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World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update – XIII – Oral immunotherapy for CMA – Systematic review

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ABSTRACT

Background: Allergy to cow's milk is the most common food allergy in infants and it is usually outgrown by 5 years of age. In some individuals it persists beyond early childhood. Oral immunotherapy (OIT, oral desensitization, specific oral tolerance induction) has been proposed as a promising therapeutic strategy for persistent IgE-mediated cow's milk allergy. We previously published the systematic review of OIT for cow's milk allergy (CMA) in 2010 as part of the World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines.

Objective: To systematically synthesize the currently available evidence about OIT for IgE-mediated CMA and to inform the updated 2022 WAO guidelines.

Methods: We searched the electronic databases including PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the websites of selected allergy organizations. We included all studies irrespective of the language of the original publication. The last search was conducted in February 2021. We registered the protocol on Open Science Framework (10.17605/OSF.IO/AH2DT).

Results: We identified 2147 unique records published between 2010 and 2021, including 13 randomized trials and 109 observational studies addressing cow's milk OIT. We found low-certainty evidence that OIT with unheated cow's milk, compared to elimination diet alone, increased the likelihood of being able to consume $\geq$150 ml of cow's milk in controlled settings (risk ratio (RR): 12.3, 95% CI: 5.9 to 26.0; risk difference (RD): 25 more per 100, 95% CI 11 to 56) as

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well as accidently ingest a small amount (≥5 ml) of cow's milk (RR: 8.7, 95% CI: 4.7 to 16.1; RD: 25 more per 100, 95% CI 12 to 50). However, 2–8 weeks after discontinuation of a successful OIT, tolerance of cow's milk persisted in only 36% (range: 20%–91%) of patients. OIT increased the frequency of anaphylaxis (rate ratio: 60.0, 95% CI 15 to 244; rate difference 5 more anaphylactic reactions per 1 person per year, 95% CI: 4 to 6; moderate evidence) and the frequency of epinephrine use (rate ratio: 35.2, 95% CI: 9 to 136.5; rate difference 268 more events per 100 person-years, 95% CI: 203 to 333; high certainty). OIT also increased the risk of gastrointestinal symptoms (RR 6.9, 95% CI 1.6–30.9; RD 28 more per 100, CI 3 to 100) and respiratory symptoms (RR 49.0, 95% CI 3.12–770.6; RD 77 more per 100, CI 62 to 92), compared with avoidance diet alone. Single-arm observational studies showed that on average 6.9% of OIT patients (95% CI: 3.8%–10%) developed eosinophilic esophagitis (very low certainty evidence). We found 1 trial and 2 small case series of OIT with baked milk.

Conclusions: Moderate certainty evidence shows that OIT with unheated cow's milk in patients with IgE-mediated CMA is associated with an increased probability of being able to drink milk and, at the same time, an increased risk of serious adverse effects.

Keywords: Milk allergy, Oral immunotherapy, Systematic review, Meta-analysis, GRADE

INTRODUCTION

Description of the condition

IgE-mediated cow's milk allergy (CMA) is the most common food allergy in infants, affecting approximately 2% of the population under 4 years of age worldwide.[1] International studies have highlighted significant between-country differences, with a reported incidence of IgE-mediated CMA ranging from less than 1% to about 2.3% in children aged up to 2 years.[2,3] Up to 50% of individuals suffering from CMA outgrow it by 3 to 5 years of age,[4–6] with further reduction during childhood and adolescence.[7,8] The prevalence of challenge-confirmed CMA in adults varies depending on the methods of data collection and outcome ascertainment,[9] ranging between 0.1% and 0.3%.[1,3,10,11]

Cow's milk is the third most common food, after peanut and tree nuts, to elicit food-induced anaphylaxis in pediatric and mixed-age populations responsible for 10 to 19% of cases,[12–14] even though recent report from the United Kingdom suggests a more prominent role for cow's milk.[15]

The mainstay of therapy is strict avoidance of cow's milk and using rescue epinephrine in the event of anaphylaxis.[16–18] However, eliminating cow's milk from the diet can be difficult and can pose nutritional as well as quality of life concerns since cow's milk is a ubiquitous food in many cultures and diets and is a prominent nutritional source in early childhood.[19] This adds to the already significant anxiety and quality of life impairment associated with the unpredictability of allergic reactions.[20]

Due to the scarcity of therapeutic options and the difficulty in implementing them, there is a growing public, medical, and commercial interest in the therapeutic potential of oral immunotherapy (OIT).[21–23]

Description of the intervention

OIT for CMA involves a titrated administration of cow's milk orally at regular intervals to modulate specific immune response to milk proteins in patients with CMA.

Despite the differences among published protocols,[24] they share some common key features. Usually, an OIT schedule begins with a build-up phase in which an increasing amount of milk is administered by a physician in a specialized clinical setting properly equipped in case of anaphylaxis. Thereafter, the highest tolerated dose is taken daily at home. The doses are usually increased either weekly or every other week until a

determined threshold dose is reached. At this stage, a maintenance phase begins, during which patients usually consume a daily consistent dose of cow's milk and dairy products (often the maximum tolerated amount at the end of a build-up phase). Schedules differ in number of doses, administered product (fresh or baked milk, mixed in different excipient types), amount of milk proteins per dose, interval in-between doses, and maintenance dose. Furthermore, multiple protocols have been developed for OIT either for single-food or for multiple-foods simultaneously.

The previous World Allergy Orgnization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines in 2010 were informed by a systematic review, which found an increased probability to safely consume milk following OIT treatment (ie, desensitization) as compared with avoidance diet alone.[25] Furthermore, the review highlighted how benefits in milk desensitization were associated with some safety concerns, namely a significant increase in the risk of allergic reactions and a greater necessity for rescue therapy. The aim of this review is to update our previous evidence synthesis and inform the novel WAO DRACMA guidelines.

METHODS

Search strategy and selection criteria

This is an update of the systematic review we performed in 2010.[25] A systematic literature search has been performed from January 2010 to February 2021. We ran separate searches for fresh milk and baked milk OIT. In both cases we have conducted searches for systematic reviews, randomized controlled trials (RCTs), and non-randomized studies (NRSs), in the data repositories described below:

a) Systematic reviews: PubMed (NLM), Cochrane Reviews, Database of Abstracts of Reviews of Effects, National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Agency for Healthcare Research and Quality (AHRQ), and Epistemonikos;

b) RCTs and NRSs: OVID Embase and MEDLINE, Cochrane Central Register of Controlled Trials, and PubMed (NLM).

We searched for published and unpublished data in any language comparing cow's milk OIT with no OIT (placebo or strict milk avoidance) for the treatment of CMA. A professional librarian in collaboration with clinical and methodology experts developed specific search strategies without any methodology filters or language restrictions. We also reviewed the references of identified studies and selected narrative review articles.

Searching for systematic reviews we also included guidelines reporting a systematic review investigating cow's milk OIT for IgE-mediated CMA. Searching for individual studies we included both RCTs and NRSs (with at least 5 patients) of cow's milk OIT (either fresh or baked) in patients with confirmed IgE-mediated CMA. We present a detailed description of the search strategies and the inclusion and exclusion criteria in the online Supplemental Appendices 1 and 2.

Types of outcome measures

The WAO DRACMA guideline panel members specified *a priori* all outcomes of interest for this review. Panel members also rated the relative importance of all outcomes for decision-making following the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[26,27] We sought information for outcomes classified as either critical or important. Outcomes critical to the decision were: anaphylaxis; use of intramuscular (IM) epinephrine, adverse events leading to treatment discontinuation; severe gastrointestinal symptoms; severe respiratory symptoms; generalized erythema or urticaria-angioedema; ability to drink cow's milk and eat dairy products without a reaction; ability to accidently consume a small amount of cow's milk without a reaction; tolerance of cow's milk when it is reintroduced after a period of not consuming milk and milk products (i.e. sustained unresponsiveness); and emergency department visits. We accepted study authors' definitions of severe adverse effects. The outcomes deemed important but not critical for the decision were: hospital admission; death; mild respiratory symptoms; lip or mouth pruritus; angioedema; eosinophilic esophagitis; quality of life of pediatric patients; quality of life of caregivers. The same set of outcomes and respective importance ratings were considered for OIT with both fresh and baked cow's milk.

Data collection, evaluation, and analysis

We screened titles and abstracts of the identified records and subsequently reviewed full-text articles in duplicate using standardized pre-piloted forms on Rayyan online software.

