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World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update – XI – Milk supplement/replacement formulas for infants and toddlers with CMA – Systematic review

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ABSTRACT

Background: Cow's milk allergy (CMA) is the most complex and common food allergy in infants. Elimination of cow's milk from the diet and replacement with a specialized formula for infants with cow's milk allergy who cannot be breastfed is an established approach to minimize the risk of severe allergic reactions while avoiding nutritional deficiencies. Given the availability of multiple options, such as extensively hydrolyzed cow's milk-based formula (eHF-CM), aminoacid formula (AAF), hydrolyzed rice formula (HRF), and soy formula (SF), there is some uncertainty regarding which formula might represent the most suitable choice with respect to health outcomes. The addition of probiotics to a specialized formula has also been proposed as a potential approach to possibly increase the benefit. We systematically reviewed specialized formulas for infants with CMA to inform the updated World Allergy Organization (WAO) DRACMA guidelines.

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Objective: To systematically review and synthesize the available evidence about the use of specialized formulas for the management of individuals with CMA.

Methods: We searched from inception PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the websites of selected allergy organizations, for randomized and non-randomized trials of any language investigating specialized formulas with or without probiotics. We included all studies irrespective of the language of the original publication. The last search was conducted in January 2024. We synthesized the identified evidence quantitatively or narratively as appropriate and summarized it in the evidence profiles. We conducted this review following the PRISMA, Cochrane methods, and the GRADE approach.

Results: We identified 3558 records including 14 randomized trials and 7 observational studies. Very low certainty evidence suggested that in infants with IgE-mediated CMA, eHF-CM, compared with AAF, might have higher probability of outgrowing CMA (risk ratio (RR) 2.32; risk difference (RD) 25 more per 100), while showing potentially lower probability of severe vomiting (RR 0.12, 95% CI 0.02 to 0.88; RD 23 fewer per 100, 95% CI 3 to 26) and developing food protein-induced enterocolitis syndrome (FPIES) (RR 0.15, 95% CI 0.03 to 0.82; RD 34 fewer per 100, 95% CI 7 to 39). We also found, however, that eHF-CM might be inferior to AAF in supporting a physiological growth, with respect to both weight (−5.5% from baseline, 95%CI -9.5% to −1.5%) and length (−0.7 z-score change, 95%CI -1.15 to −0.25) (very low certainty). We found similar effects for eHF-CM, compared with AAF, also in non-IgE CMA. When compared with SF, eHF-CM might favor weight gain for IgE CMA infants (0.23 z-score change, 95%CI 0.01 to 0.45), and tolerance acquisition (RR 1.86, 95%CI 1.03 to 3.37; RD 27%, 95%CI 1%–74%) for non-IgE CMA (both at very low certainty of the evidence (CoE)). The comparison of eHF-CM vs. HRF, and HRF vs. SF, showed no difference in effect (very low certainty). For IgE CMA patients, low certainty evidence suggested that adding probiotics (*L. rhamnosus GG, L. casei* CRL431 *and B. lactis* Bb-12) might increase the probability of developing CMA tolerance (RR 2.47, 95%CI 1.03 to 5.93; RD 27%, 95%CI 1%–91%), and reduce the risk of severe wheezing (RR 0.12, 95%CI 0.02 to 0.95; RD -23%, 95%CI -8% to −0.4%). However, in non-IgE CMA infants, the addition of probiotics (*L. rhamnosus* GG) showed no significant effect, as supported by low to very low CoE.

Conclusions: Currently available studies comparing eHF-CM, AAF, HRF, and SF provide very low certainty evidence about their effects in infants with IgE-mediated and non-IgE-mediated CMA. Our review revealed several limitations in the current body of evidence, primarily arising from concerns related to the quality of studies, the limited size of the participant populations and most importantly the lack of diversity and standardization in the compared interventions. It is therefore imperative for future studies to be methodologically rigorous and investigate a broader spectrum of available interventions. We encourage clinicians and researchers to review current World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines for suggestions on how to use milk replacement formulas in clinical practice and what additional research would be the most beneficial.

Keywords: Milk allergy, Infant formulas, Systematic review, Meta-analysis, GRADE approach

INTRODUCTION

Cow's milk allergy (CMA) is among the most prevalent and complex food allergies of infancy worldwide.[1–6] The underlying response mechanism can be either IgE-mediated or non-IgE-mediated, with each type associated with different timing of symptoms after exposure to cow's milk and involvement of different body systems.

