



Timing of Cow's Milk or Cow's Milk Formula Introduction to the Infant Diet and Atopic Risk in Children: a Systematic Review and Meta-analysis

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Abstract

Infant feeding is an important early-life exposure that may influence the development of atopic disease. The optimal timing of introduction of food allergens, including cow's milk (CM), is not known. This study aims to systematically review the evidence describing the effects of timing of CM or cow's milk formula (CMF) introduction to the infant diet on the development of atopic diseases during childhood. Pubmed, Embase, CINAHL, Cochrane CENTRAL, and CNKI were searched through May 30, 2019. Study screening and data extraction by two reviewers followed the PRISMA statement. Data were extracted independently in duplicate, and meta-analyses were performed by pooling unadjusted and adjusted odds ratio (OR) separately. Heterogeneity was explored using I^2 and publication bias by funnel plots and Begg's tests. In total, 45 studies from 20 countries were included. Meta-analyses using adjusted data showed that no associations were observed between early introduction of CM or CMF and the risk of asthma (< 4 vs. $\geq$ 4 months: OR 1.16, 95% confidence interval (CI) 0.89, 1.51), wheeze (< 6 vs. $\geq$ 6 months: OR 1.15, 95% CI 0.85, 1.56), and eczema or atopic dermatitis (< 6 vs. $\geq$ 6 months: OR 0.96, 95% CI 0.65, 1.41). Overall, quite little high-quality evidence was identified to allow for definitive conclusions on the association between early CM or CMF introduction and risk of allergic diseases. Our meta-analysis on this topic highlights the specific gaps in information for public recommendations regarding CM or CMF feeding practice in an early stage of life, particularly before 3 months of age.

Keywords Timing of introduction · Cow's milk · Infant formula · Allergy · Systematic review · Meta-analysis

Introduction

The prevalence of childhood atopic disease has been increasing considerably in the worldwide last few years [1]. Infant

feeding is a crucial early-life exposure that may influence the development of atopic disease [2]. It is universally acknowledged that breast milk is the preferred nutrition source for the growth of infants, containing essential nutrients (such as fat, carbohydrates, proteins, vitamins, and minerals) and multiple bioactive constituents (such as secretory IgA and IgG) [3–5]. Early exposure to human milk is conducive to the development of host defense mechanisms and stimulates infant immune systems [6]. The World Health Organization (WHO) recommended that “infants should be fed exclusively on breast milk from birth to 6 months of age” [7]. However, many infants receive cow's milk (CM) in the form of infant formula very early in life [8–17].

With the rapid development of economy and urbanization, the rate of commercial infant formula consumption has dramatically increased [18]. Most infant formulas are derived from cow's milk, which contains powerful food allergens. Although several studies assessing the role of infant formulas in the risk of atopic disease development have been performed to date, the findings were controversial [2, 8–13, 19–21]. Previous systematic reviews describing the association

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between exposure to CM or cow's milk formula (CMF) and childhood allergy had been published but are limited in scope [2, 19, 20, 22]. Early introduction of food allergens, such as peanut, to the infant diet has been recommended in food allergy prevention guidelines [23, 24]. However, the optimal timing of other different allergens introduction, including cow's milk, is not known. Current evidence and theoretical concerns that exposure to food proteins during a critical early window, likely to be 4–6 months of life, could benefit the development of immune tolerance [25], whereas too early exposure to the allergen may give rise to a higher risk of allergic or autoimmune diseases due to immature gut colonization and local immune networks [26]. The effects of CM or CMF on childhood allergy may vary by the period of exposure.

Thus, the present review aims to systematically summarize the effects of timing of CM or CMF introduction to the infant diet on the risk of developing atopic diseases including wheeze, asthma, eczema or atopic dermatitis, rhinitis or conjunctivitis, food allergy, and cow milk allergy.

Methods

We reported this systematic review following the PRISMA statement [27] (Online Resource 1). The protocol of this systematic review was registered within the International Prospective Register of Systematic Reviews (PROSPERO) (registration ID: CRD42018102108). The search results were updated in May 2019.

Search Strategy

We searched Pubmed, Embase (via OVID) (1974 to present), CINAHL (1937 to present), Cochrane CENTRAL (1992 to present), and CNKI (China National Knowledge Infrastructure) electronic databases through May 30, 2019. Reference lists from included studies were scanned to identify other relevant studies. Gray literature sources OpenGrey, Zetoc, Conference Proceeding Citation Index (CPCI), and Science Citation Index (SCI) were also searched. There was no language restriction. The MeSH (medical subject headings) terms and free-text keywords for relevant exposures or interventions (cow's milk, milk products, infant formula, breastfeeding, breast milk) and outcomes (atopic diseases, wheeze, eczema, atopic dermatitis, asthma, rhinitis, conjunctivitis, food allergy, and cow milk allergy) were searched (Online Resource 2).

Study Selection

Randomized controlled trials (RCT), prospective cohort or longitudinal studies, retrospective cohort studies, nested

case-control studies, or other case-control studies were included where the timing of the introduction of CM or CMF before 1 year of age is clearly described. If the authors did not specify the types of formula given to the infant, we considered the formula to be CMF. We excluded studies comparing CMF with hydrolyzed formula, soy formula, or milk from other animals. The studies focussing on infants experiencing specific diseases or conditions at baseline, such as preterm birth and low birth weight, were also excluded. The primary outcomes were allergic diseases, including asthma, wheeze, eczema/atopic dermatitis, allergic rhinitis/conjunctivitis, food allergy, and cow's milk allergy (CMA). We included studies published as full-text publications rather than only abstracts. Two researchers (M.Y. and M.T.) independently screened titles and abstracts of the relevant studies and selected the full-text articles for eligibility. Any disagreement during the screening process was discussed and re-examined. A third person (S.S.) was consulted when no consensus was reached.

Quality Assessment

We used the Cochrane Collaboration's Risk of Bias Tool [7] to access the risk bias for RCT studies (Online Resource 3) and the Newcastle-Ottawa quality assessment scale [28] for cohort studies (Online Resource 3) and case-control studies (Online Resource 3). The quality of all full-text reports was accessed independently by two reviewers (M.Y. and M.T.), and any disagreements were resolved by a third reviewer (S.S.).

We classified each RCT study into one of the following categories: low risk of bias (low risk of bias for all key domains); unclear (1 or more items assessed as unclear); high risk of bias (1 or more items assessed as high risk) [29]. We classified each cohort study or case-control study into high quality with a Newcastle-Ottawa scale score ≥ 7 and low quality with a score < 7 , because standard validated criteria for cutting points of different quality level have not been established. According to the method used in a previous systematic review, we set the critical endpoints based on the mean values, 6.5 scores, for the cohort studies [30].

Data Extraction

Data were extracted in duplicate and summarized in an excel spread sheet. For RCT studies, the extracted information included study ID, location, interventions, controls, follow-up time, sample size, outcomes, age at outcomes, measurements, and response rate (Table 1). For cohort studies, the extracted information included study ID, study design (prospective or retrospective cohort), location, cohorts' name, allergic disease risk, exposures (CM or CMF), timing of CM or CMF introduction, sample size, outcomes, age at outcomes, measurements, and follow-up rate (Table 2). For the case-control study, the extracted information included study ID, location,

Table 1 Characteristics of included randomized control trials

Study ID	Location	Intervention	Exposure time	Sample size	Outcomes	Age at outcome	Measures of outcomes	Follow-up rate	Quality
Juvonen 1996	Sweden	Human milk (HM), cow's milk formula (CMF) during the first 3 days of life	First 3 days	CMF: 39 HM: 53	Eczema	< 3 years	Unclear	CMF: 88.6- % HM: 91.4- %	High risk
Lindfors 1988	Sweden	Infants were randomized to receive either early feeding with formula before normal breastfeeding was started or "normal feeding" with breast milk	Early feeding before normal breastfeeding was started	CMF:109 HM:98	Wheeze/eczema	18 months	Examined by pediatricians	CMF: 97.3- % HM: 94.2- %	High risk
Lindfors 1992	Sweden	One group received cow milk formula during the first days of life before the mother's breast milk production started and was then breastfed; the other was not given any formula before normal breastfeeding started.	Early feeding before normal breastfeeding was started	CMF: 95 HM:88	Asthma/Rhino-conj FA/CMA	4–6 years	Examined by pediatricians SPT	CMF: 84.8- % HM: 84.6- %	High risk
Saarinen 1999 Saarinen 2000	Finland	The infants who required supplementary milk at the hospital because of insufficient secretion of breast milk were randomly assigned to one of 3 study groups according to the supplement given: liquid CM formula; pasteurized human milk	First few days at Maternity Hospital	CMF:1758 HM: 1844	CMA	2.8–12.7 months	A challenge test with cow's milk at the hospital	CMF: 98.3- % HM: 99.2- %	High risk

CM, cow's milk; CMA, cow's milk allergy; CMF, cow's milk formula; DBPCFC, double-blind, placebo-controlled food challenge; FA, food allergy; RCT, randomized controlled trial; Rhino-conj, rhinitis+conjunctivitis; SPT, skin prick test

sample size, definitions of the case, feeding CM or CMF, the timing of introduction, age at outcomes, and methods of case ascertainment (Table 3). Original data for each outcome at different timing of introduction extracted from the included studies were shown in tables in the supplementary file (Online Resource 3).

Data Analysis and Synthesis

For the observational studies, the timing of CM or CMF introduction varied. Therefore, we used the following categories for the timing of introduction to enable the combination of multiple studies: < 1 vs. ≥ 1 or < 3 vs. ≥ 3 or < 4 vs. ≥ 4 or < 6 vs. ≥ 6 months duration. The event data were extracted from the included study. If we cannot get event data from the study, unadjusted odds ratio (OR) was used for meta-analysis. We

also extracted adjusted OR and included those in the meta-analysis. If a study reported zero events in a group, it was not included in the meta-analysis. When studies had several time points for examining outcomes, the most complete dataset or the largest observational case number was selected. When studies used multiple methods to assess the same outcome, clinical assessments or validated instruments were preferred. For example, we prioritized skin prick test or double-blind, placebo-controlled food challenge for diagnosis of CMA over the parental report.

The included studies were grouped by different outcomes being assessed within each time point comparison. The data are reported using OR with 95% confidence intervals (CI). Meta-analyses were undertaken using Review Manager (RevMan) (Version 5.3). Heterogeneity of the included studies was tested using a chi-squared test ($p < 0.1$ to determine

Table 2 Characteristics of included 37 cohort studies

Study ID	Design	Location	Cohort name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
Batool 2016	PC	Canada	FAMILY	Normal	CM or CMF	Yes	< 6 m, $\geq$ 6 m	818	FA	1 y	Parental report	99.2%	6
Cogswell 1987	PC	UK		High-risk	CM or CMF	Yes	< 4 weeks, 4–13 weeks, $\geq$ 14 weeks	73	Eczema	1 y	Diagnosed by the pediatrician	73.0%	6
Azad 2017	PC	Canada	CHILD	Normal	CMF	No	< 3 m, $\geq$ 3 m	2773	Wheeze	1 y	ISAACQ	84.0%	8
Elbert 2017	PC	Netherlands	Generation R	Normal	CM or CMF	Yes	< 6 m, $\geq$ 6 m	5202	FA/eczema	Before 10 y	Eczema: parental report of physician diagnosis of eczema Food allergy: parental report	71.0%	8
Filipiak-Pittroff 2018	Secondary analysis of RCT	Germany	GINI-plus Birth Cohort	High risk	CMF	No	< 4 m, $\geq$ 4 m	2252	Asthma/eczema/allergic rhinitis	3–15 y 1–15 y 4–15 y	Parental report	90.5%	4
Fergusson 1990	PC	New Zealand		Normal	CM or CMF	Yes	< 4 m, $\geq$ 4 m	1210	Eczema	10 y	Mother's diary records or maternal recall or family doctor	95.7%	6
Gustafsson 1992	PC	Sweden		Normal	CMF	Yes	First 8 days	736	Asthma/Rhino-conj/eczema	7 y	Hospital records Physician's findings	97.6%	7
Host 1991	PC	Denmark		Normal	CMF	Yes	0 m, < 1 m, 1–3 m, $\geq$ 4 m	1749	CMA	1 y	SPT and AL-RAST	100.0%	7
Ito 2014	PC	Japan		Normal	CMF	Yes	0 m, < 6 m, $\geq$ 6 m	38,757	AD	6 to 42 m	Parental report of physician diagnosis	82.4%	7
Katz 2010	PC	Israel		Normal	CMF	Yes	< 1 m, $\geq$ 1 m	11,633	CMA	3–5 y	Blood test	98.4%	7
Kemeny 1991	PC	UK		Normal	CM	Yes	0 m, < 3 m, $\geq$ 3 m	189	Wheeze/eczema/CMA	< 1 y	Wheeze/eczema: examined by physician; CMA: SPT	94.2%	6
Kiltingberg 2019	PC	Sweden	ABIS	Normal	CMF	No	< 2.5 weeks $\geq$ 2.5 to < 14 weeks Never	9727	Asthma	0–15 y	National Patient Register	60.7%	8
Klopp 2017	PC	Canada	CHILD	Normal	CMF	Yes	0 m, < 3 m, $\geq$ 3 m	2534	Asthma	3 y	History report and physical examination	76.9%	8
Kumar 2010	RC	USA		Normal	CMF	Yes	< 6 m, $\geq$ 6 m	789	FA Eczema	0–21 y 0–21 y	Blood test or SPT Parental report of physician diagnosis	7 6	7
Lossius 2018	PC	Norway	MoBa	Normal	CMF	Yes	< 4 m, 4–5.9 m, $\geq$ 6	31,930	Asthma	7 y	Based on dispensed prescriptions	40.3%	7
Luccioli 2014	PC	USA	Y6FU	Normal	CM or CMF	Yes	4 m, 4–5 m, 6–12 m	All: 1258 High-risk: 752	FA	6 y	Parental report of physician diagnosis	81.6%	7
Marini 1996	PC	Italy		High-risk High-risk Normal	CMF CMF CMF	Yes	0 m, < 4 m, $\geq$ 4 m 0 m, < 4 m, $\geq$ 4 m 0 m, < 4 m, $\geq$ 4 m	221 62	Wheeze/AD/Rhino-conj	< 3 y	Physician-diagnosed	78.8%	5

Table 2 (continued)

Study ID	Design	Location	Cohort name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
Moore 1985	PC	UK		High risk	CM	Yes	< 6 m, $\geq$ 6 m 1–4 weeks (0 week), 5–8 weeks, 9–12 weeks, > 12 weeks	62 475	Eczema	3 m	Medical history and clinical examination	90.5%	6
Nwaru 2010	PC	Finland	DIPP	High risk	CM or CMF	Yes	< 0.92 m, 0.92–4 m, > 4 m	994	FA	5 y	Blood test	93.2%	6
Nwaru 2013a	PC	Finland	DIPP	Normal	CM or CMF	Yes	Cow's milk	3781	Asthma/eczema/allergic rhinitis	5 y	ISAACQ	82.0%	6
Nwaru 2013b	PC	UK	SEATON	Normal	CM	Yes	< 5.75 m, $\geq$ 5.75 m	934	Wheeze/asthma/eczema	Up to 10 y	ISAACQ	49.0%	8
Perters 2019	PC	Australia	HealthNuts	Normal	CMF	Yes	< 0.5 m, $\geq$ 0.5 m < 3 m, $\geq$ 3 m	2183	CMA	1 y	Parent-reported reaction to milk and IgE-mediated allergy and SPT.	41.4%	5
Poyss 1989	PC	Finland		High risk	CMF	Yes	< 3 m, 3–6 m, > 6 m	70	Eczema	5 y	Parental report	70.0%	5
Roduit 2012	PC	Austria, Finland, France, Germany, Switzerland	PASTURE	Normal	CM	Unknown	3–12 m, > 12 m	912	AD	Up to 4 y	Parental report/SCORAD scores	80.5%	8
Ruiz 1992	PC	UK		High risk	CMF	Yes	< 4 m, $\geq$ 4 m	39	AD	< 1 y	Hanifin and Rajka criteria	100.0%	5
Saarin 1979	PC	Finland		Normal	CMF	Yes	< 2 m, 2–6 m, > 6 m	All: 236 High risk: 101	FA AD	< 1 y	One of author recorded signs and symptoms of atopy	92.2%	5
Simon 2008	PC	USA		Normal	CMF	Yes	0 m, < 4 m, $\geq$ 4 m	303	Wheeze	< 4 y	Parental report	44.6%	5
Snijders 2008	PC	Netherlands	KOALA	Normal	CM or CMF	Yes	0–3 m, 4–6 m, 7–9 m, > 9 m	1894	Wheeze/eczema AD CMA	2 y 2 y	Parental report United Kingdom Working Party Criteria	90.3%	7
Soto-Ramirez 2017	PC	USA	IFPS II and Y6FU	Normal	CMF	Yes	0 m, < 1 m, 1–3 m, > 3 m	1379	Eczema	6 y	Blood test Parental report of physician diagnosis	89.9%	7
Strassburger 2010	PC	Brazil		Normal	CM	Yes	< 4 m, $\geq$ 4 m	293	Wheeze/asthma	3–4 y	Parental report	73.8%	8
Tariq 1998	PC	UK		Normal	CMF	Yes	< 3 m, $\geq$ 3 m	1086	Asthma	4 y	The presence of typical diurnal variation and the response to bronchodilator medication.	74.6%	7
Tham 2018	PC	Singapore	GUSTO	Normal	CM or CMF	Yes	< 10 m, $\geq$ 10 m	870	CMA	2 y	SPT	75.5%	8