Any disagreements were resolved by consensus. We corresponded with investigators of primary studies, where appropriate, to clarify study eligibility and to request further information about missing results. We extracted data about methodological quality, characteristics of a trial, setting, eligibility criteria, population studied, intervention, comparator and outcomes of interest using a standardized data collection form in Microsoft Excel.

We used the Newcastle-Ottawa Scale (NOS) to assess the risk of bias (RoB) in NRSs and the revised Cochrane RoB tool for RCTs (RoB 2.0) separately for each outcome.[28,29] We classified studies as high RoB if at least 1 domain suggested the high risk. We evaluated the certainty of evidence (ie, quality of evidence or confidence in the estimates of effects) for each outcome following the GRADE methodology.[26,27]

For the assessment of treatment effects, we analyzed outcomes following the intention-to-treat principle.[30] When a single study was published in multiple reports, we used relevant data from all reports and analyzed them as a single study. When appropriate, we combined the results across studies using meta-analysis. We used DerSimonian-Laird random-effects model unless specifically stated otherwise.[30]

For single-arm observational studies we used the restricted Maximum-Likelihood random-effects model to estimate the pooled weighted proportion for dichotomous data (ie, outcome that occurred only once in a single person) and the pooled incidence rate for count data (ie, outcome that could occur more than once in a single person). For studies with a comparison group, we estimated a pooled risk ratio (RR) for dichotomous data and a pooled incidence rate ratio[23] for count data. For outcomes with zero events in 1 or both groups in any study we employed a continuity correction either by adding 0.5 at the numerator as described by Yates, or by adding the reciprocal of the opposite group arm size.[31,32]

For frequency data, we estimated person-time of follow-up by multiplying the number of participants by the reported duration of observation. We combined logarithmically transformed data and converted the results back to counts (*nota bene*: the numbers in the attached forest plots are natural logarithms of the outcome data). We estimated the absolute effects for dichotomous data by multiplying pooled RR by the baseline risk in the control groups and for the count data by an incidence rate difference (IRD) meta-analysis.

We evaluated the heterogeneity among studies by visual examination of forest plots and using χ^2 and I^2 statistics. We evaluated the publication bias visually by inspecting funnel plots if at least 10 studies were available for a given outcome.

We did all statistical analyses using jamovi version 1.6.[33] We used GRADEpro to create the summary of findings tables.[34]

We conducted and reported this systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), GRADE, and Cochrane standards.[30,35-37] We registered the protocol for this review in Open Science Framework (10.17605/OSF.IO/AH2DT). All decisions regarding the research question, analytic approach and RoB assessment were defined *a priori*.

RESULTS

Existing systematic reviews

We found 8 systematic reviews published after the previous WAO DRACMA guidelines in 2010 that included studies of cow's milk OIT.[25,38-44] No review was recent enough and/or reported outcomes of interest to be used for the WAO DRACMA guidelines without an update.

Included studies

Searching for individual studies we identified 2672 records and reviewed 336 full-text articles (Fig. 1). The most recent update of the search was in February 2021. We included 188 reports of 13 RCTs and 109 NRS. Of the included studies, 1 trial and 2 NRSs reported OIT with baked milk.[45-47] All reports on the same study were regarded as a single study in the analyses. Online Supplemental Table 1 provides a thorough

description of the included studies; while Online Supplemental Table 2 shows the records excluded during full-text screening together with reasons for exclusion.

Randomized studies enrolled 454 participants (mean across trials: 35, range: 11 to 60), aged 8.4 years on average (mean range, 2–14 years), undergoing OIT (whole milk: 10 trials, pasteurized milk: 2 trials, baked milk: 1 trial) compared with no OIT (placebo: 5 trials, avoidance diet only: 7 trials). One trial[48] failed to disclose data regarding the comparator and was therefore excluded from any subsequent analysis. A total of 6131 participants was enrolled in the included NRSs (median 35; range 5–710), with a median age of 7.5 years (range 3 months–32 years). Milk allergy was confirmed by oral food challenge (OFC) at study entry in 11 RCTs and 69 NRS. The trials presented a marked heterogeneity in terms of subjects' baseline milk tolerance, which ranged from 0.5 ml to 200 ml of whole milk. The median target dose for desensitization was set to 200 ml whole milk, ranging from 76 ml[49] to 300 ml. RoB was high in 4 trials.[50–53] There were "Some Concerns" about the RoB in 6 of the included RCTs.[47,49,54–57] The other trials reporting relevant outcomes were judged to be at low RoB.[58,59] We have deemed the RoB to be not significantly different across the individual reported outcomes. The full assessment of the RoB for RCTs is available in the Online Supplemental Table 3. We did not detect any strong evidence of publication bias for all outcomes. We judged the RoB in the observational studies as high since all were single-arm studies requiring implicit comparison with historical controls (Online Supplemental Table 4).

Effects of interventions

OIT with fresh milk

Ability to drink cow's milk and eat dairy products without a reaction

In 8 trials[49,51,54–59] (283 participants; follow-up: 4–11 months), OIT might have increased the probability of completing a food challenge with ≥150 ml of cow's milk (risk ratio: 12.34, 95% CI:

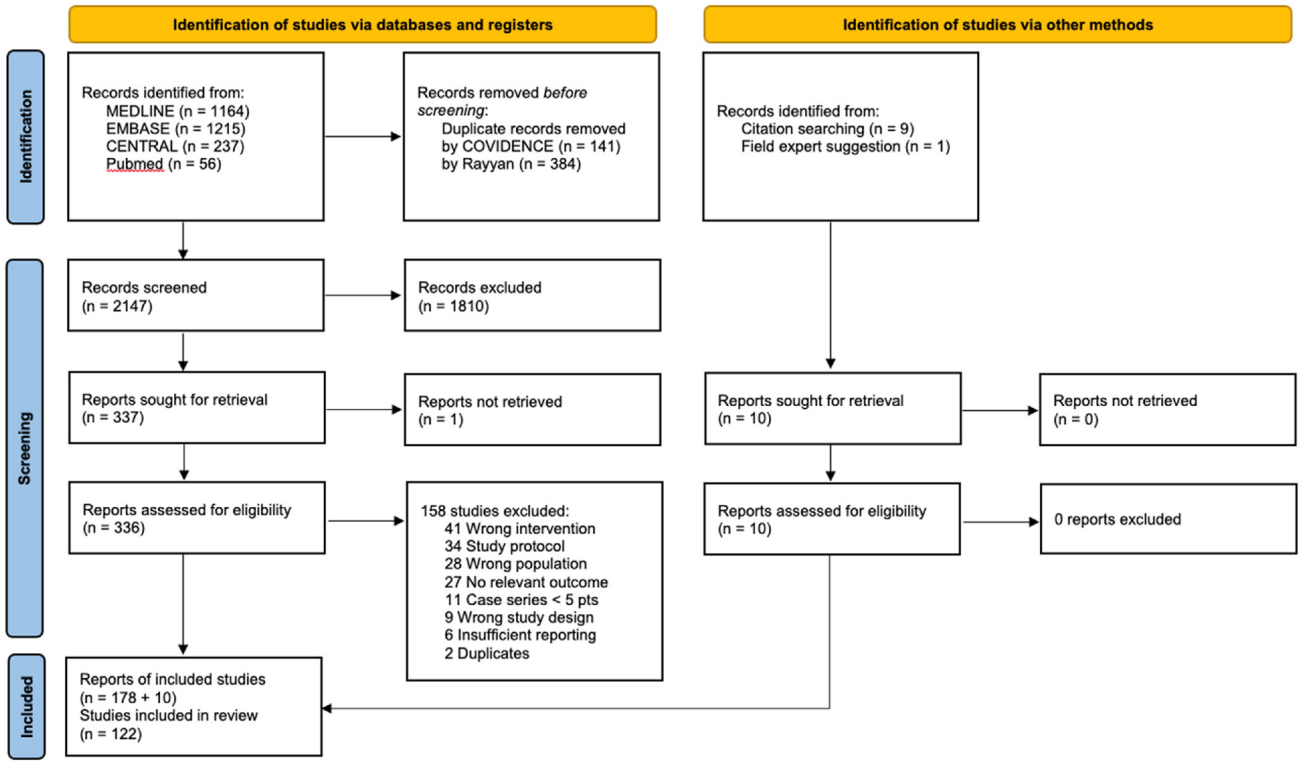

Fig. 1 PRISMA diagram for the flow of records/studies through the study selection process

