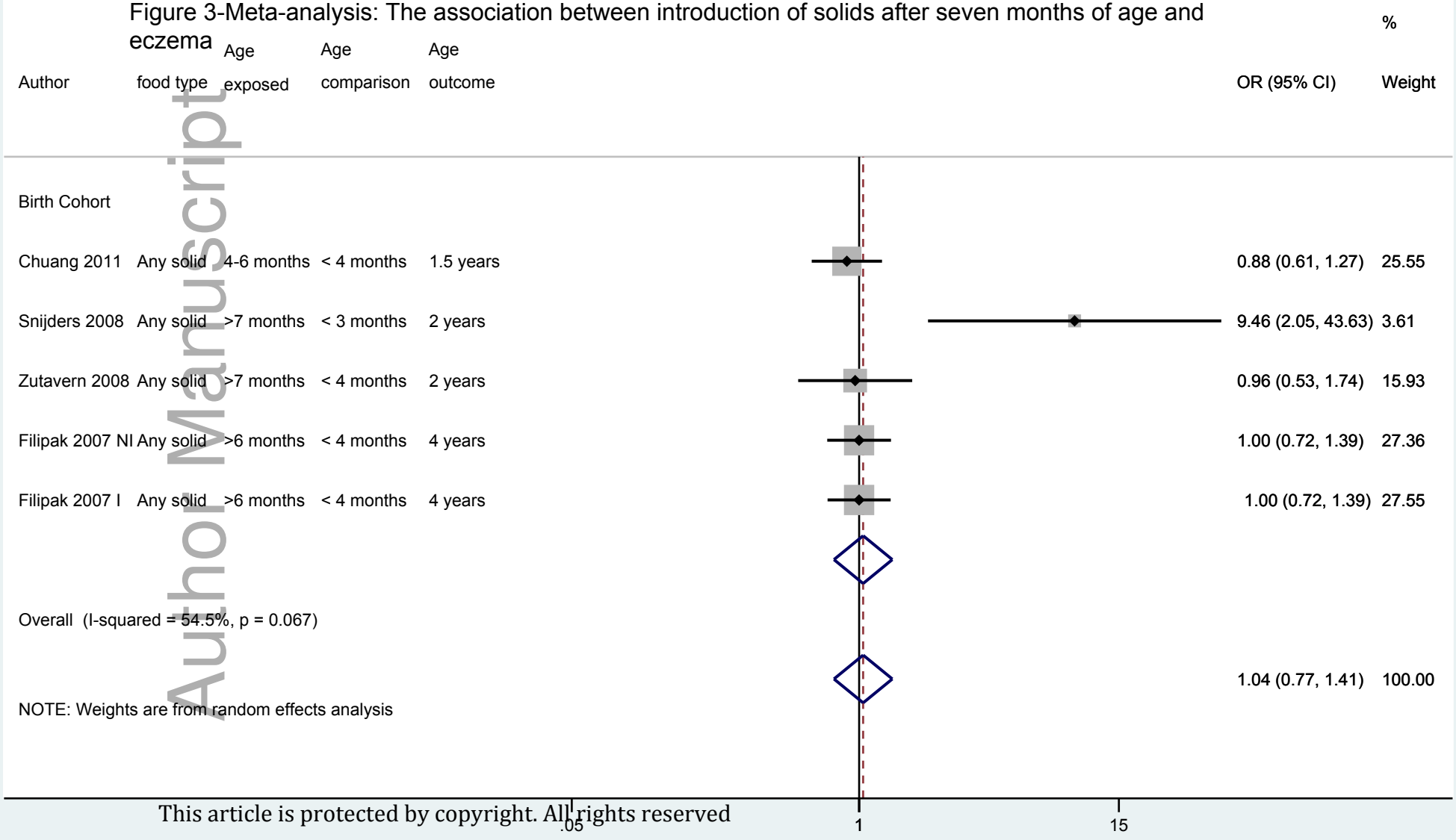


Figure 4- Meta-analysis: The association between introduction of solids after five