Table 2 (continued)

Study ID	Design	Location	Cohort name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of timing of CMF or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
Tran 2017	PC	Canada	CHILD	Normal	CM or CMF	Yes	≤ 6 m, 7–12 m, < 12	2124	CMA	1 y	SPT	60.8%	7
Tromp 2011	PC	Netherlands	Generation R	Normal	CM or CMF	Yes	< 6 m, ≥ 6 m	6905	Wheeze/eczema	4 y	ISAACQ	87.5%	8
Van Asperen 1984	PC	Australia		High risk	CM	Yes	< 4 m, ≥ 4 m	79	Wheeze/rhinitis AD	20 m	Parental report	85.9%	4
Wright 1994	PC	USA		Normal	CMF	Yes	< 6 m, ≥ 6 m	747	Allergic rhinitis	20 m	By examination	60.0%	5
Zutavern 2004	PC	UK		Normal	CM	Yes	< 6 m, ≥ 6 m	620	Wheeze/eczema	< 6 y 5.5 y	Physician diagnosis Parental report	96.6%	7

Name of cohort studies: *ABIS*, All Babies In Southeast Sweden; *CHILD*, Canadian Healthy Infant Longitudinal Development; *DIPP*, Finnish Type 1 Diabetes Prediction and Prevention; *FAMILY*, Family Atherosclerosis Monitoring In early life; *GINI*, German Infant Nutritional Intervention; *GUSTO*, Growing Up in Singapore Towards healthy Outcomes; *IFPS II*, Infant Feeding Practices Study II; *KOALA*, Child, Parent and health: lifestyle and genetic constitution (in Dutch); *MoBa*, The Norwegian Mother and Child Cohort Study; *PASTURE*, Protection Against Allergy—Study in Rural Environments; *SEATON*, Study of Eczema and Asthma To Observe the influence of Nutrition; *YoFU*, Year-6-Follow-Up Study

AD, atopic dermatitis; CM, cow's milk; CMA, cow's milk allergy; CMF, cow's milk formula; FA, food allergy; ISAACQ, international study of asthma and allergies in children questionnaire; PC, prospective study; RC, retrospective study; m, month; y, year; *Rhino-conj*, rhinitis and/or conjunctivitis; SPT, skin prick test

statistical significance) and I^2 statistic. Meta-analysis was performed when at least two studies were included in the analysis. When the number of studies in a meta-analysis was over 10, we used funnel plots and Begg's test to assess for the potential for the presence of publication bias.

We used sensitivity analyses to assess the findings restricted to high-quality studies. Additionally, we conducted subgroup analyses by including only children at high risk (family history of allergy in at least one first degree relative) of allergic diseases and excluding children who were exclusive formula fed.

Results

The searches identified 11,648 unique records, of which 463 articles were deemed potentially relevant to the review and obtained for assessment against the selection criteria (Fig. 1). Four RCT studies (Table 1), 37 cohort studies (Table 2), and four case-control studies (Table 3) from 20 countries met the inclusion criteria. Tables 1, 2, and 3 show the summary of the characteristics of the included studies.

All RCT studies were assessed as high risk of bias. Methodological quality was low in 16 (43.2%) of 37 cohort studies. In case-control studies, two of four studies were low quality (Online Resource 3).

The key results of the meta-analyses are shown in Figs. 2, 3, 4, and 5. The results of meta-analyses of cohort studies were grouped by different outcomes being assessed within each time point comparison (< 1 vs. ≥ 1 or < 3 vs. ≥ 3 or < 4 vs. ≥ 4 or < 6 vs. ≥ 6 months). There was a study only providing ORs in figures without numerical value [31]. Then, we sent an email to the authors for obtaining additional information about the data, but no response. No data of case-control studies were pooled into meta-analyses due to the different outcomes in these studies (Online Resource 3). Forest plots of the effect sizes for individual studies included in the meta-analyses were shown in Online Resource 4.

Asthma

Two RCT studies with 275 participants and five cohort studies with 48,994 participants reported asthma. Both of the two RCT studies used CMF as the intervention. Results of pooled RCT studies showed that compared with breast milk feeding, there was no association between exposure to CMF in the first few days of life and risk of asthma (unadjusted OR 0.78; 95% CI 0.21, 2.86; $I^2 = 17\%$) (Fig. 2) [32, 33]. Likewise, one cohort study not included in the meta-analyses showed that giving CMF to healthy breastfed term infants on maternity wards does not increase the risk of developing asthma (unadjusted OR 1.48; 95% CI 0.5, 4.6) [34]. However, results of pooled cohort studies showed that earlier CM or CMF introduction to

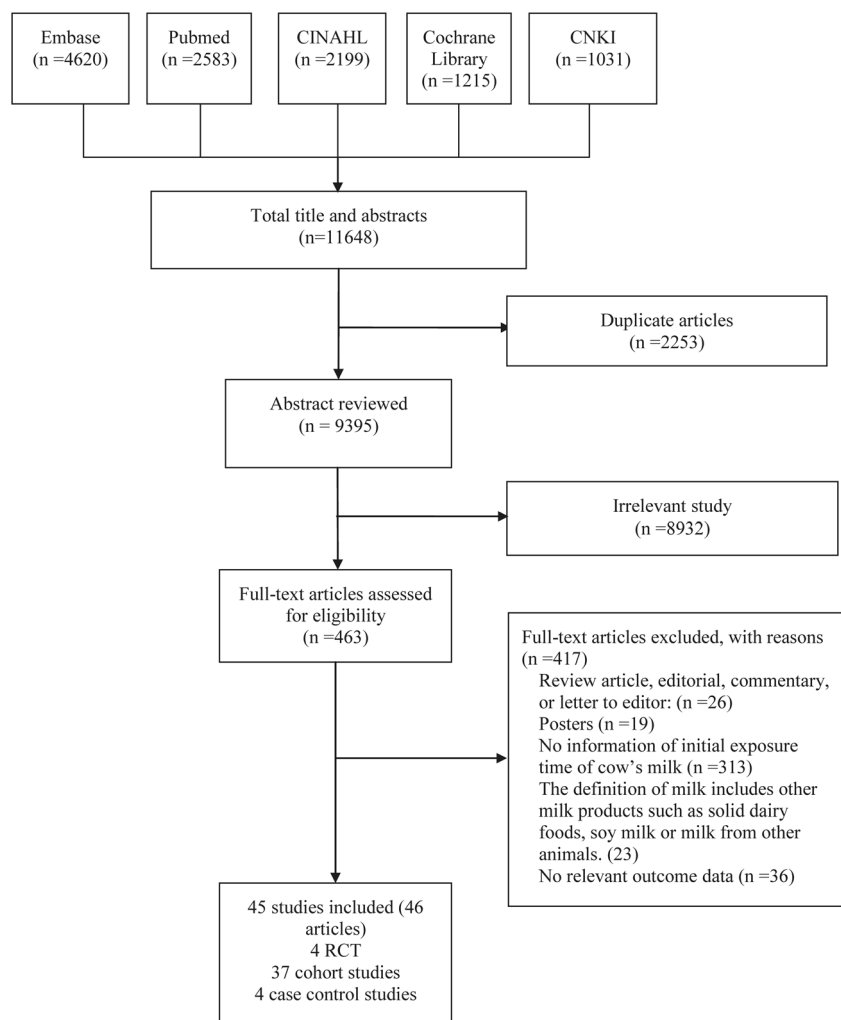
Table 3 Characteristics of included 4 case-control studies

Study ID	Location	Sample size	Case	Feeding CM/CMF	Timing of introduction	Age of diagnosis	Methods of case ascertainment	Quality scores
Grimshaw 2013	UK	Case:41 Control:82	FA	CM	22 weeks vs. 26 weeks (mean age in each group)	2 years	DBPCFC	7
Onizawa 2016	Japan	Case:51 Control:102	CMA	CMF	≤ 1 months	2–8 years	Blood test	6
Sariachvili 2010	Belgium	Case: 252 Control: 305	Eczema	CMF	< 4 months	< 4 years	ISAACQ	7
Turati 2016	Italy	Case: 329 Control: 329	AD	CM	At 1 month vs. > 5 months At 2 months vs. > 5 months At 3 months vs. > 5 months At 4 months vs. > 5 months At 5 months vs. > 5 months	3–24 months	Diagnosed by dermatologist	7

AD, atopic dermatitis; CM, cow's milk; CMA, cow's milk allergy; CMF, cow's milk formula; DBPCFC, double-blind, placebo-controlled food challenge; FA, food allergy; ISAACQ, international study of asthma and allergies in children questionnaire

the infant diet before 3 (unadjusted OR 1.56; 95% CI 1.28, 1.90; $I^2 = 0\%$) or 4 (unadjusted OR 1.20; 95% CI 1.08, 1.32; $I^2 = 0\%$) months of age was associated with higher risk of asthma (Fig. 3) [8, 11, 12, 15, 35–37]. When pooling adjusted

OR into the meta-analysis, the association between CM or CMF feeding before 4 months and risk of asthma was not significant (adjusted OR 1.16; 95% CI 0.89, 1.51; $I^2 = 7\%$) [8, 12]. Introducing CM or CMF before 6 months of age had a

Fig. 1 Flow diagram of study selection

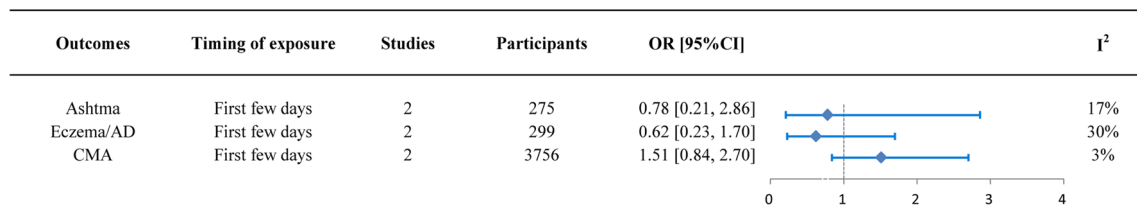


Fig. 2 Key results of the meta-analysis of the timing of CMF introduction and risk of allergic diseases from randomized control trials. AD, atopic dermatitis; CMA, cow's milk allergy; CMF, cow's milk formula

marginal association with risk of asthma (unadjusted OR 1.17; 95% CI 1.00, 1.38; $I^2 = 32\%$) (Fig. 3) [11, 35]. When we restricted the meta-analysis to high-quality studies, the results did not change significantly (Fig. 4).

Wheeze

Ten cohort studies with 14,024 participants reported CM or CMF introduction and risk of wheeze. The results of meta-analysis showed significant associations between CM or CMF introduction in earlier stages of infancy (< 1, 3, or 4 months) and risk of wheeze (< 1 vs. ≥ 1 month: unadjusted OR 2.07; 95% CI 1.30, 3.31; $I^2 = 6\%$; < 3 vs. ≥ 3 month: unadjusted OR 1.77; 95% CI 1.14, 2.73; $I^2 = 56\%$; < 4 vs. ≥ 4 month: unadjusted OR 1.62; 95% CI 1.31, 1.99; $I^2 = 0\%$) (Fig. 3) [16, 36, 38–42]. However, no association was observed in < 6 vs. $\geq$

6 months group (unadjusted OR 1.14; 95% CI 0.83, 1.57; $I^2 = 85\%$; adjusted OR 1.15; 95% CI 0.85, 1.56; $I^2 = 79\%$) (Fig. 3) [16, 35, 39, 41, 43, 44].

When the analysis was restricted to high-quality studies, six cohort studies pooled in < 4 vs. ≥ 4 month and < 6 vs. ≥ 6 months groups for meta-analyses showed that introducing CM or CMF into the infant diet before 4 months of age was still significantly associated with higher risk of wheeze (unadjusted OR 1.57; 95% CI 1.24, 2.00; $I^2 = 0\%$), but no association was found in 6 month groups (unadjusted OR 1.24; 95% CI 0.91, 1.70; $I^2 = 86\%$; adjusted OR 1.15; 95% CI 0.85, 1.56; $I^2 = 79\%$) (Fig. 4) [16, 35, 41, 43, 44]. Subgroup analysis with children at high risk of allergic diseases indicated that introducing CM or CMF before 4 months of life was not associated with the risk of wheeze (unadjusted OR 1.07; 95% CI 0.59, 1.94; $I^2 = 43\%$) (Fig. 5) [12, 39, 42]. When excluding exclusive formula-fed children,

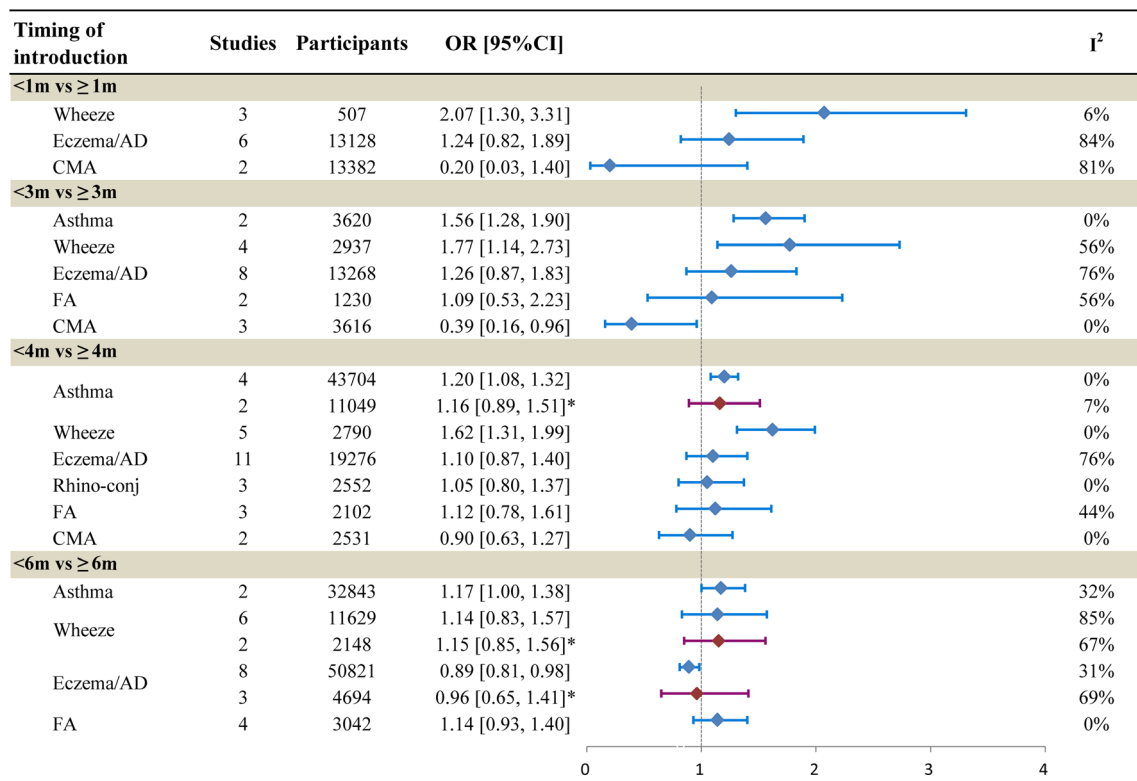


Fig. 3 Key results of the meta-analysis of the timing of CM or CMF introduction and risk of atopic diseases from cohort studies. * Adjusted OR