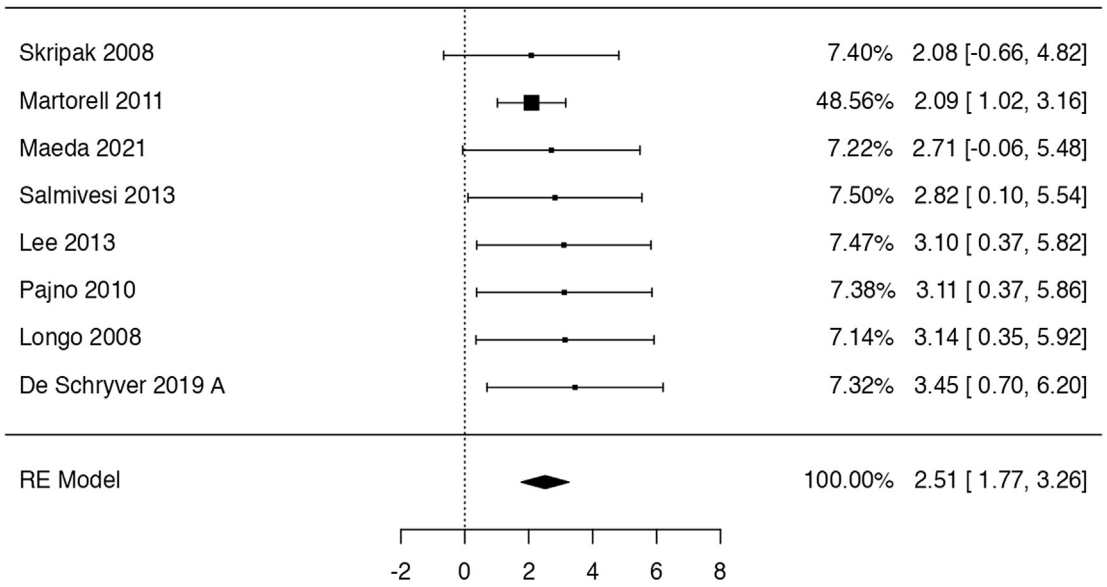

Fig. 2 Logarithm of the risk ratio of consuming at least 150 ml of milk in the RCTs

5.86 to 25.99; risk difference: 25 more per 100 patients, 95% CI: 11 to 56 more; Fig. 2). One additional study[52] explicitly included only children that could tolerate at least 60 ml of milk at baseline and found a smaller effect of OIT (risk ratio: 1.44, 95% CI: 0.98 to 2.11). Another RCT[50] published as a conference abstract reported desensitization in 4/11 children receiving OIT but failed to disclose outcome data of the control group (n = 4). We have considered the evidence for this outcome to be of low certainty due to serious indirectness, as it is not certain to what extent passing a graded food challenge represents the ability to drink milk in the real-world. There is also some risk of publication bias, as all studies were small, showing very large effects.

Ability to accidently consume at least a small amount of cow's milk (5 ml) without a reaction

Eight trials[49,51,53,55-59] completing a controlled oral food challenge with at least 5 ml of unheated milk (259 participants; follow-up: 4–11 months). The pooled results showed that OIT led to an increased probability of completing the oral food challenge with at least 5 ml of unheated milk (risk ratio: 8.67, 95% CI: 4.66 to 16.12; risk difference: 25 more per 100 patients, 95% CI: 12 to 50 more; Fig. 3). One study[51] did not report the outcome data for the control group. We have considered the study to have 0 cases among controls, then performed sensitivity analysis assuming the effect to be equal to the largest observed in other studies, which showed no difference in results or interpretation. We rated the certainty of the evidence as low due to serious indirectness as well as suspect of publication bias.

Desensitization to more than 5 ml of milk after an avoidance period

We identified 13 observational studies[60-72] (582 participants, with an avoidance period ranging from 2 to 8 weeks) with relevant data. Out of the cohort studies, only 4 reported usable data for both the intervention arms.[61,65-68] The analysis showed that OIT might increase the probability of not having an allergic reaction upon allergen reintroduction by oral food challenge (risk ratio: 3.35, 95% CI: 1.26 to 8.87; risk difference: 21 more per 100 patients, 95% CI: 2 to 72 more), but the evidence is very uncertain due to serious concerns of risk of bias and estimates' imprecision.

Anaphylaxis

Seven trials[49,51,54-56,58,59] reported either the number of patients who experienced anaphylaxis or the number of events of anaphylaxis per each group of patients. However, only 1 study[54] applied an accepted definition of anaphylaxis, considered as "the involvement of 2 organ systems and/or hypotension in response to a