months of age and eczema

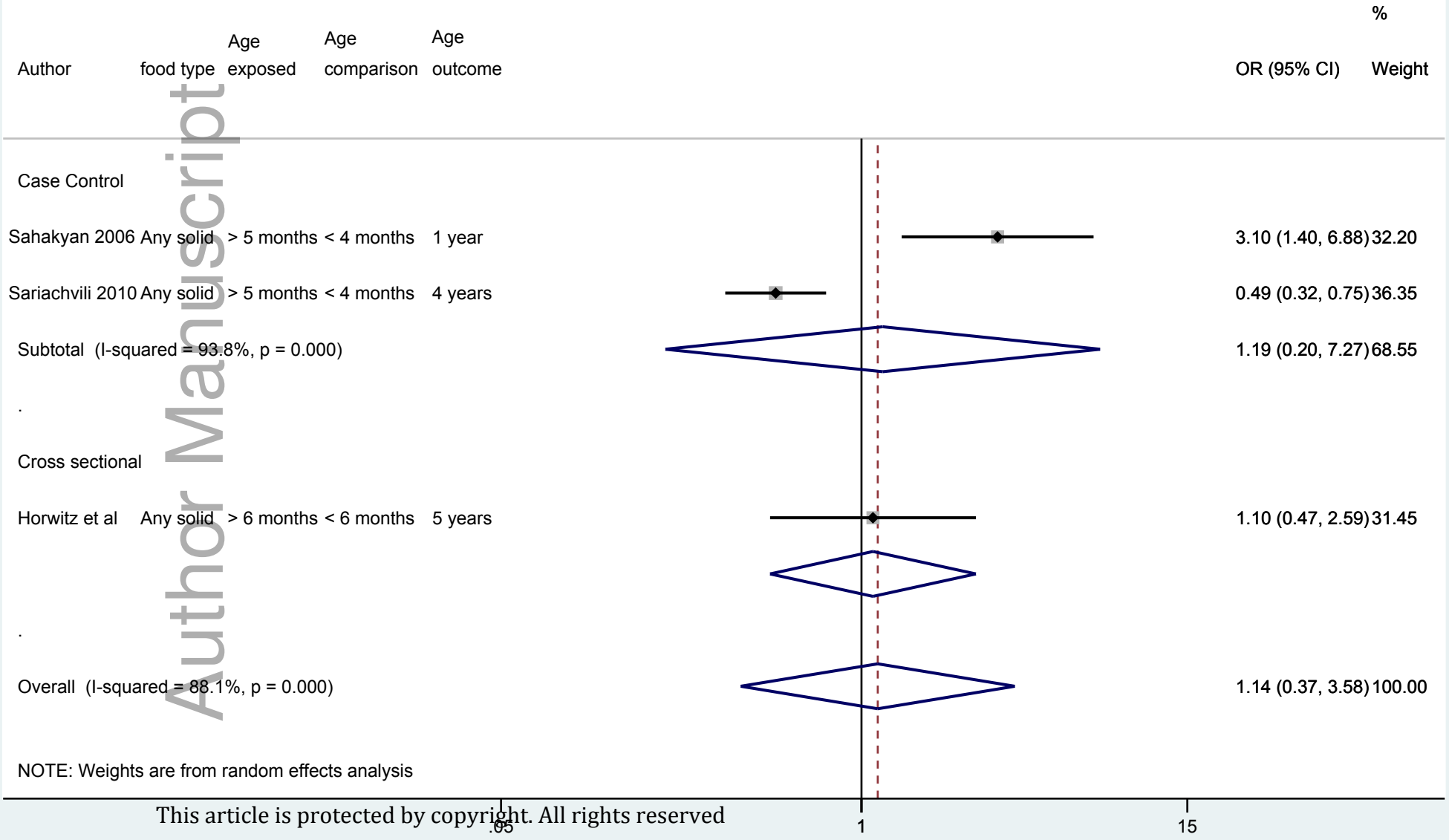
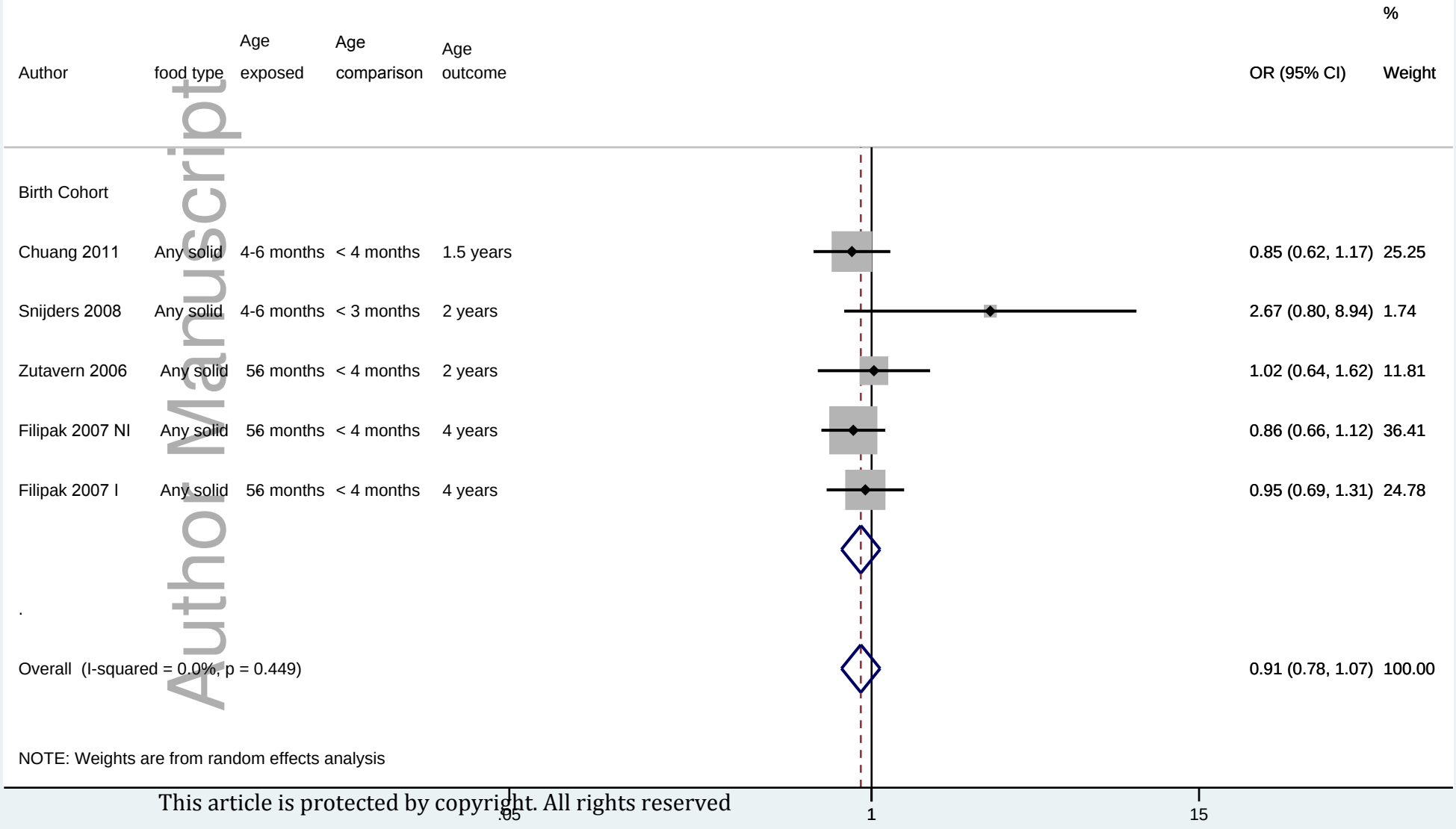


Figure 5- Meta-analysis: The association between introduction of solids between 4-6 of age and eczema



NI-non intervention group I-Intervention group