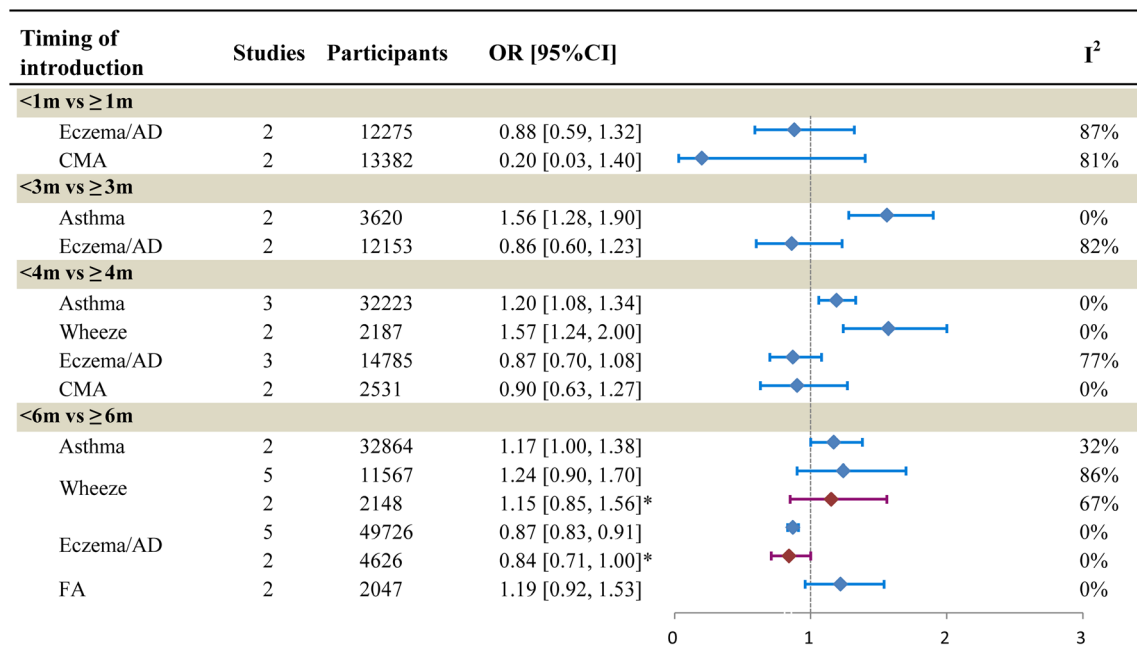


Fig. 4 Key results of the sensitive analysis of cohort studies with high quality (scores ≥ 7). * Adjusted OR. AD, atopic dermatitis; CM, cow's milk; CMA, cow's milk allergy; CMF, cow's milk formula; FA, food allergy

the pooled effects from included cohort studies showed that no significant association was observed between exposure to CMF

before 4 or 6 months of age and risk of wheeze (<4 vs. $\geq$ 4 months: unadjusted OR 1.65; 95% CI 0.81, 3.37; $I^2 = 43\%$;

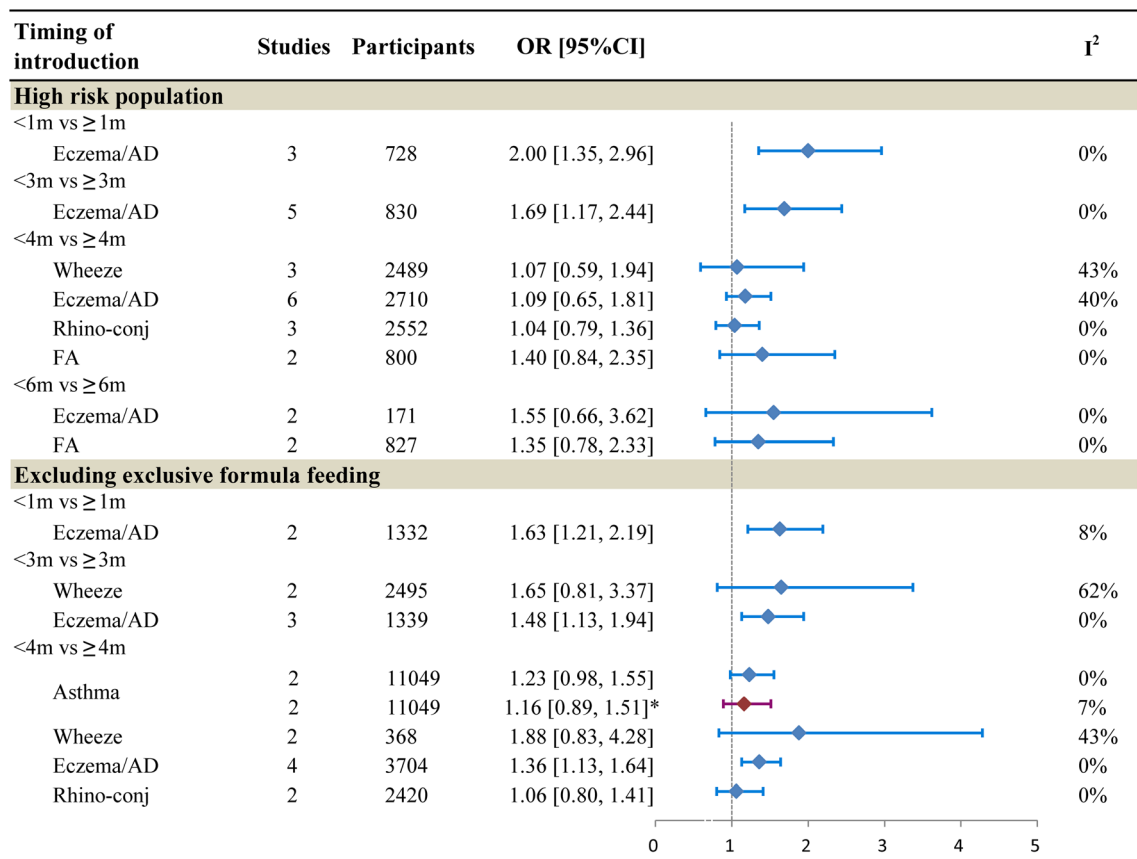


Fig. 5 Key results of the subgroup analysis of cohort studies. * Adjusted OR. AD, atopic dermatitis; CMF, cow's milk formula; FA, food allergy; Rhino-conj, allergic rhinitis or conjunctivitis

<6 vs. ≥ 6 months: unadjusted OR 1.88; 95% CI 0.83, 4.28) (Fig. 5) [16, 38–40].

Eczema/Atopic Dermatitis

We identified two RCT studies with 299 participants, 21 cohort studies with 60,024 participants, and two case-control studies with 1215 participants reporting the effects of initial exposure of CM or CMF on the risk of eczema or atopic dermatitis. A meta-analysis of two RCT studies found that there was no significant difference between feeding CMF in the first few days of life and human milk on the risk of eczema or atopic dermatitis (unadjusted OR 0.62; 95% CI 0.23, 1.70; $I^2 = 30\%$) (Fig. 2) [32, 45]. Meta-analyses of cohort studies showed that no significant associations between CM or CMF introduction and risk of eczema or atopic dermatitis were observed in <1 vs. ≥ 1 month (unadjusted OR 1.24; 95% CI 0.82, 1.89; $I^2 = 84\%$), <3 vs. ≥ 3 months (unadjusted OR 1.26; 95% CI 0.87, 1.83; $I^2 = 76\%$), and <4 vs. ≥ 4 months groups (unadjusted OR 1.10; 95% CI 0.87, 1.40; $I^2 = 76\%$) (Fig. 3) [12, 16, 38, 39, 41, 42, 46–52]. A cohort study not included in the meta-analyses also found that giving CMF to healthy breastfed term infants on the maternity wards does not increase the risk of developing eczema or atopic dermatitis (unadjusted OR 1.78; 95% CI 0.80, 4.00) [34]. One case-control study reported that introducing CMF before 4 months of age was associated with a reduced risk for eczema up to 4 years (unadjusted OR 0.55; 95% CI 0.38–0.81) [53]. The other case-control study also found that introducing CM at 1 month of age reduced the risk of atopic dermatitis (adjusted OR 0.62; 95% CI 0.40–0.96) [54]. In <6 vs. ≥ 6 months groups, results of pooling eight cohort studies indicated that introducing CMF or CM before 6 months of age was associated with a lower risk of eczema or atopic dermatitis (unadjusted OR 0.89; 95% CI 0.81, 0.98; $I^2 = 31\%$) (Fig. 3) [35, 41, 43, 44, 47, 49, 55, 56]. However, the result of pooling adjusted ORs showed no significant association observed in <6 vs. ≥ 6 months group (adjusted OR 0.96; 95% CI 0.65, 1.41; $I^2 = 69\%$) (Fig. 3) [35, 39, 57]. Another cohort study not in this meta-analysis showed that introducing CM within the first year of life showed an inverse association with the development of atopic dermatitis up to 4 years of age (adjusted OR 0.46; 95% CI 0.32, 0.65) [58].

In sensitivity analysis with only high-quality studies, we found that introducing CM or CMF before 6 months of age had a protective effect on the development of eczema or atopic dermatitis (unadjusted OR 0.87; 95% CI 0.83, 0.91; $I^2 = 0\%$; adjusted OR 0.84; 95% CI 0.71, 1.00; $I^2 = 0\%$) (Fig. 4) [35, 41, 43, 44, 47, 57]. In subgroup analyses of high-risk children, we found those given CM or CMF before 1 or 3 months of age had a higher risk of eczema or atopic dermatitis than those given later (<1 vs. ≥ 1 month: unadjusted OR 2.00; 95% CI 1.35, 2.96; $I^2 = 0\%$; <3 vs. ≥ 3 month: unadjusted OR 1.69;

95% CI 1.17, 2.44; $I^2 = 0\%$) (Fig. 5) [39, 48, 49, 56, 59]. In other comparative groups, no associations were observed in the high-risk children (<4 vs. ≥ 4 months: unadjusted OR 1.09; 95% CI 0.65, 1.81; $I^2 = 40\%$; <6 vs. ≥ 6 months: unadjusted OR 1.55; 95% CI 0.66, 3.62; $I^2 = 0\%$) (Fig. 5) [12, 39, 42, 49, 50, 56]. When excluding exclusive formula-fed children, introducing CM or CMF before 1, 3, or 4 months of age was associated with higher risk of eczema or atopic dermatitis (<1 vs. ≥ 1 month: OR 1.63; 95% CI 1.21, 2.19; $I^2 = 8\%$; <3 vs. ≥ 3 month: OR 1.48; 95% CI 1.13, 1.94; $I^2 = 0\%$; <4 vs. ≥ 4 month: OR 1.36; 95% CI 1.13, 1.64; $I^2 = 0\%$) (Fig. 5) [12, 38, 39, 48, 52].

Allergic Rhinitis and/or Conjunctivitis

For allergic rhinitis and/or conjunctivitis outcomes, six cohort studies with 4097 participants reported the risk of allergic rhinitis and/or conjunctivitis with the timing of CM or CMF introduction. Data from three cohort studies showed that there was no association between CM or CMF introduction before 4 months of age and risk of allergic rhinitis and/or conjunctivitis (unadjusted OR 1.05; 95% CI 0.80, 1.37; $I^2 = 0\%$) (Fig. 3) [12, 39, 42]. The results did not substantially change in subgroup analyses. Likewise, one cohort study not in the meta-analysis found that giving CMF to healthy breastfed term children on the maternity wards does not increase the risk of developing rhinoconjunctivitis (unadjusted OR 0.6; 95% CI 0.2, 1.7) [34].

Food Allergy

We identified six cohort studies with 9297 participants and one case-control study with 123 participants reporting food allergy. Data from five cohort studies were pooled and showed that no associations between CM or CMF introduction and risk of food allergy were observed in different timing cut-off groups (<3 vs. ≥ 3 month: OR 1.09; 95% CI 0.53, 2.23; $I^2 = 56\%$; <4 vs. ≥ 4 month: OR 1.12; 95% CI 0.78, 1.61; $I^2 = 44\%$; <6 vs. ≥ 6 month: OR 1.14; 95% CI 0.93, 1.40; $I^2 = 0\%$) (Fig. 3) [55, 56, 60–62]. One cohort study not in the meta-analysis found that children introduced to cow's milk before 10 months of age were more likely to become allergic than those introduced later [10].

When pooling the data from studies with high-risk children into the meta-analysis, no association between timing of CM or CMF introduction before 4 or 6 months of life and risk of food allergy was observed (<4 vs. ≥ 4 month: OR 1.40; 95% CI 0.84, 2.35; $I^2 = 0\%$; <6 vs. ≥ 6 month: OR 1.35; 95% CI 0.78, 2.33; $I^2 = 0\%$) (Fig. 5) [56, 61]. When we restricted to high-quality studies, there was no significant association observed in <6 vs. ≥ 6 -month group (OR 1.19; 95% CI 0.92, 1.53; $I^2 = 0\%$) (Fig. 4) [55, 61]. A case-control study indicated that the age at

introduction of cow's milk was earlier in the food allergy group than that in the control group ($P = 0.049$) [63].

Cow's Milk Allergy

Two RCT studies with 3756 participants, seven cohort studies with 19,530 participants, and one case-control study with 153 participants reported CMA. Data of two RCT studies showed that there was no difference between feeding human milk and CMF in the first few days of life on the risk of CMA (OR 1.51; 95% CI 0.84, 2.70; $I^2 = 3\%$) (Fig. 2) [33, 51]. Data from cohort studies indicated that early exposure to CM or CMF before 1 or 4 months of age was not associated with risk of CMA (< 1 vs. ≥ 1 months: unadjusted OR 0.20 95% CI 0.03, 1.40; $I^2 = 81\%$; < 4 vs. ≥ 4 months: unadjusted OR 0.90; 95% CI 0.63, 1.27; $I^2 = 0\%$) (Fig. 3) [38, 41, 64, 65]. Feeding CM or CMF before 3 months was associated with lower risk of CMA (unadjusted OR 0.39; 95% CI 0.16, 0.96; $I^2 = 0\%$) (Fig. 3) [21, 38, 64]. One cohort study not in the meta-analysis reported that compared with 7–12 months, introducing CM between 0 and 6 months of life had a protective effect on the development of CMA (adjusted OR 0.29; 95% CI 0.10, 0.70) [14]. Likewise, a case-control study found that compared with the children starting regular CMF within the first month of life, the delayed introduction was associated with a higher risk of CMA (adjusted OR 23.74; 95% CI 5.39, 104.52) [66].

When we restricted to high-quality studies, no association was observed in 1- or 4-month groups (< 1 vs. ≥ 1 months: unadjusted OR 0.20; 95% CI 0.03, 1.40; $I^2 = 81\%$; unadjusted OR 0.90; 95% CI 0.63, 1.27; $I^2 = 0\%$) (Fig. 4) [41, 64, 65].

Evaluation of Small-Study Effects

For the publication bias of the effects of introducing CM or CMF before 4 months of age on the risk of developing eczema or atopic dermatitis from 11 estimates, visual inspection of funnel plots and Begg's tests did not provide any evidence for meaningful small-study effects (Online Resource 4).

Discussion

In this systematic review, we reviewed and comprehensively summarized the evidence about the associations between timing of CM or CMF introduction and development of atopic diseases. Overall, the pooled analyses of included cohort studies indicated unadjusted risks of asthma and wheeze in the children who were introduced CM or CMF in very early stage of life. However, these associations were not significant when pooling adjusted data into the meta-analysis. The inconsistent results might be attributed to some important confounders. For example, the onset of wheeze and asthma is also associated with respiratory viral

infections which are related to the duration of breastfeeding. [67, 68] The definitions of wheeze and asthma were not very clear in most included studies. It is difficult to identify which one was actually caused by allergy. In addition, the absence of breastfeeding may increase risk of respiratory viruses that cause wheezing, which might be independent of allergy. However, we could not explore how these associations might be altered by restricting the analysis to long-term breastfed children due to the limited number of studies conducted in breastfed children to examine the impact of CM or CMF as a supplement with breast milk on the development of allergy. One cohort study found that exposure to infant formula before 14 weeks of age associated with higher risk of asthma after adjustment for the duration of breastfeeding and other covariates (adjusted OR 1.41; 95% CI 1.14, 1.74) [8]. Another study conducted in children with breastfeeding at least 4 months found that feeding CMF as a supplement to breast milk during the first 4 months of age was not associated with the cumulative incidence of asthma from 3 to 15 years of age (adjusted RR 1.05; 95% CI 0.67, 1.66). [12] In this review, the meta-analysis of RCT studies with high risk of bias found no association between CMF introduction in the first few days of life and risk of asthma, eczema or atopic dermatitis, or CMA. In summary, these findings do not provide strong evidence for the association between early introduction of CM or CMF to the infant diets and risk of atopic diseases.

Previous evidence indicated that genetics, microbial colonization, and nutrition had essential impacts on the allergy development by regulating the permeability of the gut barrier and passage of antigens in the early stage of life [69]. Proteins as one of the biologically active substances presenting in cow's milk have a positive effect on human health [70]. However, some proteins, such as casein fractions and β -lacto globulin, which are naturally not present in human milk, may cause positive reactions in human [71]. A previous systematic review concerning early feeding practice in infants and risk of atopic diseases indicated that exposure to CM during the first days of life was associated with a higher risk of CMA [72]. In a guinea pig model, researchers evaluating the allergenicity of different infant formulas found that feeding pasteurized cow milk and CMF had more anaphylactic sensitivity to antigens than feeding whey hydrolyzed formula [73]. In this review, pooling unadjusted data from included cohort studies showed that exposure to CM or CMF before 3 months was associated with a lower risk of CMA. However, the results of included RCTs showed that there was no significant association between exposure to CM during the first days of life and risk of CMA. The inconsistent results might be attributed to the heterogeneity of the risk bias of included studies, study designs, measurement of exposures and outcomes, populations (high risk or normal), or complex interactions of nutrition with the immune system.