Author(s): JLB, AB
Question: OIT with cow's milk compared to no IT for IgE-mediated CMA [SR]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT with cow's milk	no IT	Relative (95% CI)	Absolute (95% CI)		
Ability to drink cow's milk and eat dairy products without a reaction (follow-up: range 4 months to 11 months; assessed with: passing a supervised graded food challenge with >150 ml of cow's milk and/or ability to drink cow's milk and eat dairy products with no symptoms)												
10[1,2,3,4,5,6,7,8,9,10,a]	randomised trials	not serious[b]	not serious	serious[c]	not serious[d]	publication bias strongly suspected[e,f]	107/158 (67.7%)	3/135 (2.2%)	**RR 12.34** (5.86 to 25.99)[a]	**25 more per 100** (from 11 more to 56 more)	⨁⨁◯◯ Low	CRITICAL
Ability to accidentally consume a small amount of cow's milk without a reaction (follow-up: range 4 months to 11 months; assessed with: passing a supervised graded food challenge with ≥5 ml of cow's milk)												
10[1,2,3,4,5,6,7,8,10,a]	randomised trials	not serious[b]	not serious	serious[c]	not serious	publication bias strongly suspected[e,f]	107/137 (78.1%)	4/122 (3.3%)[x]	**RR 8.67** (4.66 to 16.12)	**25 more per 100** (from 12 more to 50 more)[x]	⨁⨁◯◯ Low	CRITICAL
								13.0%[x]		**100 more per 100** (from 48 more to 100 more)[x]		
Anaphylaxis (follow-up: range 6 to 17 months)												
7[1,2,3,4,5,6,11]	randomised trials	not serious[g]	serious[h]	not serious	not serious[i]	none	6 studies reported anaphylaxis but only one (De Schryver 2019) used current definition of anaphylaxis. Based on this study the rate of anaphylaxis was 0.01 per 1 person-year (i.e. 1 per 100 persons per year) without OIT and 5.5 per 1 person-year with OIT (rate ratio: 60.0; 95% CI: 15 to 244; rate difference: 5 more anaphylactic reactions per 1 person per year (95% CI: 4 to 6)). One study (Skripak 2008) defined anaphylaxis as "some combination of respiratory, gastrointestinal, and/or skin reaction" and reported similar results. Maeda 2021 reported that "the annual rate of anaphylactic symptoms was about one per patient" among those receiving OIT. The 4 remaining studies reported that there were no anaphylactic reactions, however, Salmviesi 2013 equaled anaphylaxis with epinephrine use and the other 3 studies did not provide the definition of anaphylaxis that was used.				⨁⨁⨁◯ Moderate	CRITICAL
Use of IM epinephrine (follow-up: range 4 to 12 months)												
9[1,2,3,4,5,6,7,8,11]	randomised trials	not serious[j]	not serious	not serious	not serious	none	85/134	2/120	**Rate ratio 35.16** (9.00 to 136.50)	**268 more per 100 patient(s) per year** (from 203 more to 333 more)[k]	⨁⨁⨁⨁ High	CRITICAL
Gastrointestinal symptoms (severe) (follow-up: range 4 to 17 months)												
5[1,3,4,5,6]	randomised trials	not serious[j]	not serious	serious[l]	serious[m]	none	45/91 (49.5%)	4/84 (4.8%)	**RR 6.9** (1.6 to 30.9)[n]	**28 more per 100** (from 3 more to 100 more)	⨁⨁◯◯ Low	CRITICAL
Severe respiratory symptoms/wheezing (follow-up: 12 months; assessed with: "nebulized epinephrine for respiratory symptoms")												
1[4]	randomised trials	not serious[j]	not serious	not serious	serious[o]	none	24/30 (80.0%)	0/30 (0.0%)	**RR 49.00** (3.12 to 770.59)	**77 more per 100** (from 62 more to 92 more)[k]	⨁⨁⨁◯ Moderate	CRITICAL
Generalized erythema or urticaria (follow-up: range 4 to 17 months)												
5[1,3,4,5,6]	randomised trials	not serious[j,p]	not serious	serious[q]	serious[r]	none	27/89 (30.3%)	7/82 (8.5%)	**RR 2.72** (0.76 to 9.68)[s]	**15 more per 100** (from 2 fewer to 74 more)	⨁⨁◯◯ Low	CRITICAL
Emergency department visit												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT with cow's milk	no IT	Relative (95% CI)	Absolute (95% CI)		
3[1,4,8]	randomised trials	serious[t]	not serious	not serious	very serious[u]	none	There were 4 events among 62 children in OIT group and no events in control groups. Six series of cases (Berti 2019, Longo 2012, Mantyla 2018, Ono 2018, Barbi 2012, Sugiura 2020) reported that a mean of 3.3% (95% CI: 0.5% to 6.2%) children receiving OIT required at least one ED visit.				⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. One study (Morisset 2007) explicitly included only children that could tolerate at least 60 ml of milk at baseline and found a smaller effect of OIT RR: 1.44 (95% CI: 0.98 to 2.11). Another RCT published as a conference abstract only reported tolerance in 4/11 children receiving OIT but did not report how many children achieved tolerance in control group (n = 4) (Filho 2015).
b. In some studies participants were not blinded but the results were consistent across all studies. Although the true effect might be smaller than the presented estimate, we did not rate down the certainty of evidence for risk of bias given the very strong association.
c. It is not certain whether all those passing a graded food challenge in a clinic will also be able to tolerate an equivalent total amount of milk without a graded challenge.
d. Total 85 events among 217 patients
e. There is some suggestion of publication bias as all studies were small and all showed very large effect. We did not reduce the certainty of evidence because we already reduced it for indirectness.
f. There was a very large association that does increase the confidence in the estimated effect on an indirect outcome. However, because of this indirectness we thought that very strong association may not apply to the outcome of interest.
g. The only study (De Schryver 2019) that reported direct evidence was not blinded and was stopped early because of apparent benefit. However, both of those biases are likely to underestimate adverse effects.
h. 2 studies reported the rate of anaphylaxis with OIT between 4.7 and 5.5 per person per year and other 4 studies reported no anaphylactic reactions with OIT. This difference could not be explained with population characteristics or the type of OIT. It is possible that the difference is related to the definition of anaphylaxis used in individual studies; 3 studies did not report what definition was used. We did not reduce the certainty because of indirectness (one study provided a direct outcome measure) but rather because of inconsistency, as they seem to be related.
i. We did not lower the certainty because of imprecision, because the results of one study that could be used provided precise estimates. If data from other studies could be used then the judgment about precision might change.
j. Most studies were not blinded but it is unlikely that this would overestimate the risk of adverse effects.
k. There were no events in control groups; 95% CI around the risk difference was estimated from risk difference meta-analysis.
l. Studies did not report GI symptoms consistently – some may have had very different importance for patients than the others.
m. The CI does not exclude an appreciably increased risk of GI symptoms or no difference.
n. In 2 studies the rate of reactions per patient was reported. Across these studies the rate of GI symptoms was 21.4 times higher (95% CI: 8.9 to 51.8) with OIT than without.
o. Only 24 events; 95% confidence interval does not exclude an appreciable benefit or an appreciable harm.
p. Few studies reported this outcome that we considered obvious to measure and report; in general adverse effects were reported inconsistently, using variable definitions, and sometimes precluding meaningful conclusions.
q. The severity of symptoms was not reported in any of the relevant included studies.
r. There were only 34 events and the pooled confidence interval does not exclude harm from OIT or no difference.
s. Two additional studies measured urticaria as rate of events per patient. Rate of generalized urticaria was 8.3 times higher (95% CI: 3.2 to 21.1) with OIT than without.
t. Only 2 of 7 studies reported this outcome.
u. Only 2 events in one study.

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Table 1. Evidence Profile of fresh milk OIT compared to no OIT

cow's milk protein exposure". The rate of anaphylaxis in this study was 1 per 100 patient-years with elimination diet alone and 550 per 100 person-years with OIT (rate ratio: 60.0, 95% CI: 15 to 244). In another study, Skripak and colleagues[49] defined anaphylaxis as "some combination of respiratory, gastrointestinal, and/or skin reaction" and reported the effect estimates pointing in the same direction (rate ratio: 790, 95% CI: 0 to 3 × 10^9). The remaining 5 studies reported no anaphylactic reactions; however, they either did not provide the definition of anaphylaxis that they used or equated it with epinephrine use (Table 1).

Use of intramuscular (IM) epinephrine (adrenaline)

Nine trials[49,51,53–59] reported data on intramuscular (IM) epinephrine injection, with a

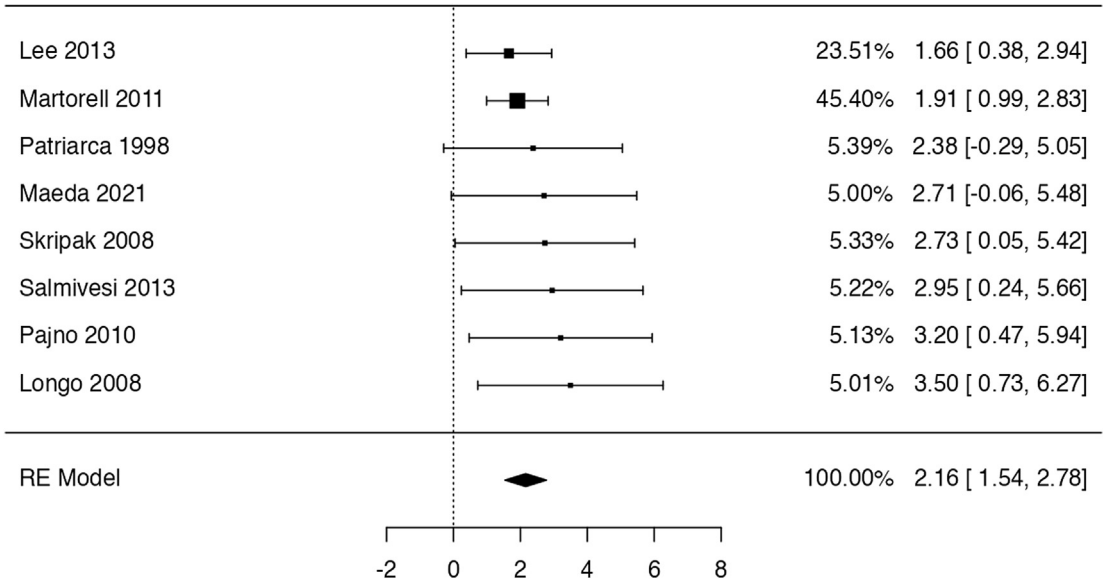

Fig. 3 Logarithm of risk ratio for consuming at least 5 ml of milk in the RCTs

follow-up range of 4–12 months. In 8 studies,[49,51,53–58] OIT increased need for IM epinephrine (rate ratio: 35.16, 95% CI: 9 to 136.5; rate difference: 268 more per 100 patient -years 95% CI: 203 to 333 more per 100 patient-years; Fig. 4). The finding was supported by the combined relative estimates from studies[49,51,53,55,57,59] reporting dichotomous outcomes both for the induction and maintenance phases (risk ratio: 2.2, 95% CI: 0.57 to 8.58 for induction; 3.1, 95% CI: 0.85 to 11.17 for maintenance).