Sensitivity analysis of high-quality studies found that exposure to CM or CMF before 6 months of age had a protective

effect on the risk of eczema or atopic dermatitis in general population. However, in the subgroup analyses, we found the earlier introduction of (before 1 or 3 months of age) CM or CMF to the infant was associated with a higher risk of eczema or atopic dermatitis in high-risk children or non-exclusive formula-fed children. The inconsistent results may be due to the confounding bias or reverse causality by a family history of atopic diseases. In addition, the included studies differed in the diagnostic measurement of outcomes. Some studies used physical examination and some based on parental reporting. Besides, feeding practice was measured by the self-report approach in most of the included studies. This approach causes recall bias and can alter the validity of the findings. Many mothers may fail to recall the formula given while in the maternity hospital. In addition, the evaluation of the effects of early and late introduction of CM or CMF could not disregard the impact of other solid food introduction. The heterogeneity identified in our meta-analysis indicates a need for more standardized approaches to evaluate the effects of early feeding practice on children's health.

The current evidence and theoretical concerned that early exposure to food proteins during a critical time window, likely to be 4–6 months of life, could benefit the development of immune tolerance [25]. However, too early exposure to the allergen may give rise to a higher risk of allergic or autoimmune diseases due to immature gut colonization and local immune networks [26]. One cohort studies found that compared with children exposure to infant formula after 6 months of age, introducing between 4 and 6 months associated with a higher risk of asthma at age 7 years (adjusted RR 1.21; 95 CI 1.03, 1.44), but no significant association observed between introducing before 4 months and the risk of asthma (adjusted RR 1.10; 95 CI 0.98, 1.25) [11]. In this review, the timing of CM or CMF introduction between comparison groups in included studies was varied. Initially, we want to identify a critical window of CM or CMF exposure during infancy, which was associated with the risk of atopic diseases. However, according to the data distribution and the limit number of eligible studies for each outcome, we just set several timing cut-off points for meta-analyses. Therefore, we could not identify the critical periods related to the outcomes, for example, between 4 to 6 months or 7 to 9 months of age.

There are several strengths of our systematic review. We included multiple databases, searches of gray literature, and hand searching of citations to reduce the likelihood of missing the primary research corresponding to our inclusion criteria. In this review, we excluded the studies comparing CM or CMF with hydrolyzed formula, soy formula, or milk from other animals to minimize the heterogeneity of comparative groups. Different types of foreign proteins may have different effects on the health of children. [19, 74–77]. In addition, the

potential for the presence of heterogeneity and small-study effects were quantitatively evaluated. Studies were identified across a range of countries (20 countries), increasing generalizability.

This review has some limitations. First, for some outcomes, the statistical power was limited due to the sizes of the included studies. Second, most of the data extracted from included studies for meta-analysis was unadjusted data. The results might be affected by some significant confounders such as duration of breastfeeding, respiratory viral infections, the gender of children, maternal age at delivery, parental social status, and smoking status. Third, most included studies were observational studies. As a result, the observed associations may be attributable to confounding by factors other than the exposure being investigated. However, it is probably unethical to conduct a controlled trial in which some participants are randomized to “early feeding of infant formula” group.

Based on the findings of this review, we think that future studies should employ a large sample size, a prospective design (which could establish the temporal direction of the associations), use validated exposure and outcome measurement methods (e.g., diet records for the infants, medical records for the diseases and long-term follow-up), and adjust for a wide range of potential confounders (e.g., duration of breastfeeding, respiratory viral infections, gender of children, maternal smoking status, and timing of other allergic food introduction).

Conclusion

Pooled analysis of the cohort studies indicated an unadjusted risk of asthma and wheeze in the children who were introduced CM or CMF in a very early stage of life. However, these results should be interpreted with caution due to the limitations of included studies and the limited number of studies included for each outcome. Overall, quite little high-quality evidence was identified to allow for definitive conclusions. Our meta-analysis on this topic highlights the specific gaps in information for public recommendations regarding infant feeding practice, particularly in an early stage; therefore, more future high-quality research is needed.

Author's Contribution The authors' responsibilities were as follows: MY, XQ, GNT, KC: designed research; MY and MT: conducted search, extracted the data, and performed statistical analysis; MY, DM, SS: drafted, edited, and critically reviewed and revised the manuscript; DM, XQ, GNT, KKC: critically reviewed, revised, and supervised the manuscript; MY and KK: had primary responsibility for final content. All authors: read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals Not applicable.

Informed Consent Not applicable

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PRISMA 2009 Checklist

Title: Timing of cow's milk or cow's milk formula introduction to the infant diet and atopic risk in children: a systematic review and meta-analysis

Journal Name: Clinical Reviews in Allergy & Immunology

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online Resource 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Online Resource 3: Supplemental Table 3-5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Online Resource 3: Supplemental Tables 6-8 Online Resource 4: Supplemental Figure 1-20
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Resource 4: Supplemental Figure 21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 4-5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17



PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org. Page 2 of 2

**Title: Timing of cow's milk or cow's milk formula introduction to the infant diet
and atopic risk in children: a systematic review and meta-analysis**

Journal Name: Clinical Reviews in Allergy & Immunology

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Supplemental Table 2. Search Strategies

Databases	
Embase	1. infant/ 2. exp baby/ 3. child/ 4. newborn/ 5. breast feeding.ab,ti. 6. breastfeeding.ab,ti. 7. breast fed.ab,ti. 8. breastfed.ab,ti. 9. breast feeding/ 10. breast milk/ 11. formula\$.ab,ti. 12. bottlefed.ab,ti. 13. bottle fed.ab,ti. 14. artificial milk/ 15. bottle feeding/ 16. baby food\$.ab,ti. 17. baby food/ 18. infant nutrition/ 19. exp infant feeding/ 20. milk.ti,ab. 21. milk/ 22. diet/ 23. diet.ti,ab. 24. diets.ti,ab. 25. dietetic.ab,ti. 26. dietary.ab,ti. 27. allerg\$.ab,ti. 28. asthma\$.ab,ti. 29. wheeze.ab,ti. 30. wheezing.ab,ti. 31. eczema.ab,ti. 32. rhinitis.ab,ti.

	33. rhinoconjunctivitis.ab,ti. 34. conjunctivitis.ab,ti. 35. atopic disease.ab,ti. 36. atopic dermatitis.ab,ti. 37. atopy.ab,ti. 38. hypersensitiv\$.ab,ti. 39. exp hypersensitivity/ 40. asthma/ 41. wheezing/ 42. eczema/ 43. rhinitis/ 44. rhinoconjunctivitis/ 45. conjunctivitis/ 46. obesity.ab,ti. 47. overweight.ab,ti. 48. BMI.ab,ti. 49. body mass index.ab,ti. 50. exp obesity/ 51. exp body mass/ 52. iron stauts.ab,ti. 53. iron deficiency anemia.ab,ti. 54. iron deficiency anemia/ 55. exp iron blood level/ 56. exp food allergy/ 57. exp milk allergy/ 58. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 59. exp cohort analysis/ 60. exp longitudinal study/ 61. exp prospective study/ 62. exp follow up/ 63. cohort\$.tw.
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	64. exp case control study/ 65. (case\$ and control\$).tw. 66. 59 or 60 or 61 or 62 or 63 or 64 or 65 67. (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. 68. RETRACTED ARTICLE/ 69. 67 or 68 70. (animal\$ not human\$).sh,hw. 71. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ 72. (random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ 73. 69 not (70 or 71 or 72) 74. 66 or 73 75. 1 or 2 or 3 or 4 76. complementary food\$.ab,ti. 77. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 76 78. 58 and 74 and 75 and 77 79. 78 not animals.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
Pubmed	((("child"[MeSH Terms] OR "infant"[MeSH Terms])) AND (((((((("milk, human"[MeSH Terms] OR "milk"[MeSH Terms]) OR "dairy products"[MeSH Terms]) OR ("infant

	formula"[MeSH Terms] OR "infant formula"[MeSH Terms])) OR "breast feeding"[MeSH Terms]) OR "infant nutritional physiological phenomena"[MeSH Terms]) OR "bottle feeding"[MeSH Terms])) AND ((((((((("obesity"[MeSH Terms] OR "overweight"[MeSH Terms]) OR "body mass index"[MeSH Terms]) OR ("body height"[MeSH Terms] OR "body weight"[MeSH Terms])) OR "anthropometry"[MeSH Terms]) OR ("hypersensitivity"[MeSH Terms] OR "allergy and immunology"[MeSH Terms])) OR "eczema"[MeSH Terms]) OR "asthma"[MeSH Terms]) OR "respiratory sounds"[MeSH Terms]) OR "dermatitis, atopic"[MeSH Terms]) OR "food hypersensitivity"[MeSH Terms]) OR "milk hypersensitivity"[MeSH Terms]) OR ("anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms])))) AND ((((((((cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB])))) OR "Epidemiologic Studies"[Mesh:noexp]) OR ("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as
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	Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab]))) OR ("Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB]))
Cochrane CENTRAL	#1: child:ti,ab,kw (Word variations have been searched) #2: "infant":ti,ab,kw (Word variations have been searched)

	#3: "newborn":ti,ab,kw (Word variations have been searched) #4: "baby":ti,ab,kw (Word variations have been searched) #5: #1 or #2 or #3 or #4 #6: "breastfeeding":ti,ab,kw (Word variations have been searched) #7: "breast feeding":ti,ab,kw (Word variations have been searched) #8: "milk":ti,ab,kw (Word variations have been searched) #9: formula*:ti,ab,kw (Word variations have been searched) #10: "bottle feeding":ti,ab,kw (Word variations have been searched) #11: breast fed:ti,ab,kw (Word variations have been searched) #12: breastfed:ti,ab,kw (Word variations have been searched) #13: bottlefed:ti,ab,kw (Word variations have been searched) #14: complementary food:ti,ab,kw (Word variations have been searched) #15: MeSH descriptor: [Breast Feeding] explode all trees #16: MeSH descriptor: [Milk, Human] explode all trees #17: MeSH descriptor: [Bottle Feeding] explode all trees #18: (introduc* near/2 food*):ab,ti #19: #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 #20: allerg*:ti,ab,kw (Word variations have been searched)
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	#21: "atopic disease":ab,ti #22: hypersensitiv*:ab,ti #23: atopy:ab,ti #24: asthma*:ti,ab,kw (Word variations have been searched) #25: wheeze:ti,ab,kw (Word variations have been searched) #26: "wheezing":ti,ab,kw (Word variations have been searched) #27: eczema:ti,ab,kw (Word variations have been searched) #28: "atopic dermatitis":ab,ti #29: rhinitis:ti,ab,kw (Word variations have been searched) #30: rhinoconjunctivitis:ab,ti #31: conjunctivitis:ab,ti #32: rhinoconjunctivitis:ti,ab,kw (Word variations have been searched) #33: MeSH descriptor: [Dermatitis, Atopic] explode all trees #34: MeSH descriptor: [Asthma] explode all trees #35: MeSH descriptor: [Eczema] explode all trees #36: MeSH descriptor: [Rhinitis, Allergic] explode all trees #37: MeSH descriptor: [Food Hypersensitivity] explode all trees #38: "cow's milk allergy":ti,ab,kw (Word variations have been searched) #39: MeSH descriptor: [Anemia, Iron-Deficiency] explode all trees #40: MeSH descriptor: [Anemia] explode all trees
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	#41: MeSH descriptor: [Obesity] explode all trees #42: MeSH descriptor: [Overweight] explode all trees #43: MeSH descriptor: [Body Mass Index] explode all trees #44: MeSH descriptor: [Body Height] explode all trees #45: MeSH descriptor: [Body Weight] explode all trees #46: MeSH descriptor: [Growth] explode all trees #47: #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 #48: #5 and #19 and #47
CINAHL	S1 (MH "Infant+") S2 (MH "Child+") S3 (MH "Breast Feeding+") S4 (MH "Infant Feeding+") S5 (MH "Infant Nutritional Physiology+") S6 (MH "Milk+") S7 (MH "Dairy Products+") S8 S1 OR S2 S9 S3 OR S4 OR S5 OR S6 OR S7 S10 (MH "Asthma+") S11 (MH "Eczema") S12 (MH "Respiratory Sounds+") S13 (MH "Dermatitis, Atopic") S14 (MH "Rhinitis, Allergic, Perennial") OR (MH "Rhinitis, Allergic, Seasonal") S15 (MH "Food Hypersensitivity+")

	S16 (MH "Milk Hypersensitivity") S17 (MH "Obesity+") S18 (MM "Body Mass Index") OR (MH "Body Weights and Measures+") S19 (MH "Body Weight+") S20 (MM "Body Height") S21 (MH "Anemia+") OR (MM "Anemia, Iron Deficiency") S22 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 S23 S8 AND S9 AND S22
CNKI	(“婴儿” OR “新生儿” OR “儿童”) AND (“牛奶”OR “奶粉”OR “母乳”OR “奶制品”OR “乳制品”OR “喂养”OR “辅食”) AND (“过敏”OR“哮喘”OR“喘息”OR“过敏性鼻炎”OR“特异性皮炎”OR“湿疹”OR“食物过敏”OR“牛奶过敏”OR“肥胖”OR“超重”OR“缺铁性贫血”) AND (“临床试验”OR“对照试验”OR“随机”OR“临床观察”OR“临床研究”OR“随机对照试验”OR“队列”OR“观察性研究”OR“病例对照”)

Title: Timing of cow's milk or cow's milk formula introduction to the infant diet and atopic risk in children: a systematic review and meta-analysis

Journal Name: Clinical Reviews in Allergy & Immunology

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Supplemental Table 3. Risk of bias of randomized clinical trials using the Cochrane Collaboration Risk of Bias Tool

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall
Juvonen 1996	High risk	High risk	Unclear	Unclear	Low risk	Unclear	High risk
Lindfors 1988	High risk	High risk	High risk	Low risk	Unclear risk	Unclear	High risk
Lindfors 1992	High risk	High risk	High risk	Low risk	Unclear risk	Unclear	High risk
Saarinen 1999 Saarinen 2000	High risk	High risk	Low risk	Low risk	Unclear risk	Unclear	High risk

Supplemental Table 4. Quality ratings for the 37 cohort studies included on the basis of Newcastle-Ottawa quality assessment scale

Outcomes	Study ID	Representative of exposed cohort	Selections of non-exposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up period	Adequacy of follow-up ($\geq 70\%$)	Total Score
Wheeze	Azad 2017	1	1	0	1	2	1	1	1	8
FA	Batool 2016	1	1	1	1	0	0	1	1	6
Eczema	Cogswell 1987	0	1	1	1	0	1	1	1	6
Eczema/ FA	Elbert 2017	1	1	0	1	2	1	1	1	8
Eczema	Fergusson 1990	1	1	0	1	1	0	1	1	6
Asthma/ Eczema/ Rhinitis	Filipiak-Pittroff 2018	0	0	1	1	0		1	1	4
Asthma/ Rhino-conj / Eczema	Gustafsson 1992	1	1	1	1	0	1	1	1	7
CMA	Host 1991	1	1	0	1	1	1	1	1	7
AD	Ito 2014	1	1	0	1	2	0	1	1	7
CMA	Katz 2010	1	1	0	1	1	1	1	1	7
Wheeze/ Eczema/ CMA	Kemeny 1991	1	1	0	1	0	1	1	1	6
Asthma	Kilingberg 2019	1	1	1	1	2	1	1	0	8
Asthma	Klopp 2017	1	1	0	1	2	1	1	1	8
FA	Kumar 2010	1	1	0	0	2	1	1	1	7
Eczema		1	1	0	0	2	0	1	1	6
Asthma	Lossius 2018	1	1	0	1	2	1	1	0	7
FA	Luccioli 2014	1	1	0	1	2	0	1	1	7
Wheeze /AD /Allergic rhino-conj	Marini 1996	0	1	0	1	0	1	1	1	5
Eczema	Moore 1985	0	1	1	1	0	1	1	1	6
FA	Nwaru 2010	0	1	0	1	1	1	1	1	6

Outcomes	Study ID	Representative of exposed cohort	Selections of non-exposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up period	Adequacy of follow-up (≥70%)	Total Score
Asthma/ Eczema/ Rhinitis	Nwaru 2013a	0	1	0	1	1	1	1	1	6
Asthma/ Wheeze/ Eczema	Nwaru 2013b	1	1	1	1	2	1	1	0	8
CMA	Peters 2019	1	1	0	1	1	1	0	0	5
Eczema	Poysa 1989	0	1	0	1	0	1	1	1	5
AD	Roduit 2012	0	1	1	1	2	1	1	1	8
AD	Ruiz 1992	0	1	0	1	0	1	1	1	5
AD/ FA	Saarinen 1979	0	1	0	1	0	1	1	1	5
Wheeze	Simon 2008	0	1	0	1	2	0	1	0	5
Wheeze/ Eczema	Snijders 2008	1	1	0	1	2	0	1	1	7
AD/ CMA		1	1	0	1	2	1	1	1	8
Eczema	Soto-Ramirez 2017	1	1	0	1	2	0	1	1	7
Asthma/ Wheeze	Strassburger 2010	1	1	0	1	2	1	1	1	8
Asthma	Tariq 1998	1	1	0	1	1	1	1	1	7
CMA	Tham 2018	1	1	0	1	2	1	1	1	8
CMA	Tran 2017	1	1	0	1	2	1	1	0	7
Eczema/ Wheeze	Tromp 2011	1	1	0	1	2	1	1	1	8
AD	Van Asperen 1984	0	1	0	1	0	1	1	1	5
Wheeze/ Rhinitis		0	1	0	1	0	0	1	1	4
Rhinitis	Wright 1994	1	1	0	1	1	0	1	0	5
Wheeze/ Eczema	Zutavern 2004	1	1	0	1	2	0	1	1	7

AD atopic dermatitis; **CMA** cow's milk allergy; **FA** food allergy; **Rhino-conj** rhinitis+conjunctivitis

Supplemental Table 5. Quality ratings for the 5 case-control studies included on the basis of Newcastle-Ottawa quality assessment scale

Study ID	Selection (score)				Comparability (score)	Exposure (score)			Total Score
	Case definition	Representative of cases	Selections of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for participants	Nonresponse rate	
Grimshaw 2013	1	1	1	1	1	0	1	1	7
Onizawa 2016	1	1	0	1	1	0	1	1	6
Sariachvili 2010	1	1	1	1	1	0	1	1	7
Turati 2016	1	1	0	1	1	0	1	1	6

Supplemental Table 6. Original data extracted from the included clinical trial studies for each outcome.