Adverse effects leading to the discontinuation of treatment

In 8 trials,[49,51,54–59] with 306 patients, OIT likely increased the risk of discontinuing treatment due to adverse effects, but the estimates are imprecise (risk ratio: 1.92, 95% CI: 0.92 to 3.99; risk difference: 6 more per 100 patients, 95% CI: from 0 to 18 more; Fig. 5). One study[54] did not report whether 4 discontinuations in the control group were due to AE. We assumed they were, but if we had assumed the discontinuations to be not AE-related, still there would have been no

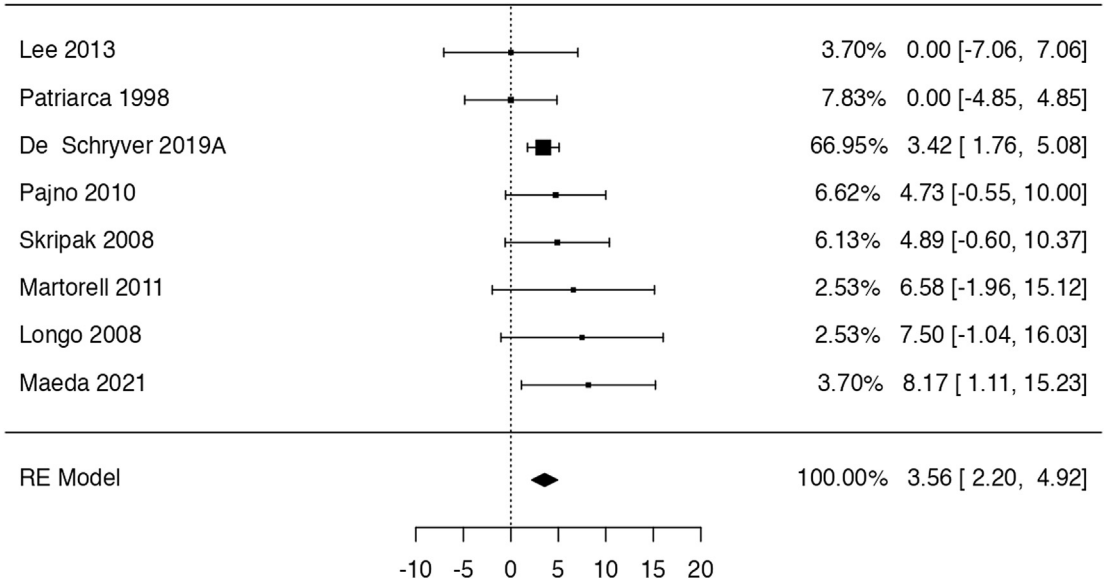

Fig. 4 Logarithm of the rate ratio of IM epinephrine injections per patient-month in the RCTs

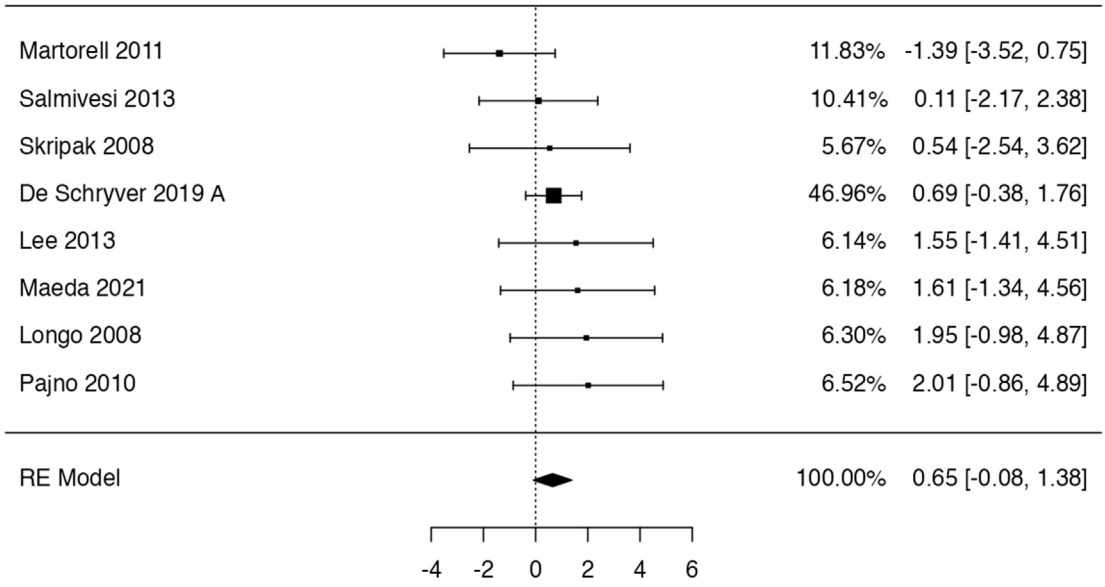

Fig. 5 Logarithm of the risk ratio of AE leading to discontinuation of treatment in the RCTs

difference in the effect estimate (risk ratio: 2.52, 95% CI: 0.9 to 7.1; risk difference: 9 more per 100 patients, 95% CI: from 1 fewer to 38 more). The certainty of evidence for this outcome was rated as moderate, given the limited number of events among both groups (only 31), and that the confidence interval includes both appreciable harm with OIT and no difference.

Severe gastrointestinal symptoms

Five trials[49,55,56,58,59] reported data on gastrointestinal symptoms (175 participants; follow up: 4–17 months), however no study provided information about their severity. Four studies[55,56,58,59] reported the risk of any GI symptoms. In these trials OIT might have increased the risk for developing any GI symptoms (risk ratio: 6.9, 95% CI: 1.6 to 30.9; risk difference: 28 more per 100 patients, 95% CI: 3 to 100 more; Fig. 6). The rate of GI reactions per patient was reported in 2 studies[49,55] and was 21.4 times higher with OIT than without (95% CI: 8.9 to 51.8). The certainty of evidence for this outcome was low, because of serious indirectness (no information about severity of symptoms) and imprecision.

Severe respiratory symptoms/wheezing

Only 1 trial[55] reported relevant data on severe respiratory symptoms, defined as "nebulized epinephrine for respiratory symptoms" (60 participants, 12 months follow-up). The risk of severe respiratory symptoms was likely higher among those who received OIT, compared with those who did not (risk ratio: 49, 95% CI: 3.1 to 770.6; risk difference: 77 more per 100 patients, 95% CI: 62 to 92 more). The certainty of evidence has been rated as moderate, due to the fragility of the results (only 24 events in 1 group) and some suspicion of reporting bias (only 1 study reported severe respiratory symptoms). Remaining studies either did not report this outcome or reported explicitly mild/moderate symptoms.

Generalized erythema and/or urticaria

We identified 5 studies reporting relevant data, but severity of symptoms was not described in any. In 4 trials[55,56,58,59] with a total of 171 participants and 4–17 months of follow-up OIT might have increased the risk of generalized erythema or urticaria, but the confidence interval did not exclude appreciable harm or no effect (risk ratio: 2.72, 95% CI: 0.76 to 9.68; risk difference: 15 more per 100 patients, 95% CI: 2 fewer to 74 more; Fig. 7). Two studies[49,55] reported the rate of events per patient, which was found to be 8.3 times higher (95% CI: 3.2 to 21.1) with OIT than without. We considered this outcome to be of low certainty due to serious imprecision and indirectness.

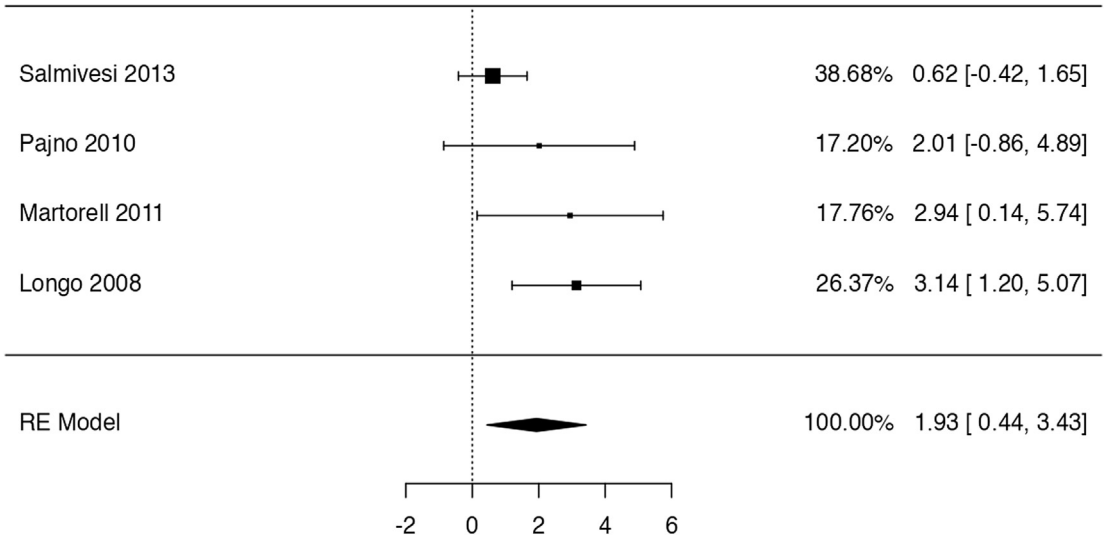

Fig. 6 Logarithm of the risk ratio of gastrointestinal AE in the RCTs

Angioedema

Four included trials[55,56,58,59] (111 participants, with follow-up from 4 to 17 months) reported the occurrence of angioedema. One study[55] failed to disclose data for both the intervention arms, hence we excluded it from this analysis. The pooled estimate showed that OIT probably increases the risk of angioedema (risk ratio: 4.66, 95% CI: 0.85 to 25.85; risk difference: 12 more per 100 patients, 95% CI: 2 to 22 more). Considering the imprecision in the resulting effect estimate, we have judged the evidence to be of moderate certainty.