Outcomes	Study ID	Cases in each comparative group	
		All population	High-risk population
Wheeze	Lindfors 1988	CMF: 6/109, HM: 8/98	CMF:3/50, HM:5/57
Eczema	Juvonen 1996	HM: 3/53, CMF: 3/39	
	Lindfors 1988	CMF: 10/109, HM: 18/98	CMF:3/50, HM:11/57
Asthma	Lindfors 1992	CMF: 9/95, HM: 8/88	CMF: 6/53, HM:7/56
Allergic rhinitis/ conjunctivitis	Lindfors 1992	CMF: 9/95, HM: 2/88	CMF: 7/53, HM: 1/56
Cow's milk allergy	Lindfors 1992	CMF:3/80, HM: 2/74	
	Saarinen 1999	CMF: 43/1758, HM: 32/1844	
	Saarinen 2000		
Food allergy	Lindfors 1992	CMF: 3/80, HM: 0/74	
	Perkin 2016	3-6m: 42/595, >6m: 32/567	

CMF: cow's milk formula; **HM:** human milk

Supplemental Table 7. Original data extracted from the included cohort studies for each outcome.

Outcomes	Study ID	Exposure time	Cases in each comparative group / Unadjusted OR (95%CI), N				Adjusted OR (95%CI), N
Asthma	Filipiak-Pittroff 2018	<4m (RG), ≥4m	0.94 (0.60- 1.47), N=2252				1.05 (0.67- 1.66), N=2252
	Gustafsson 1992	≤8d, >8d	≤8d: 8/240	>8d: 10/496			
	Kilingberg 2019	< 14 weeks Never (RG)	1.30 (1.00–1.70), N=9229				1.27 (0.95–1.71), N=8797
	Klopp 2017	0m, <3m, ≥3m	0m:56/354	<3m: 98/659	≥3m: 165/1521		
	Lossius 2018	<4m, 4-5.9m, ≥6m	<4m: 426/8351	4-5.9m: 168/3261	≥ 6m: 854/20318		
	Nwaru 2013a	<0.92m, 0.92-4m, >4m	No data				
	Nwaru 2013b	CM: <5.75m (RG), ≥ 5.75m	0.99 (0.73–1.34) , N=934				0.91 (0.66–1.25) , N=934
		CMF: <0.5m (RG), ≥0.5m	0.70 (0.51–0.94) , N=934				0.72 (0.47–1.12) , N=934
	Strassburger 2010	<4m, ≥4m	<4m:12/119	≥4m:15/174			
Wheeze	Tariq 1998	<3m, ≥3m	<3m:114/667	≥3m:43/419			1.8 (1.2-2.6), N=1086
	Azad 2017	<3m, ≥3m (RG)	1.28 (1.07-1.53), N=2366				1.16 (0.97-1.39), N=2366
	Azad 2017	<6m, ≥6m (RG)	1.64 (1.38-1.96), N=1214				1.47 (1.23-1.75), N=1214
	Kemeny 1991	0m, <3m, ≥3m	0m:14/60	<3m:18/64	≥3m:8/65		
	Marini 1996	CMF: 0m, <4m, ≥4m (all children)	0m: 9/53	<4m: 4/41	≥4m: 6/127		
		CMF: 0m, <4m, ≥4m (hig risk)	0m: 5/38	<4m:1 /22	≥4m: 3/98		
		CM: <6m, ≥6m (RG) (normal children)					0.5 (0.1-1.1), N=62
	Nwaru 2013b	CM: <5.75m (RG), ≥5.75m	0.98 (0.70, 1.39) , N=934				0.97 (0.68–1.39) , N=934
		CMF: <0.5m (RG), ≥0.5m	0.75 (0.54–1.05) , N=934				0.75 (0.47–2.00) , N=934
	Simon 2008	0m, <4m, ≥4m	0m: 49/103	<4m:44/101	≥4m:35/99		
	Snijders 2008	0–3m, 4–6m, 7–9m, >9m	0-3m: 127/730	4–6m: 83/589	7-9m: 44/519	>9m: 5/56	
	Strassburger 2010	<4m, ≥4m	<4m: 28/119	≥4m: 34/174			
	Tromp 2011	<6m, ≥6m (RG)	0.96 (0.77-1.21), N=6905				0.96 (0.77-1.19) , N=6905
	Van Asperen 1984	<4m, ≥4m	<4m: 16/51	≥4m: 6/28			
	Zutavern 2004	<6m, ≥6m	<6m 120/407	≥6m 69/213			
Eczema/Atopic Dermatitis	Cogswell 1987	<4w, 4-13w, ≥14w	<4w:7/33	4-13w: 6/31	≥14w: 2/9		
	Elbert 2017	<6m, ≥6m (RG)					0.82 (0.63, 1.07), N=3692
	Fergusson 1990	<4m, ≥4m	<4m: 79/998	≥4m: 11/212			
	Filipiak-Pittroff 2018	<4m (RG), ≥4m	0.80 (0.61- 1.05), N=2252				0.73 (0.55- 0.97), N=2252

	Gustafsson 1992	≤8d, >8d	≤8d: 17/240	>8d: 22/496			
	Ito 2014	0m, <6m, ≥6m	0m: 502/2217	<6m:7213/27861	≥6m:2474/8679		
	Kemeny 1991	0m, <3m, ≥3m	0m:10/60	<3m:15/64	≥3m:11/65		
	Kumar 2010	<6m, ≥6m	<6m: 236/464	≥6m:155/325			
	Marini 1996	CMF: 0m, <4m, ≥4m (all children)	0m: 16/53	<4m: 10/41	≥4m: 17/127		
		CMF: 0m, <4m, ≥4m (high risk)	0m: 9/38	<4m:3/22	≥4m: 3/98		
		CM: <6m, ≥6m (RG) (normal children)					4.2 (1.1- 14.5), N=68
	Moore 1985	1-4w, 5-8w, 9-12w, >12w	1-4w : 37/162 (0w: 7/35)	5-8w: 4/39	9-12w:3/26	>12w:34/248	
	Nwaru 2013a	<0.92m, 0.92-4m, >4m	No data				
	Nwaru 2013b	CM: <5.75m (RG), ≥5.75m	1.15 (0.92–1.43), N=934				1.16 (0.92–1.46), N=934
		CMF: <0.5m (RG), ≥0.5m	0.97 (0.78–1.22), N=934				0.93 (0.68–1.29), N=934
	Poysa 1989	<3m, 3-6m, >6m	<3m: 6/25	3-6m: 4/14	>6m: 7/31		
	Roduit 2012	3-12m, >12m (RG)					Normal: 0.68 (0.44,1.05) High risk:0.86 (0.51,1.45)
	Ruiz 1992	<4m, ≥4m	<4m:4/22	≥4m: 7/17			
	Saarinen 1979	All: <2m, 2-6m, >6m	<2m: 21/105	2-6m:13/77	>6m:5/54		
		High risk: <2m, 2-6m, >6m	<2m: 10/38	2-6m:8/38	>6m:3/25		
	Snijders 2008	0–3m, 4–6m, 7–9m, >9m	0-3m:297/976	4–6m: 239/800	7-9m: 219/664	>9m: 28/70	
	Soto-Ramirez 2017	0m, <1m, 1-3m, ≥4m	0m: 84/487	<1m: 83/323	1-3m: 20/122	≥4m: 88/447	
	Tromp 2011	<6m, ≥6m (RG)	0.95 (0.77-1.17), N=6905				0.95 (0.77-1.15), N=6905
	Van Asperen 1984	<4m, ≥4m	≤4m: 22/51	>4m: 16/28			
	Zutavern 2004	<6m, ≥6m	≤6m 131/407	>6m 88/213			
Allergic rhinitis/ conjunctivitis	Filipiak-Pittroff 2018	<4m, ≥4m (RG)	0.95 (0.71- 1.27), N=2252				0.94 (0.70- 1.26), N=2252
	Gustafsson 1992	≤8d, >8d	≤8d: 6/240	>8d: 19/496			
	Marini 1996	CMF: 0m, <4m, ≥4m (all children)	0m: 4/53	<4m: 2/41	≥4m: 4/127		
		CMF: 0m, <4m, ≥4m (high risk)	0m: 2/38	<4m: 1/22	≥4m: 2/98		
		CM: <6m, ≥6m (RG) (normal children)					0.4 (0.1- 1.1), N=62
	Nwaru 2013a	<0.92m, 0.92-4m, >4m	No data				
	Van Asperen 1984	≤4m, >4m	≤4m: 27/51	>4m: 17/28			
	Wright 1994	<6m, ≥6m	<6m:244/571	≥6m:57/176			

Food allergy	Batool 2016	<6m, ≥6m (RG)	<6m: 58/143	≥6m: 271/675			1.30 (0.90–1.88), N=642
	Elbert 2017	<6m, ≥6m (RG)					1.44 (0.76, 2.73), N=3006
	Kumar 2010	<6m, ≥6m	<6m: 249/464	>6m: 162/325			
	Luccioli 2014	All: 4m, 4–5m, 6–12m	<4m: 60/899	4–5m: 4/59	6–12m: 16/300		
		High risk: 4m, 4–5m, 6–12m	<4m: 53/530	4–5m: 4/42	6–12m: 14/180		
	Nwaru 2010	<0.92m (RG), 0.92–4m, >4m	0.92–4m: 1.09 (0.72–1.65)				0.92–4m: 1.25 (0.77–2.03)
			>4m: 1.20 (0.80–1.81), N=994				>4m: 1.51 (0.93–2.46), N=994
	Saarinen 1979	All: <2m, 2–6m, >6m	<2m: 25/81	2–6m: 10/56	>6m: 8/40		
		High risk: <2m, 2–6m, >6m	<2m: 11/28	2–6m: 4/27	>6m: 4/20		
Cow's milk allergy	Katz 2010	<1m (RG), ≥1m	12.2 (5.2–28.6), N=11633				
	Kemeny 1991	0m, <3m, ≥3m	0m: 0/60	<3m: 1/64	≥3m: 1/65		
	Host 1991	<1m, 1–3m, ≥4m	0m: 2/145	<1m: 0/190	1–3m: 4/505	≥4m: 10/909	
	Perters 2019	<3m, ≥3m (RG)		<3m: 3/784	≥3m: 18/1399		0.30 (0.09–1.02), N=2183
	Snijders 2008	0–3m, 4–6m, 7–9m, >9m	0–3m: 50/270	4–6m: 54/235	7–9m: 44/255	>9m: 2/22	
	Tham 2018	<10m, ≥10m	<10m: 2/687	≥10m: 1/183			
	Tran 2017	≤6m, 7–12m (RG)					0.29 (0.10, 0.70), N=2124

CM: cow's milk; **CMF:** cow's milk formula; **d:** day; **m:** month; **RG:** reference group; **w:** week

Supplemental Table 8. Original data extracted from the included case-control studies for each outcome.

Outcomes	Study ID	Sample size	Timing of introduction	Cases in each comparative group / OR 95%CI
Food allergy	Grimshaw 2013	123 Case:41 Control:82	Median age of weeks	Case:22w Control:26w
Cow's milk allergy	Onizawa 2016	153 Case:51 Control:102	≤1m	Case: 6/51 Control: 60/102
Eczema/Atopic Dermatitis	Sariachvili 2010	Case: 252 Control: 305	<4m	Case:169/252 Control: 240/305
	Turati 2016	Case: 329 Control: 329	No cow's milk before 5 m(RG) at 1m at 2m at 3m at 4m at 5m	at 1m: 0.62 (0.40–0.96) at 2m: 0.64 (0.41–1.00) at 3m: 0.57 (0.37–0.89) at 4m: 0.64 (0.38–1.09) at 5m: 0.61 (0.28–1.30)

m: month; **w:** week

**Title: Timing of cow's milk or cow's milk formula introduction to the infant diet
and atopic risk in children: a systematic review and meta-analysis**

Journal Name: Clinical Reviews in Allergy & Immunology

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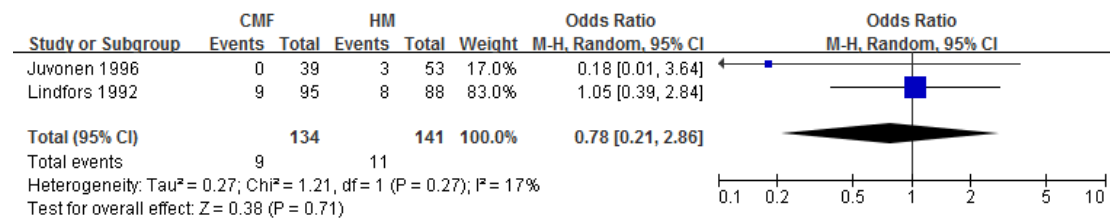
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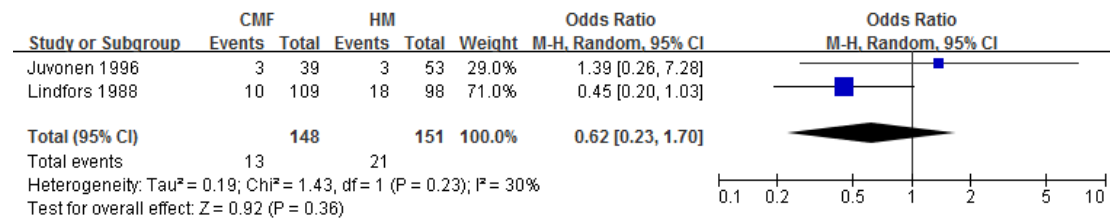
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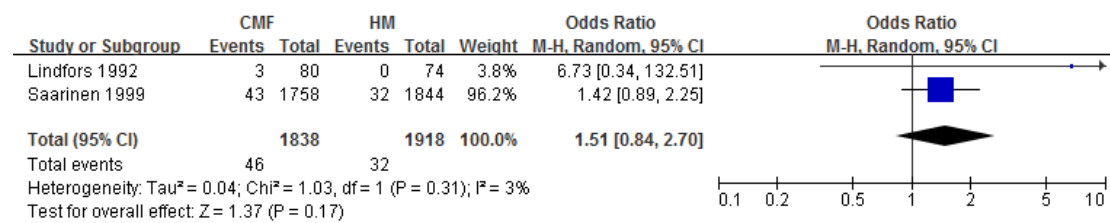
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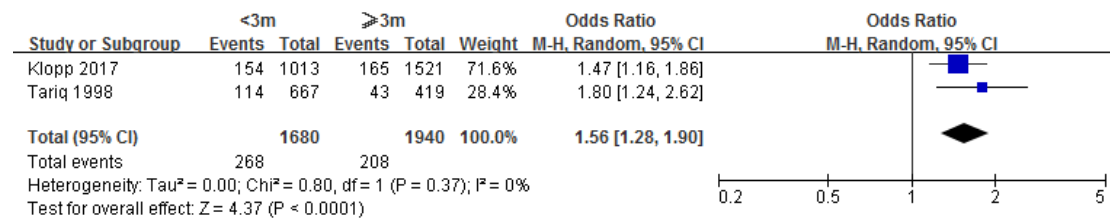


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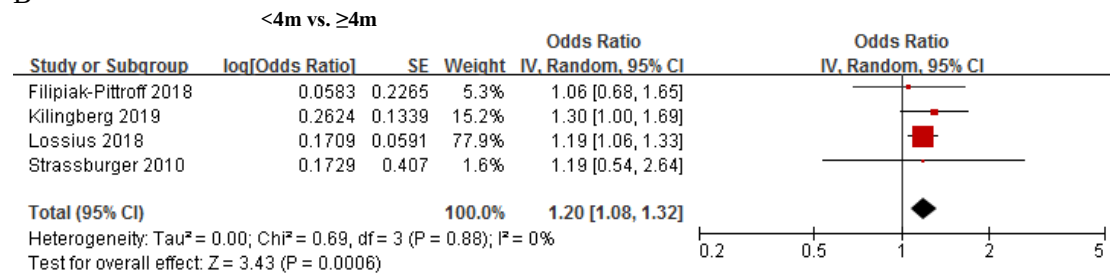


Supplemental Figure 1. Summary of risk of allergic diseases for introducing cow's milk formula versus human milk during the first days of life from clinical trials: **(A)** asthma **(B)** eczema/atopic dermatitis **(C)** cow's milk allergy. CMF: cow's milk formula; HM: human milk.

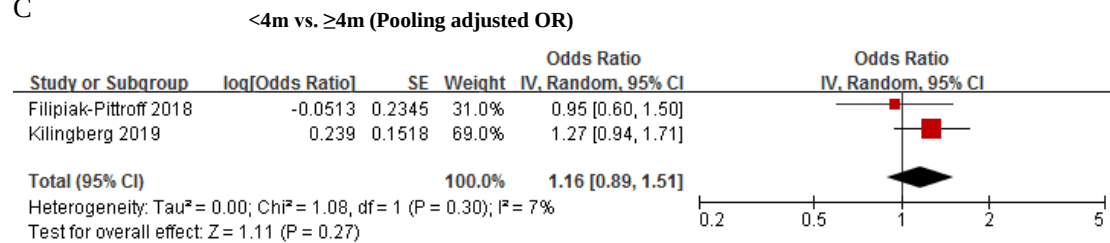
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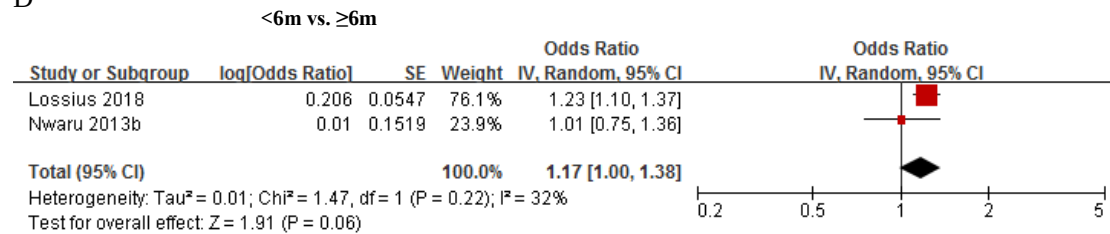
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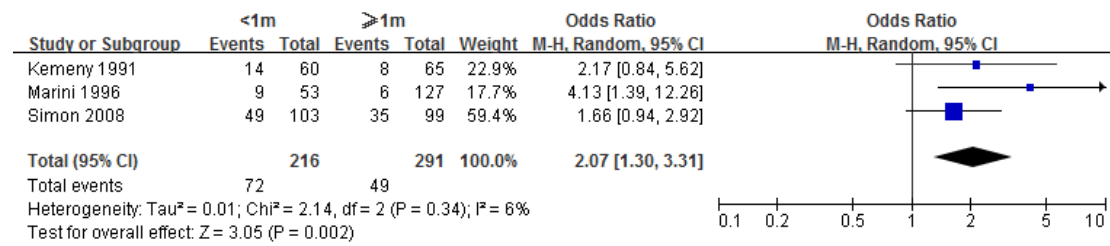


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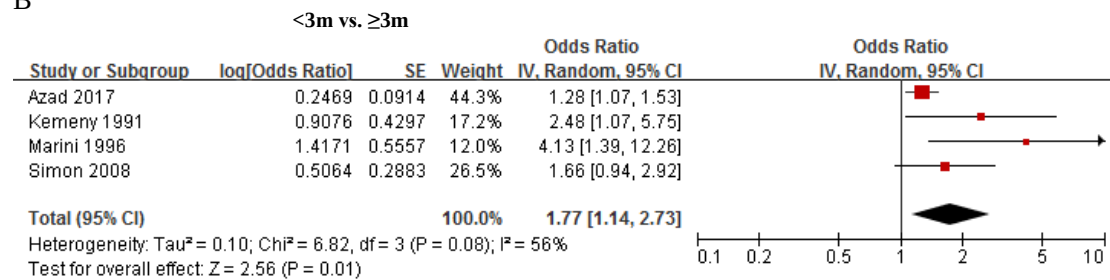


Supplemental Figure 2. Summary of risk of asthma for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <3 vs. ≥3 months; **(B)** exposure time <4 vs. ≥4 months; **(C)** exposure time <4 vs. ≥4 months, pooling adjusted OR; **(D)** exposure time <6 vs. ≥6 months.

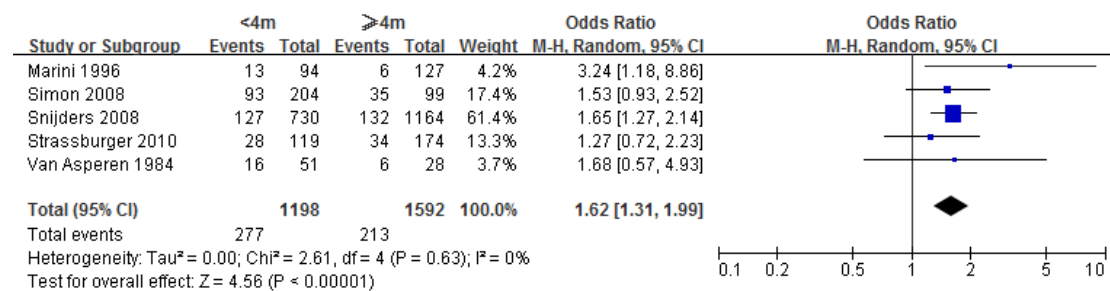
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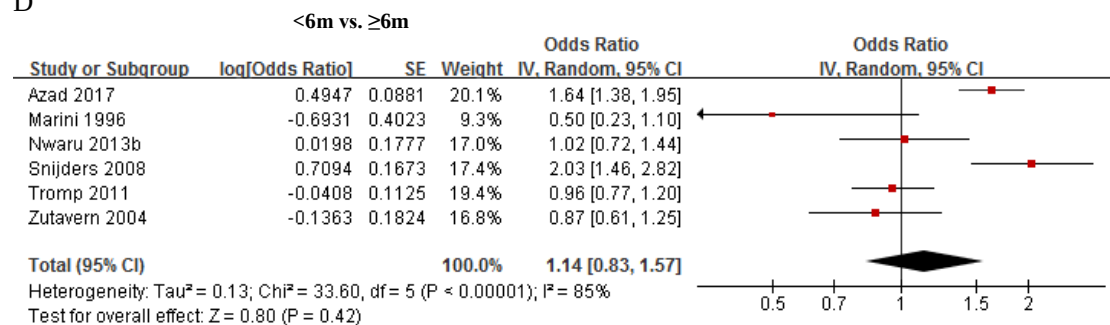
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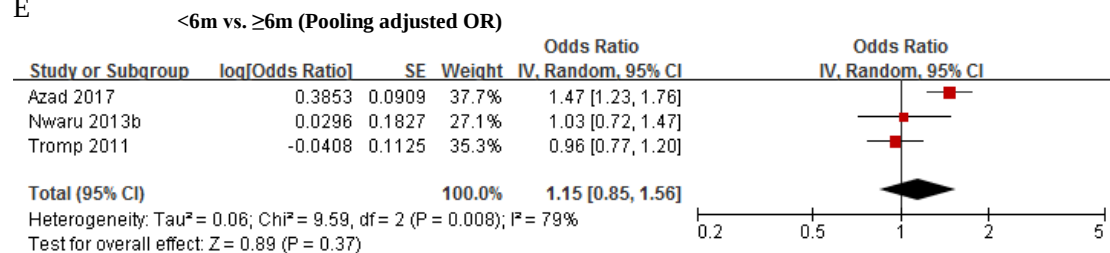
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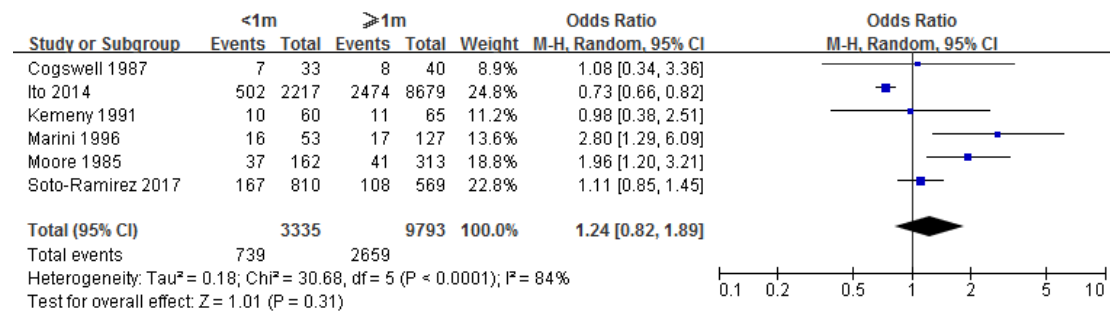


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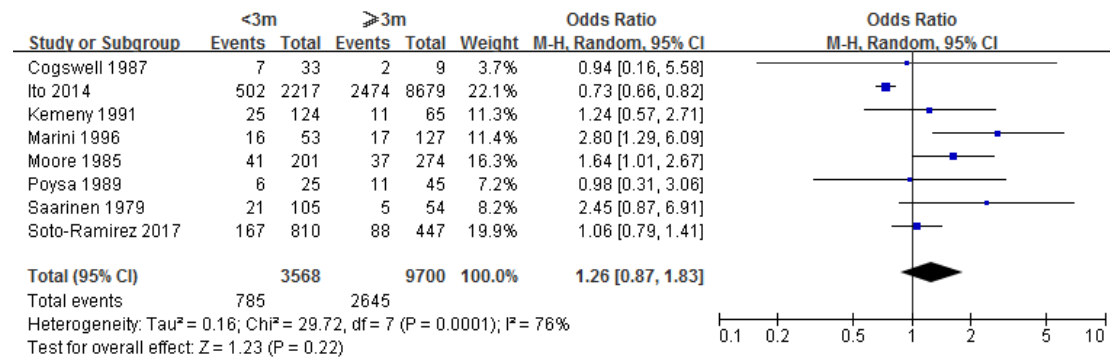


Supplemental Figure 3. Summary of risk of wheeze for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months; **(E)** exposure time <6 vs. ≥6 months, pooling adjusted OR

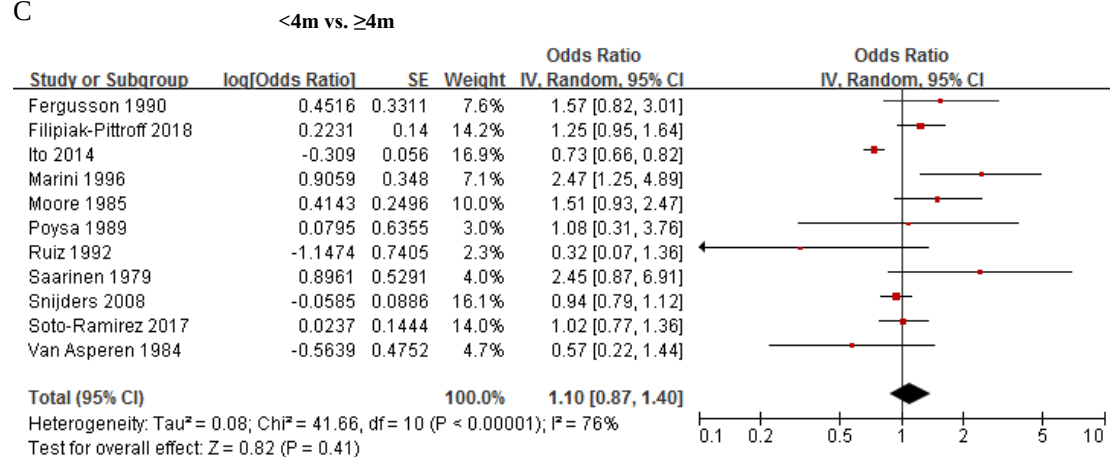
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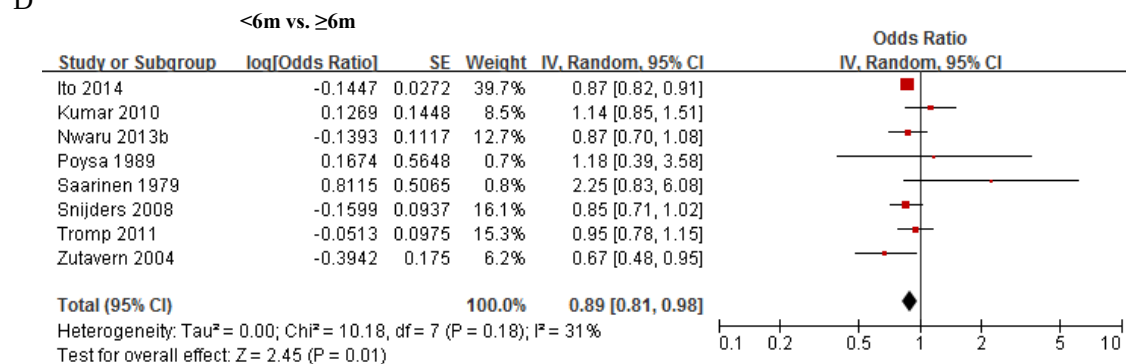
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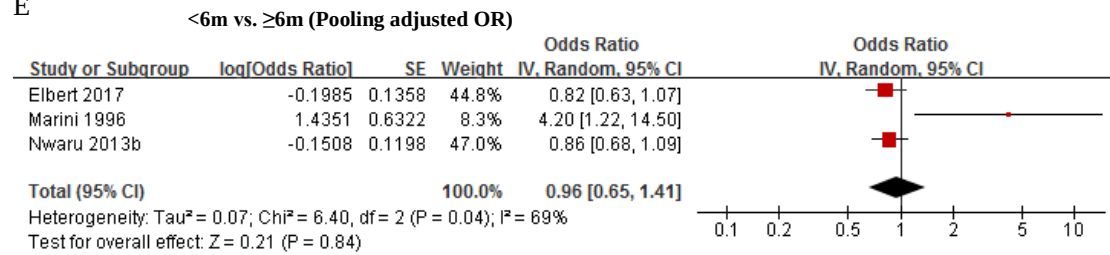
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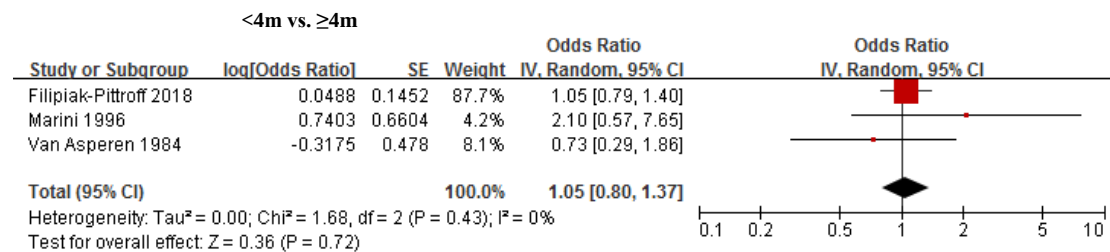
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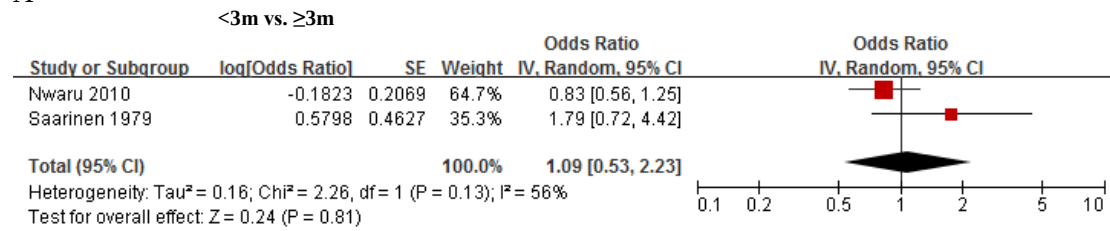


Supplemental Figure 4. Summary of risk of eczema/atopic dermatitis for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months; **(E)** exposure time <6 vs. ≥6 months, pooling adjusted OR

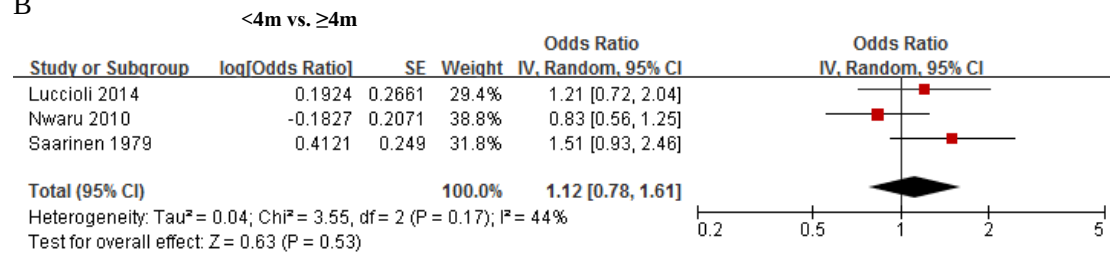


Supplemental Figure 5. Summary of risk of allergic rhinitis and/ or conjunctivitis for timing of cow's milk or cow's milk formula introduction from cohort studies: exposure time <4 vs. ≥4 months.