Emergency department visit

Only 3 RCTs[55,57,59] reported emergency department visits. There were 4 events among 62 children receiving OIT, and none in the control group. Since there were no events in any control group, we did not calculate a pooled risk ratio but rather estimated a pooled proportion of emergency department visits in those receiving OIT which was 5% (95% CI: 0 to 10). The certainty of the evidence for this outcome has been rated as very low due to very serious imprecision and risk of bias. Because of the very low certainty evidence from RCTs we also reviewed 6 single-

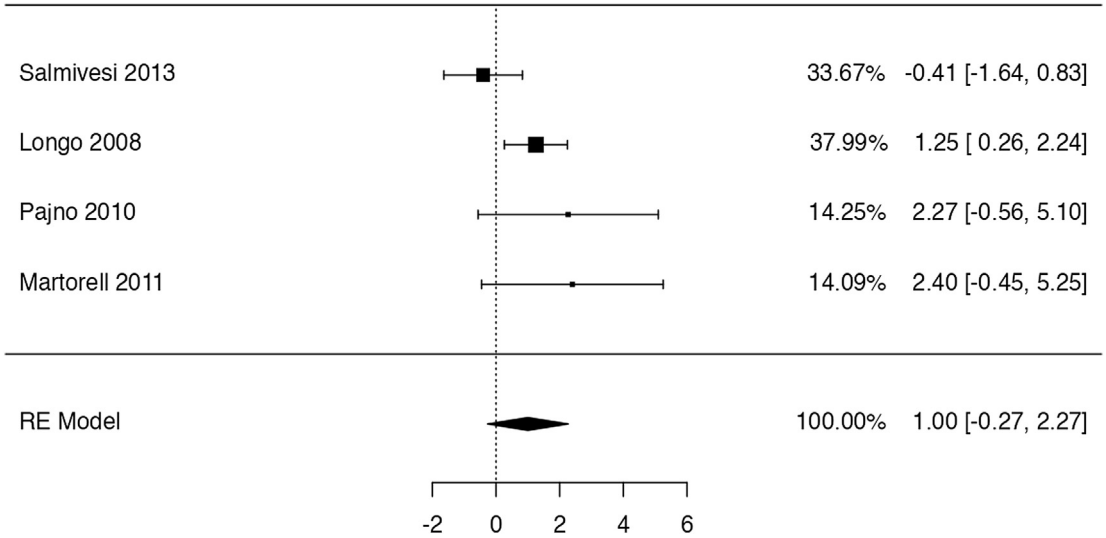

Fig. 7 Logarithm of the risk ratio of generalized erythema or urticaria in the RCTs

arm studies[73-78] in which the pooled proportion of emergency department visits was 3.3% (95% CI: 0.5%–6.2%).

Hospital admission

No RCT reported hospital admissions. Six non-randomized studies[73,74,76,79-81] reported that there were no hospitalizations among the 264 patients.

Lip or perioral pruritus

We found 4 trials[51,55,56,59] (144 participants, with follow-up from 4 to 17 months) reporting on this outcome, yet 1 study[51] failed to disclose the control group data, hence it has been excluded from this analysis. The quantitative analysis showed that OIT might increase the risk to present perioral pruritus (risk ratio: 12.76, 95% CI: 2.5 to 65.4; risk difference: 17 more per 100 patients, 95% CI: 2 to 95 more; Fig. 8). The certainty of the evidence for this outcome has been rated as low due to imprecision in effect estimates as well as concerns about risk of bias.

Eosinophilic esophagitis

Fourteen series of cases[82-95] (1545 participants with 2 years follow-up) reported that, on average, 6.9% (95% CI: 3.8%–10%) of patients receiving OIT developed eosinophilic esophagitis (EoE) (Fig. 9). The certainty of the evidence has been rated as very low due to indirectness (EoE was not confirmed with biopsy in most studies) and very serious concerns about risk of bias. The synthesis from studies with biopsy sampling yielded a slightly more conservative mean percentage of 5.0% (95% CI: 4.5%–5.4%).

Death

Seven trials (follow-up: 4–11 months) reported no deaths in either intervention or control groups, with an overall study population of 277 children between 2 and 14 years of age.[48,50,51,54-56,58] The certainty of the evidence has been rated as high.

Impact on quality of life

Five observational studies[96-100] reported relevant data, with the outcome being measured after a median of 5 months following the OIT (range 1–43 months). In 4 of these studies, the authors employed either the parent or patient forms of the food allergy quality of life (FAQL) questionnaires. Epstein Rigbi and colleagues asked parents to assess the QoL of their children (n = 82; mean age 6 years) using the food allergy quality of life questionnaire parent form (FAQLQ-PF; minimal important difference: 0.5 point).[96] Authors found that after 4 months of OIT total FAQLQ score improved in 37% of children, did not change in 38% and deteriorated in 26%. Carraro and colleagues also used FAQLQ-PF to assess QoL in 30 children (age: 3-12 years) 2 months after completion of OIT.[97] The authors did not report a total score or the proportion of children who improved or