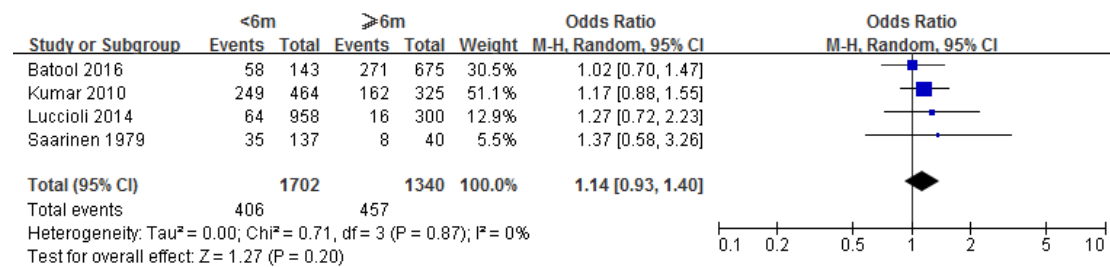
A



B

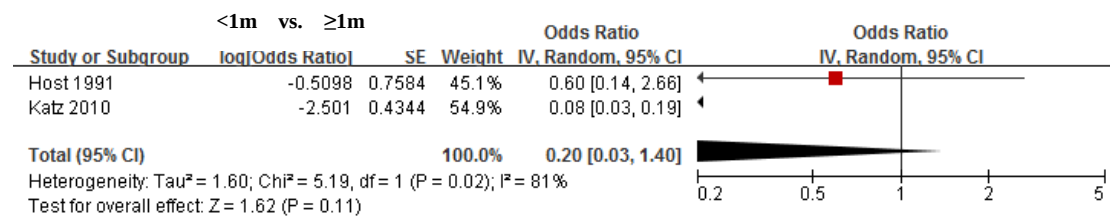


C

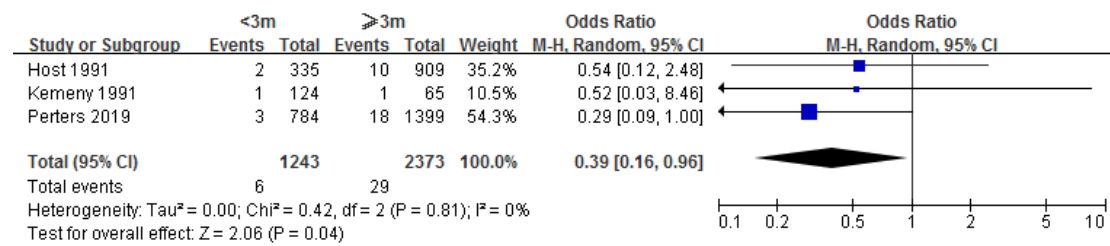


Supplemental Figure 6. Summary of risk of food allergy for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <3 vs. ≥3 months; **(B)** exposure time <4 vs. ≥4 months; **(C)** exposure time <6 vs. ≥6 months.

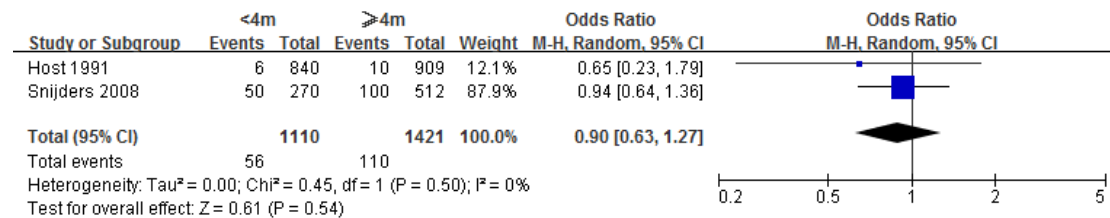
A



B

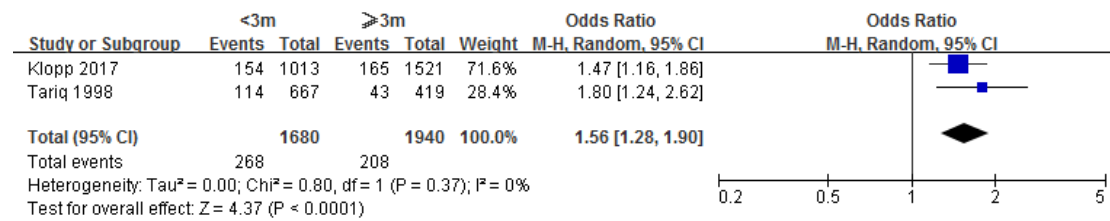


C

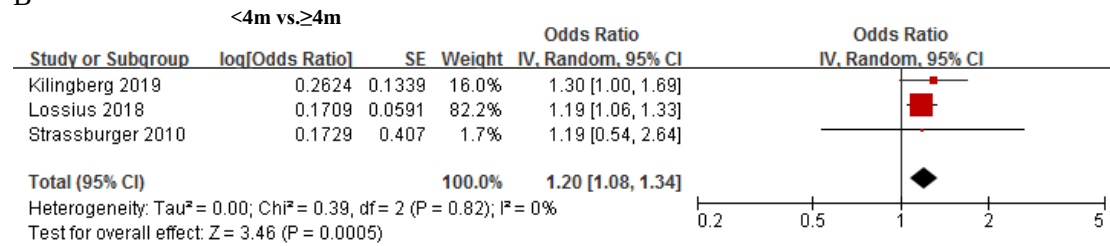


Supplemental Figure 7. Summary of risk of cow's milk allergy for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months.

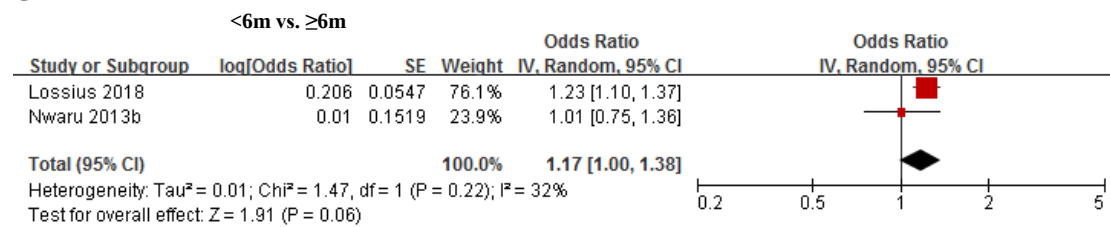
A



B

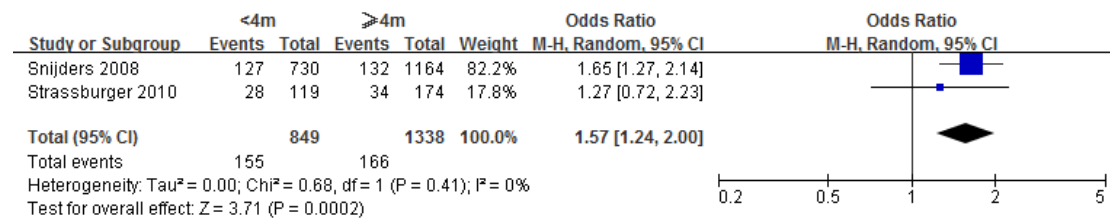


C

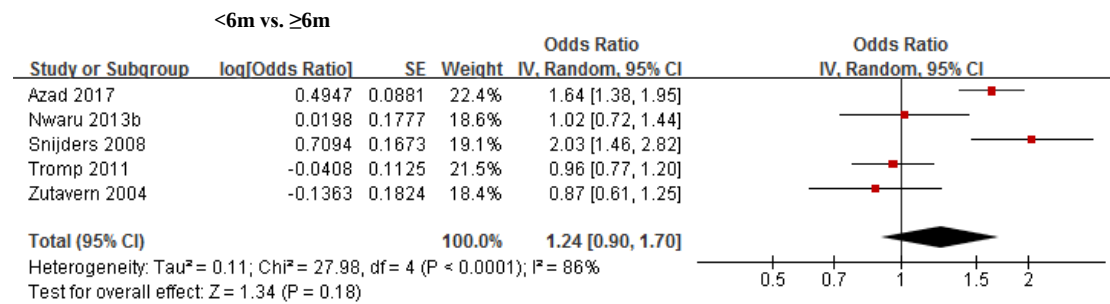


Supplemental Figure 8. Sensitive analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of asthma: **(A)** exposure time <3 vs. ≥3 month; **(B)** exposure time <4 vs. ≥4 months; **(C)** exposure time <6 vs. ≥6 month.

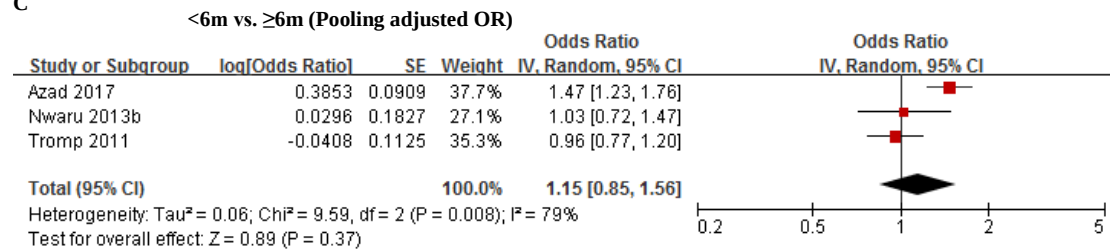
A



B

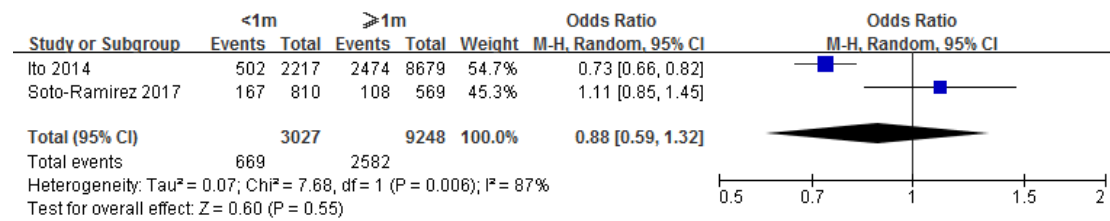


C

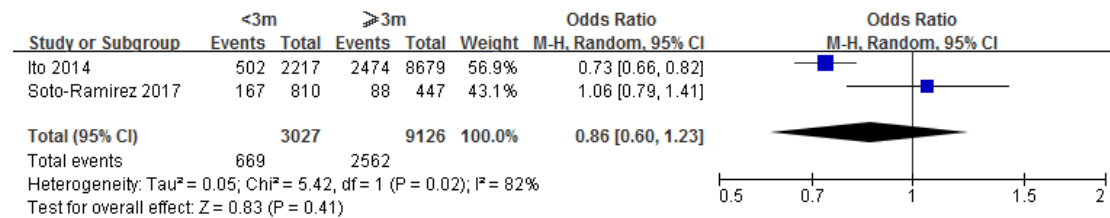


Supplemental Figure 9. Sensitive analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of wheeze: **(A)** exposure time <4 vs. ≥4 month; **(B)** exposure time <6 vs. ≥6 months; **(C)** exposure time <6 vs. ≥6 months, pooling adjusted OR

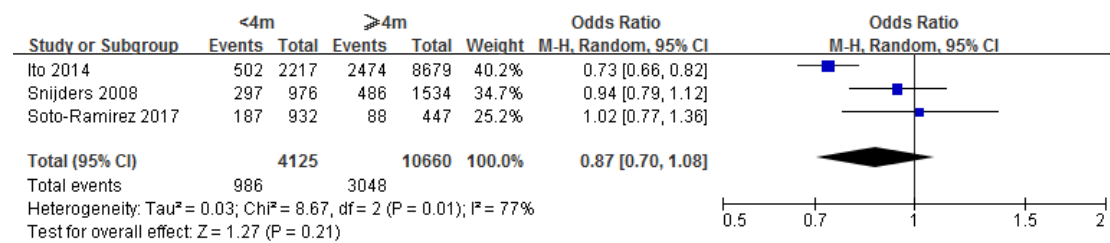
A



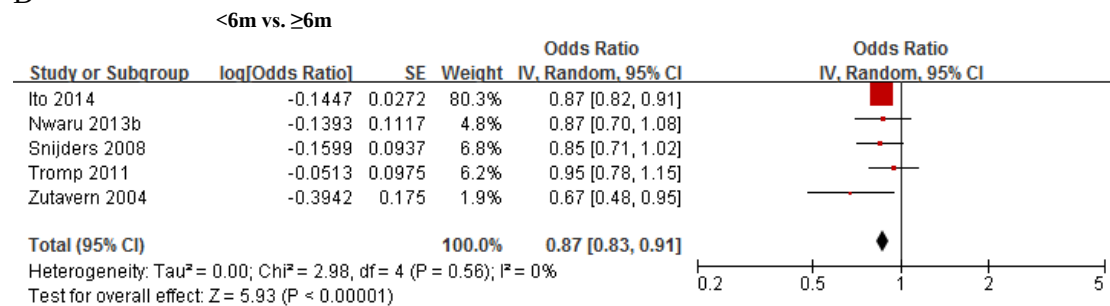
B



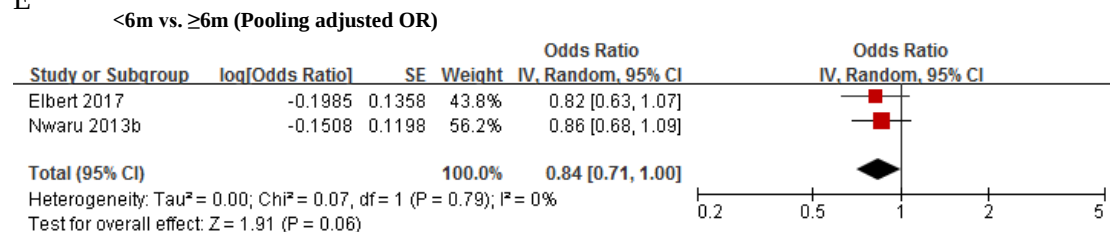
C



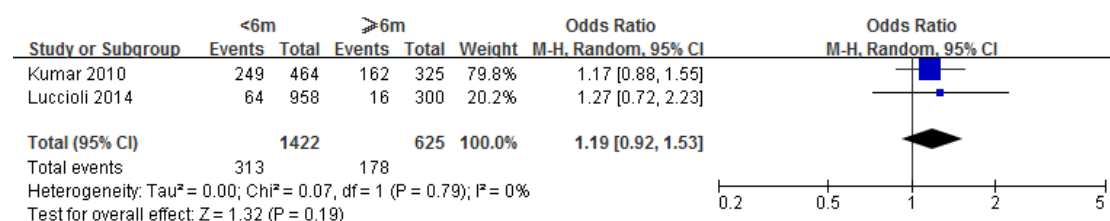
D



E

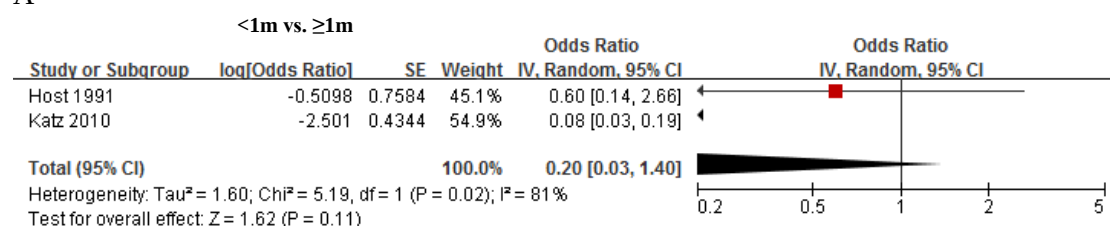


Supplemental Figure 10. Sensitive analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of eczema/atopic dermatitis: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months; **(E)** exposure time <6 vs. ≥6 months, pooling adjusted OR

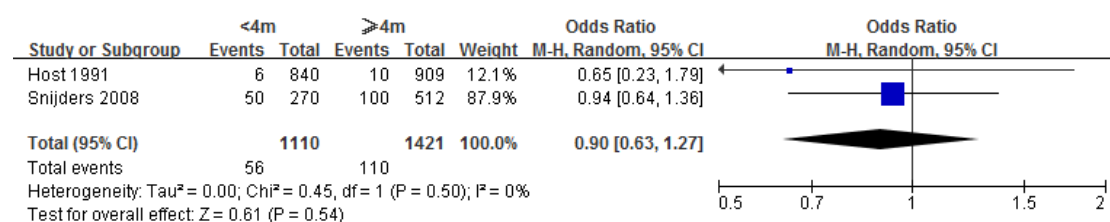


Supplemental Figure 11. Sensitive analysis of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of food allergy: exposure time <6 vs. ≥6 months.