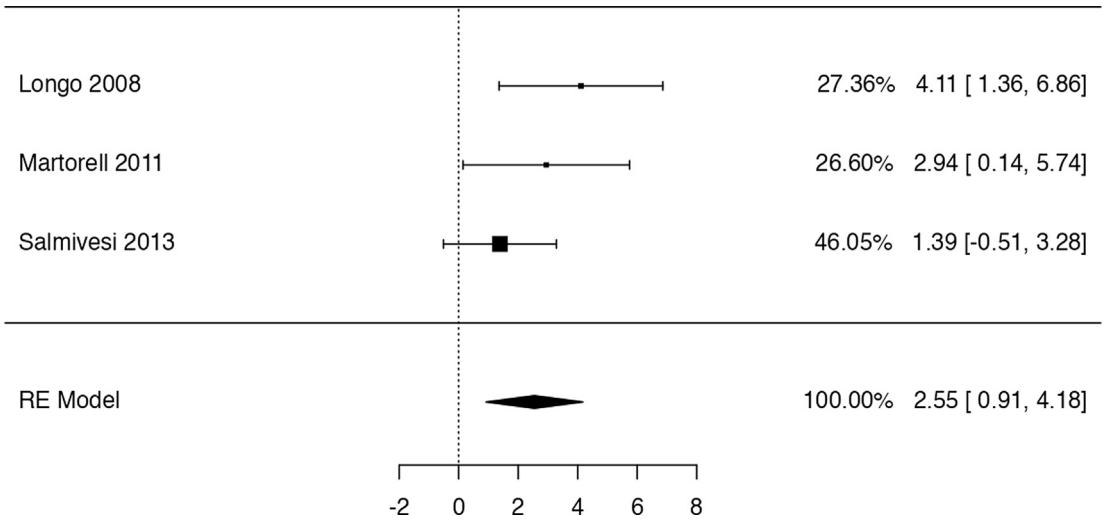

Fig. 8 Logarithm of risk ratio of manifesting perioral pruritus in the RCTs

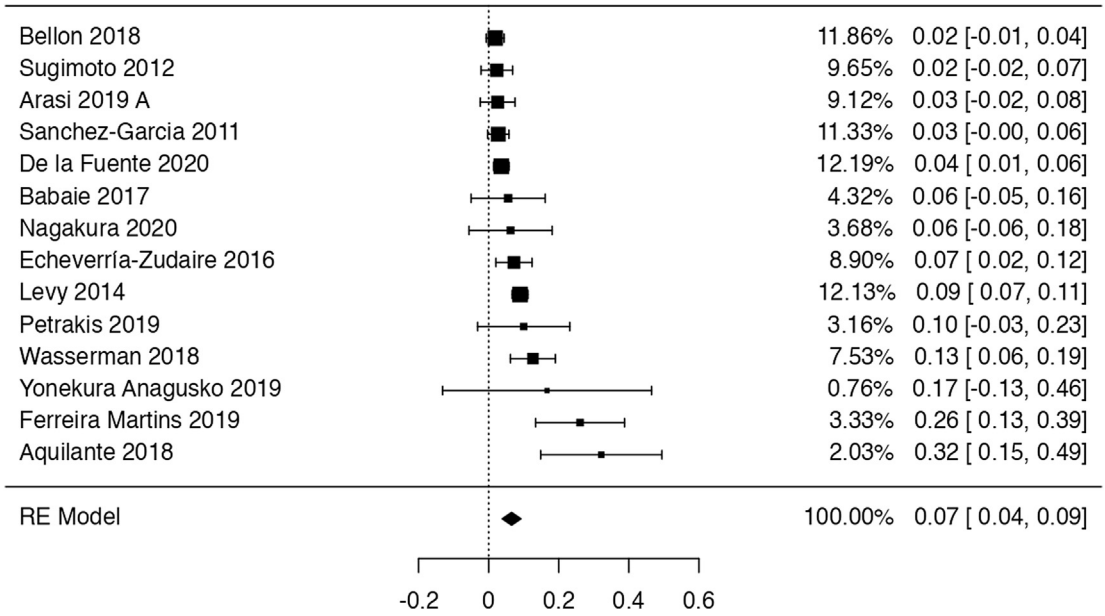

Fig. 9 Weighted mean proportion of patients developing EoE after OIT in the NRS

deteriorated by $\geq$ 0.5 points. However, they noted that a difference between the median pre and post-OIT scores of −0.7 point for emotional impact, −0.94 point for food-related anxiety, and −1.5 point for social and dietary limitations, which might show a potential overall improvement in QoL. Hayashi and colleagues reported their results only as a conference abstract.[98] Forty-six children with prior history of anaphylaxis underwent rush OIT. Study authors reported a consistent reduction in the percentage of both children and parents fearing the consequences of accidental allergen exposure or experiencing severe anxiety due to the allergic condition. Katz and colleagues assessed the QoL in 192 children 25 months after completion of OIT.[99] They also reported their results only as a conference abstract. The authors did not report how quality of life was measured but stated that 88.9% of children improved.

Kauppila and colleagues used both the FAQLQ and the generic health-related quality of life (HRQoL) questionnaires (15D, 16D, and 17D).[100] The authors measured the outcome post OIT in 295 patients (response rate for FAQLQ 48% and for generic HRQoL 54%). No difference in generic HRQoL was observed between OIT patients and the age- and gender-standardized general population. There was also no difference in the HRQoL scores between those who achieved desensitization and those who did not. However, mean FAQLQ scores were lower (better QoL) in those who achieved desensitization, compared with those who did not (FAQLQ-children, n = 47, score 1.7 vs 2.8; FAQLQ-teenager, n = 64, score 2.1 vs 2.9; FAQLQ-adult, n = 31, score 2.3 vs 2.7). We rated the certainty of the evidence as very low, due to very serious concerns of risk of bias and imprecision. Additionally, we noticed a major heterogeneity in the outcome measurement modalities across the included studies.

We have not found any eligible study measuring the impact of OIT specifically on caregivers' quality of life.

OIT with baked milk

We found 1 randomized controlled trial and 2 series of cases of OIT with baked milk among patients who did not tolerate both unheated and baked milk.[45-47] The mean follow-up for the 2 studies was 14 months. Tables 2A and 2B present the results of the studies.

The identified trial by Dantzer et al[47] shows that OIT with baked milk might increase the probability to ingest dairy products without a reaction (risk ratio: 23, 95% CI: 1.48 to 358; risk difference: 0 fewer per 100 patients). On the other hand, the study provides evidence of very low certainty for the remainder for the reported outcomes, not

Question: OIT with baked milk compared to no OIT in patients with IgE-CMA who do not tolerate baked milk

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baked Milk OIT	No OIT	Relative (95% CI)	Absolute (95% CI)		
Ability to drink cow's milk and eat dairy products without a reaction (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	11/15 (73.3%)	0/15 (0.0%)	**RR 23.00** (1.48 to 358.00)	**0 fewer per 100** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Use of IM epinephrine (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	3/15 (20.0%)	1/15 (6.7%)	**RR 3.00** (0.35 to 25.68)	**13 more per 100** (from 4 fewer to 100 more)	⨁◯◯◯ Very low	CRITICAL
Severe gastrointestinal symptoms (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/15 (6.7%)	1/15 (6.7%)	**RR 1.00** (0.07 to 14.53)	**0 fewer per 100** (from 6 fewer to 90 more)	⨁◯◯◯ Very low	CRITICAL
Severe respiratory symptoms/wheezing (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/15 (6.7%)	2/15 (13.3%)	**RR 0.50** (0.05 to 4.94)	**7 fewer per 100** (from 12 fewer to 52 more)	⨁◯◯◯ Very low	CRITICAL
Generalized urticaria or erythema (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	2/15 (13.3%)	1/15 (6.7%)	**RR 2.00** (0.20 to 19.78)	**7 more per 100** (from 5 fewer to 100 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life of children (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	Most of OIT patients experienced an overall improvement in QoL. The only age group in which a between-group comparison could be done was children between 8-12 years of age, surveyed through the FAQOL-CF questionnaire (OIT: 5; Placebo: 5). The results suggest that patients in the OIT arm, were more likely to have a QoL improvemement (>0.5 MCID).				⨁◯◯◯ Very low	IMPORTANT
Quality of life of the caregivers (follow-up: 12 months)												
1[1]	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	The parents of 26 patients (OIT: 12; Placebo: 14) were surveyed through the FAQOL-PF questionnaire. The results highlighted no overall difference between groups, but the parents in the placebo arm appeared more likely to experience an improvement (>0.5 MCID) in the emotional domain.				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. RoB.2 some concerns for risk of bias
b. Few events among only 30 patients and the effect estimate crosses several thresholds of effect size
c. Few events among only 30 patients and the effect estimate does not distinguish between appreciable benefit or harm.
d. Few events (>0.5 MCID) among a limited number of patients.

References
1.Dantzer J, Dunlop J, Psoter KJ, Keet C, Wood R. Efficacy and safety of baked milk oral immunotherapy in children with severe milk allergy: A randomized, double-blind, placebo-controlled phase 2 trial. Journal of Allergy and Clinical Immunology 2021

Table 2A. Evidence profile from the included controlled randomized trials.

Question: OIT with baked milk compared to no OIT in patients with IgE-CMA who do not tolerate baked milk

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Anaphylaxis (follow up: 17 months)									
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	publication bias strongly suspected [c]	1/20 patients (**5%**)	⨁◯◯◯ VERY LOW	CRITICAL
Use of IM epinephrine (mean follow up: 14 months)									
2 [1,2]	observational studies	serious [a]	not serious	not serious	very serious [d]	publication bias strongly suspected [c]	3/15 (**20%**) in one study and 1/20 (**5%**) in another study.	⨁◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment due to adverse effects and/or symptoms (mean follow up: 14 months)									
2 [1,2]	observational studies	serious [a]	not serious	not serious	very serious [d]	publication bias strongly suspected [c]	2/15 (**13%**) in one study and 4/20 (**20%**) in another study.	⨁◯◯◯ VERY LOW	CRITICAL
Severe gastrointestinal symptoms (mean follow up: 14 months)									
2 [1,2]	observational studies	serious [a]	not serious	serious [e]	very serious [d]	publication bias strongly suspected [c]	5/15 (**33%**) in one study and 3/20 (**15%**) in another study.	⨁◯◯◯ VERY LOW	CRITICAL
Severe respiratory symptoms/wheezing (mean follow up: 14 months)									
2 [1,2]	observational studies	serious [a]	not serious	serious [e]	very serious [d]	publication bias strongly suspected [c]	8/15 (**53%**) in one study and 2/20 (**10%**) in another study.	⨁◯◯◯ VERY LOW	CRITICAL
Generalized urticaria or erythema (follow up: 12 months)									
1 [2]	observational studies	serious [a]	not serious	serious [f]	very serious	publication bias strongly suspected [c]	5/15 patients (**33%**)	⨁◯◯◯ VERY LOW	CRITICAL
Ability to drink cow's milk and eat dairy products without a reaction (mean follow up: 14 months; assessed with: passing a supervised graded food challenge with >254 ml of fresh cow's milk or ability to eat 1.3 g of baked milk)									
2 [1,2]	observational studies	serious [a]	not serious	not serious	very serious [d]	publication bias strongly suspected [c]	4/15 (**27%**) in one study and 5/20 (**25%**) in another study.	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations
a. No control group (series of cases). Any inference requires implicit comparison.
b. Only one event
c. One additional study (Lazzarotto 2013, Lazzarotto 2014) has been completed and published only as a conference abstract with no information about the outcomes.
d. Few events among only 35 patients
e. Studies did not report how severe were the symptoms.
f. Most studies reported urticaria without mentioning its range or severity.