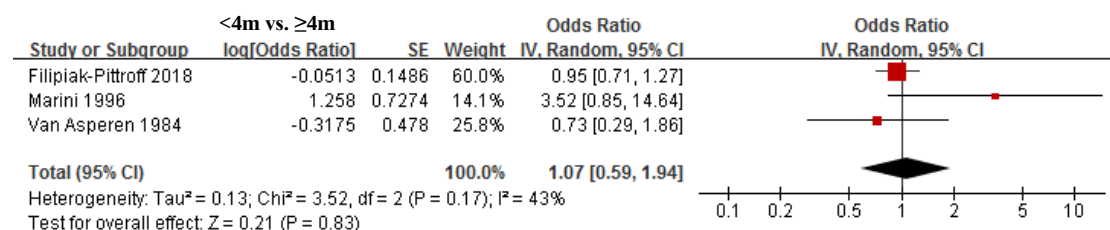
A



B

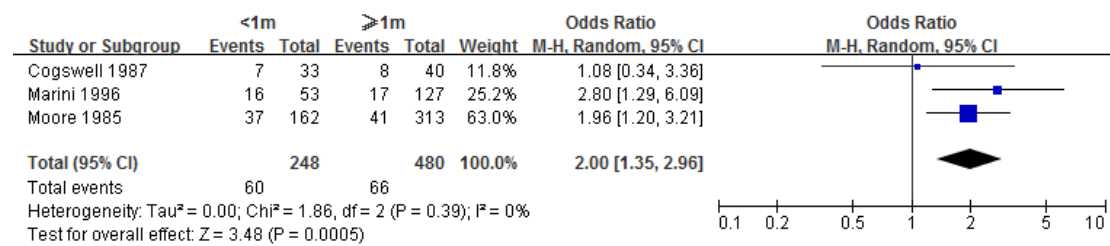


Supplemental Figure 12. Sensitive analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of cow's milk allergy: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <4 vs. ≥4 months.

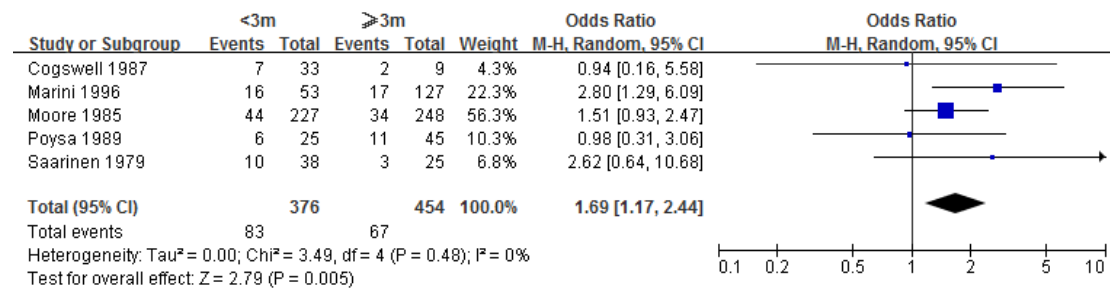


Supplemental Figure 13. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of wheeze: exposure time <4 vs. ≥4 months.

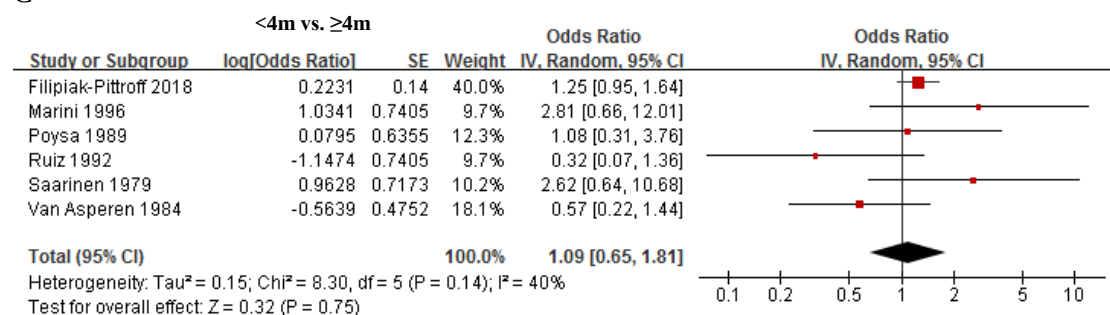
A



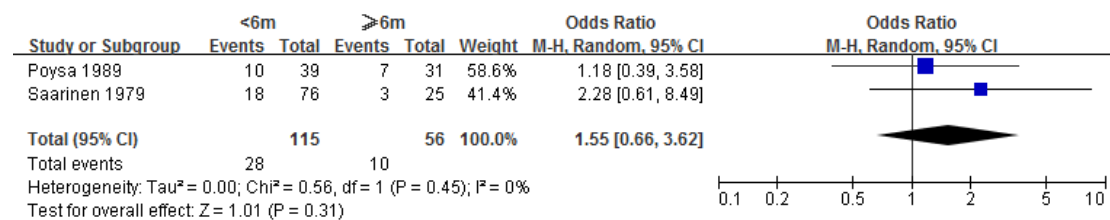
B



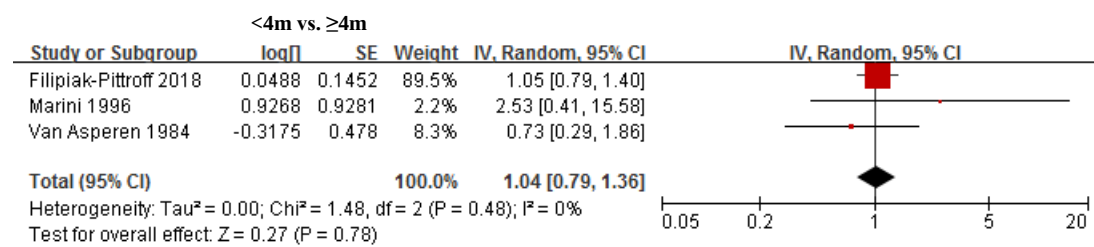
C



D

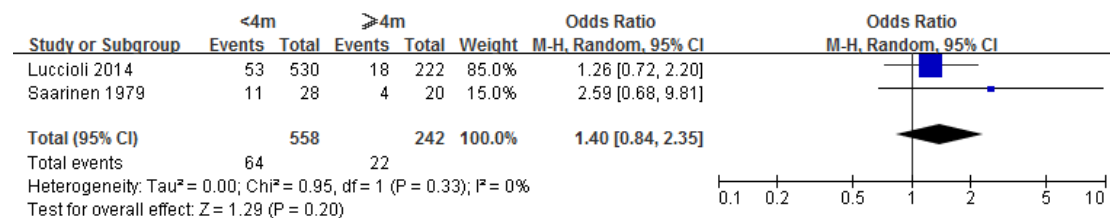


Supplemental Figure 14. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of eczema/atopic dermatitis: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months.

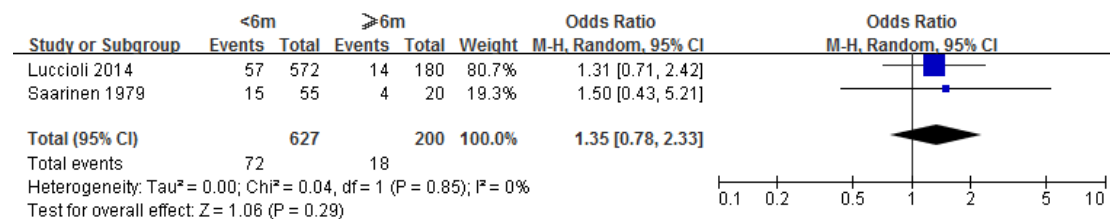


Supplemental Figure 15. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of allergic rhinitis and/ or conjunctivitis: exposure time <4 vs. ≥4 months.

A

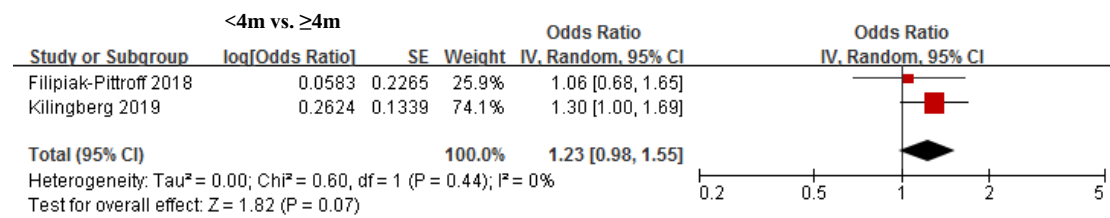


B

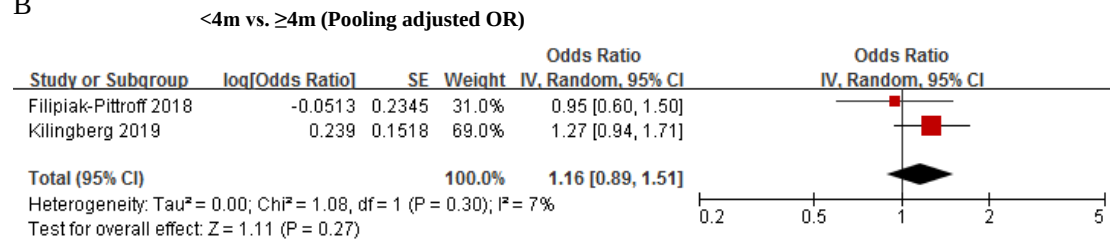


Supplemental Figure 16. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of food allergy: **(A)** exposure time <4 vs. ≥4 month; **(B)** exposure time <6 vs. ≥6 months.

A

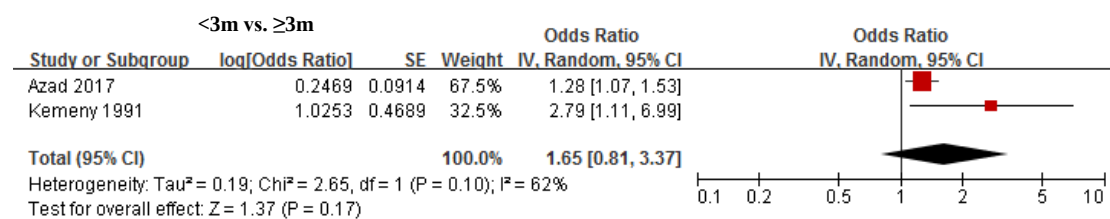


B

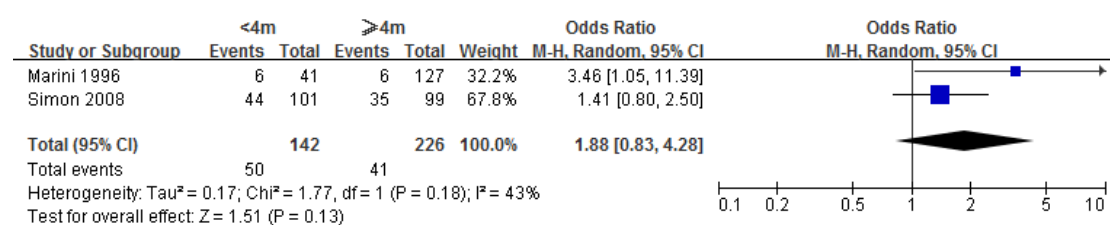


Supplemental Figure 17. Subgroup analysis on risk of asthma by excluding exclusive formula feeding children: **(A)** exposure time <4 vs. ≥4 month; **(B)** exposure time <4 vs. ≥4 months, pooling adjusted OR.

A

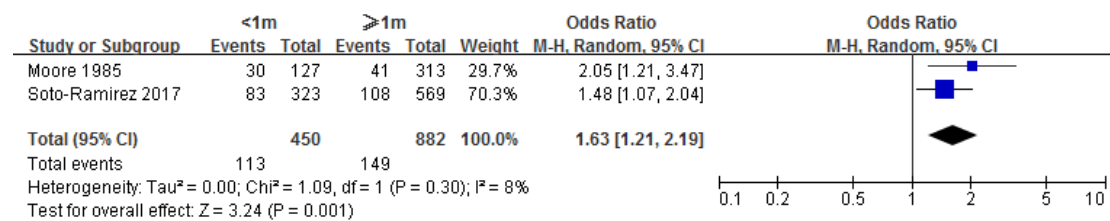


B

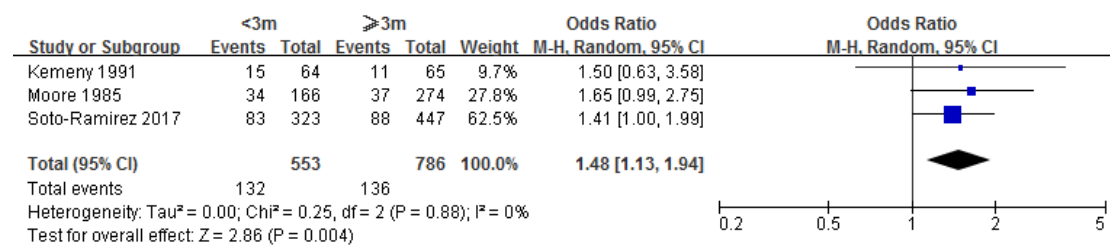


Supplemental Figure 18. Subgroup analysis on risk of wheeze by excluding exclusive formula feeding children: **(A)** exposure time <3 vs. ≥3 month; **(B)** exposure time <4 vs. ≥4 months.

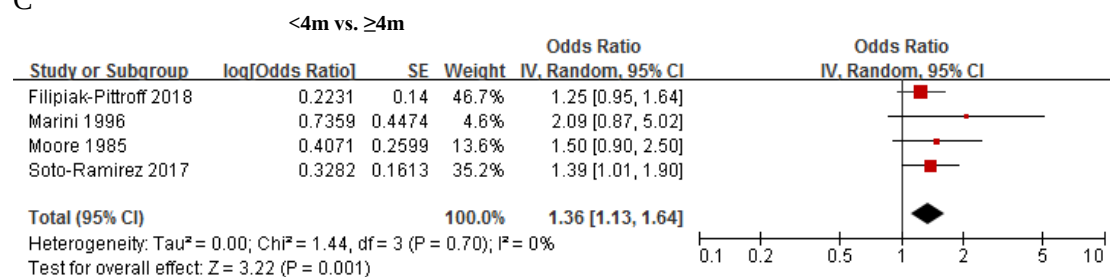
A



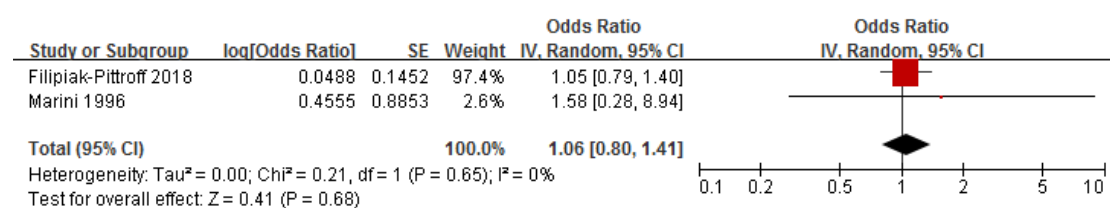
B



C



Supplemental Figure 19. Subgroup analysis on risk of eczema/atopic dermatitis by excluding exclusive formula feeding children: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4months.



Supplemental Figure 20. Subgroup analysis on risk of allergic rhinitis and/ or conjunctivitis by excluding exclusive formula feeding children: exposure time <4 vs. ≥4 month

Funnel Plots	P value for Begg's test																								
Effects of introducing CM or CMF before 4 months of age on risk of eczema or or atopic dermatitis from 11 cohort studies including 19276 subjects.																									
The funnel plot displays the standard error of the log odds ratio (SE(log(OR))) on the y-axis, ranging from 0 to 1. The x-axis represents the odds ratio (OR) on a logarithmic scale from 0.01 to 100. A vertical dashed line is positioned at OR = 1. There are 11 data points plotted, showing a general trend of increasing SE(log(OR)) as the OR deviates from 1. One point is notably lower than the others at approximately (0.3, 0.75). <table border="1"><caption>Estimated data points from the funnel plot</caption><thead><tr><th>OR (approx.)</th><th>SE(log(OR)) (approx.)</th></tr></thead><tbody><tr><td>0.3</td><td>0.75</td></tr><tr><td>0.5</td><td>0.45</td></tr><tr><td>0.6</td><td>0.35</td></tr><tr><td>0.7</td><td>0.25</td></tr><tr><td>0.8</td><td>0.15</td></tr><tr><td>0.9</td><td>0.10</td></tr><tr><td>1.0</td><td>0.15</td></tr><tr><td>1.1</td><td>0.15</td></tr><tr><td>1.2</td><td>0.25</td></tr><tr><td>1.5</td><td>0.35</td></tr><tr><td>2.0</td><td>0.50</td></tr></tbody></table>	OR (approx.)	SE(log(OR)) (approx.)	0.3	0.75	0.5	0.45	0.6	0.35	0.7	0.25	0.8	0.15	0.9	0.10	1.0	0.15	1.1	0.15	1.2	0.25	1.5	0.35	2.0	0.50	0.876
OR (approx.)	SE(log(OR)) (approx.)																								
0.3	0.75																								
0.5	0.45																								
0.6	0.35																								
0.7	0.25																								
0.8	0.15																								
0.9	0.10																								
1.0	0.15																								
1.1	0.15																								
1.2	0.25																								
1.5	0.35																								
2.0	0.50																								

Supplemental Figure 21. Evaluation of small study effects using funnel plots and Begg' tests.