References
1. Gruzelle, V., Juchet, A., Martin-Blondel, A., Michelet, M., Chabbert-Broue, A., Didier, A.. Benefits of baked milk oral immunotherapy in French children with cow's milk allergy. Pediatric Allergy and Immunology.; 2020.
2. Goldberg, M. R., Nachshon, L., Appel, M. Y., Elizur, A., Levy, M. B., Eisenberg, E., Sampson, H. A., Katz, Y.. Efficacy of baked milk oral immunotherapy in baked milk-reactive allergic patients. Journal of Allergy & Clinical Immunology; Dec 2015.

Table 2B. Evidence Profile from the included non-randomized studies.

allowing to discriminate any appreciable harm or benefit associated to OIT with baked milk (Table 2). The trial reported data on QoL for both patients and caregivers, highlighting no major difference between the age-stratified group score changes. Still, when considering a 0.5 change in score as MID for improvement, the authors found that parents in the placebo group were more likely to improve with the respect to the "emotional impact domain" of the FAQOL-PF questionnaire, adn that patients in the OIT arm, were more likely to have a QoL improvement in at least 1 domain.

With respect to the case series studies, 1 study reported data on anaphylaxis, which occurred in 5% (1/20) participants.[46] Both studies[45,46] reported the need for intramuscular (IM) epinephrine in 20% (3/15) and 5% (1/20) of patients (5%) respectively. The percentage of patients who discontinued treatment owing to adverse effects was 13% (2/15) in 1 study and 20% (4/20) in the other. Severe gastrointestinal symptoms occurred in 33% (5/15) and 15% (3/20) of participants, while severe respiratory symptoms/wheezing in 53% (8/15) and 10% (2/20). One study reported generalized urticaria or erythema in 33% (5/15) of patients. After 1 year 4/15 patients (27%) in 1 study were able to eat 1.3 g of baked milk and 5/20 (25%) in another study were able to drink 254 ml of fresh cow's milk without a reaction. No other outcome of interest was reported by studies assessing OIT with baked milk.[45,46]

For all outcomes the certainty of the evidence was very low because of serious risk of bias (all studies were single-arm series of cases) and serious imprecision (few events among only 35 patients). There was also a strong suspicion of publication bias.

DISCUSSION

In this systematic review we identified a body of evidence suggesting that the current OIT approaches likely increase the ability to ingest milk, as assessed by in-clinic supervised food challenge, while also increasing the risk of severe allergic reactions, such as anaphylaxis and other serious adverse events. The data on quality of life is very uncertain due to very high risk of bias and major lack of standardization in outcome measurement and reporting. We found only 2 small series of cases describing the effects of OIT with baked milk. Given the absence of data from non-OFC setting, the choice of outcomes has primarily focused on OFC setting, making the possibly strong assumption this might act as a surrogate of real-world scenario.

Strengths and limitations

The major strength of this review lies in the extensive and comprehensive search for both RCTs and NRSs. Furthermore, we have conducted a transparent appraisal of the evidence following the GRADE approach and summarized all findings in the evidence profiles. On the other hand, the study limitations are the limited search of the gray literature, and the employment of the NOS rather than the ROBINS-I tool to assess the risk of bias for observations studies. The decision about the assessment of the studies' quality was to account for the fact that most studies lacked a control arm, while the lack of a systematic gray literature search was justified by the assistance of the WAO DRACMA guideline panel, which informed us of the absence of any relevant information outside of the indexed data repositories.

In light of this, most of the limitation of our research stems from the shortcoming in the identified body of the evidence, with the main one being the heterogeneity of the included populations, OIT protocols, and measured outcomes. Specifically, study authors have either employed diverging outcome definitions (e.g., anaphylaxis occurrence and severity) or have failed to report them altogether.

Secondly, a significant portion of the current literature consists of observational studies, either with a single-arm design or the use of historical comparison between groups, which are not properly adjusted for confounding or equally monitored. Also, we could not have full access to data from some studies. Still, these usually had a limited sample size, hence even if included, it is unlikely they would contribute significant information or meaningfully alter the overall results. Lastly, we found limitations in the reporting by study authors, who failed to provide results stratified by potentially relevant modifiers of effect (eg, age groups), which made it impossible to account for them in the evidence synthesis process.

Research implications

There is a current debate about the aim of OIT, with most studies viewing the ability to sustain a food challenge, the current diagnostic standard for CMA, as a measure of success.

In our view, there are some limitations, coming from both the assessment of OIT success and how the procedure is implemented in research:

A) This review has highlighted a dire need for a standardization in outcome assessment and reporting, as this profoundly impacts the heterogeneity in the evidence, hence hampering our ability to estimate OIT effect.

B) The oral challenge, despite being the current golden standard, lacks a standardized interpretation, further aggravating evidence heterogeneity.

C) The assumption of OIT being successful upon completion of an oral food challenge needs to be further validated as a predictor of patients' future risk and frequency of allergic reactions in the real world (i.e., outside the clinic setting).[101]

D) The assessment of quality of life requires to be standardized through the employment of robust and comprehensive food-allergy specific tools in future RCTs.

Consistently with guidance from GRADE and other institutions,[26,102] future research on the topic should include qualitative studies investigating patients' and families' knowledge about CMA and OIT as well as their values and preferences so to set the primary measures of therapeutic efficacy and safety as better tailored patient-centered outcomes.

Also, given the scarcity of high-quality studies, the scientific community should conduct more large, randomized trials recruiting patients with moderate and severe CMA (including those with previous severe anaphylaxis). These future studies should investigate patient important outcomes and acceptability on a longer time window and carry out detailed stratifications in the analyses to account for differences in OIT protocols or type of allergen. Furthermore, a greater effort should be made to study the effect of baked milk employed in OIT setting. The necessity to intensify research to better define these last points is further highlighted by the recent death of a young patient following a BM-OIT protocol[103] and a child who suffered cardio-respiratory arrest with resulting brain damage while undergoing a OIT clinical trial.[104]

Finally, given the absence of proper economic evidence, further research is needed to understand the resource requirements and cost-effectiveness of OIT. The same necessity applies to understand how immunotherapy outcomes translate into real-world patient's prognosis, so to provide better-tailored treatment strategies based on solid decision-making frameworks.

CLINICAL IMPLICATIONS

This systematic review provides secondary evidence that current approaches to OIT promote desensitization while also increasing the risk of adverse reactions. These data advocate for the investigation and eventual introduction in clinical practice of next-generation cow-milk immunotherapy regimens with an enhanced safety profile, either in the form of additional medications (eg, anti-IgE or anti-IL4R), change in allergen amount[64] or administration modality.[105] Also, our findings highlight the need for an unequivocal definition of relevant outcomes is needed, as well as consensus on the definition of food allergy.[106] Considering the current view of OIT as a potential future model for the treatment of food allergies, combined with the prevalence of food allergy (7.5%), these findings are of major importance to the ongoing development of food allergy therapeutics and enhance patient health.

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The World Allergy Organization contributed funding to this study. The corresponding author had full access to all data and had the final responsibility for the decision to submit for publication.

Availability of data and materials

Data and materials are provided in the supplementary documents.

Authors' contributions

JLB, AF, HJS originally conceived this work. AB, DKC, RT, SA, JB wrote its first draft. SW, AB and JLB did the literature search. AB, RF and JLB screened records, evaluated full texts, and extracted data. AB and RF evaluated risk of bias.

JLB and AB did the statistical analyses. HJS, DKC, SA, and SW provided critical methodological input. All authors reviewed the manuscript and provided critical intellectual contributions to the analysis and interpretation of the data, and the revision of the manuscript.

Ethics approval
Not applicable.

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Appendix A. Supplementary data
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