IgE-mediated CMA leads to immediate allergic reactions within minutes to a few hours after milk ingestion and primarily manifests as hives, vomiting, rhinitis, wheezing, or anaphylaxis (skin, respiratory system, and upper gastrointestinal apparatus). In contrast, non-IgE-mediated CMA results in delayed reactions that can manifest several hours to days after consumption and manifest via lower gastrointestinal symptoms, including diarrhea, colic pain, eczema, failure to thrive.[7]

The prevalence of this condition, however, is still unclear, with some recent international studies suggesting estimates of less than 1%, while previous estimates ranged between 2% and 7.5% of infants before age 1 year.[8–10] Additional evidence suggests CMA is less frequent in breast-fed infants, with a maximum prevalence of 0.5%.[11–13] Most allergic individuals naturally outgrow CMA by 6 years of age, although about 1% will have persistent disease.[14–16]

Cow's milk is an important source of nutrition in early childhood and its routine consumption is engrained across many cultures. In infants with CMA, the standard of care is the strict avoidance of cow's milk, which, in early life, may impair optimal child growth and development.[17] In CMA, the optimal balance between the nutritional needs to support optimal child health outcomes while ensuring safe consumption (allergen avoidance) is complex.[7] This problem would be particularly relevant for infants who cannot be breastfed, as opposed to ones receiving maternal milk.[13]

To this end, additional nutritional sources to supplement or replace breast milk have been developed for infants. Among these, several types of specialized replacement milk formulas have been incorporated into clinical practice, with the most notable being extensively hydrolyzed formulas (eHF-CM), amino acid formulas (AAF), hydrolyzed rice formulas (HRF), and soy formulas (SF).[18]

Due to the ubiquity and recent development of many of these replacement options, uncertainties exist regarding the best choice of specialized formula for each child and their respective benefits and harms. The previous World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines were informed by a systematic review consisting of short-term trials with very low certainty evidence.[19] Considering this research gap, here we aimed to update the evidence informing the new WAO DRACMA guidelines, by systematically reviewing the evidence on the efficacy and safety of consuming eHF-CM, AAF, SF, and HRF, with or without the addition of probiotics, in infants with CMA.[20]

General description of replacement formulas

Patients with CMA are allergic to components of particular cow's milk proteins, commonly whey proteins and caseins.[21] Replacement, specialized formulas are manufactured in a manner that breaks down (eg, by hydrolysis and heat treatment) intact proteins or lacks these allergens, therefore being considered hypoallergenic alternatives to whole cow's milk. These formulations must adhere to the nutritional standards proposed for regular infant formulas, while non-formulated foods, including plant-based (rice or soy) drinks, despite sometimes being hypoallergenic, might not meet such requirements.

Clinicians verify the hypoallergenicity of these formulas by conducting oral food challenges in patients with CMA and observing for allergic reactions. In general, the definition of hypoallergenic formulas is grounded in two historical perspectives. According to Host et al, the labeling of formulas with reduced allergenicity relies arbitrarily on an immunoreactive protein content of $<1\%$ of total nitrogen-containing substances.[22] However, there is insufficient evidence supporting that such a threshold ensures a clinically significant reduction in allergenicity. Conversely, the American Academy of Pediatrics (AAP) characterized a hypoallergenic formula as one tolerated at least by 90% of individuals with CMA with a 95% confidence level, as determined through randomized, double-blind, placebo-controlled trials.[23]

An internationally-standardized definition of "hypoallergenicity" is lacking, with some heterogeneity being present across different continents and health organizations. Therefore, hypoallergenic formulas available in the European Union must adhere to the regulatory guidelines of the European Food Safety Authority,[24] while those in the United States must comply with federal nutrition and labeling regulations by the Food and Drug Administration (FDA).[25]

Description of extensively hydrolyzed formula

Extensively hydrolyzed formula is produced through multiple manufacturing processes that thermally and enzymatically break down cow's milk proteins, followed by an ultrafiltration process to remove remaining whole proteins or large protein fragments. eHF-CM are considered to be hypoallergenic but may still elicit allergic reactions in a minority of patients with higher degree of sensitization. Currently, only casein- or whey-based eHF-CM have been commercialized, and no whey/casein mixtures are used.[26] For this study, we considered the 2 interventions as equal and referred to both as eHF-CM, as we did not anticipate any effect modification based on the formula being based on whey vs casein.

Description of amino acid formula

Amino acid formula (AAF), also known as elemental formula, contains individual amino acids rather than proteins or protein fragments. Individual amino acids do not form large three-dimensional structures to which humans may be sensitized, thus they do not cause allergic reactions. Also, AAF is entirely devoid of cow's milk since no formula component originally derives from it. The further reduced allergenicity of the formula is particularly beneficial for patients deemed at higher risk of severe allergic reactions or sensitized to eHF-CM.[22]

Description of soy formula

Soy formulas (SF) contain intact soy proteins and, with other plant-based formulas, do not contain cow's milk-specific proteins, and are therefore common replacement nutritional sources for patients with CMA. About 14% of IgE-mediated CMA patients,[27] however, also present with soy protein allergy, with co-allergy being even more common in non-IgE-mediated CMA,[28,29] which may require another formula to be considered for nutritional support. Soy formula are supplemented with the amino acids methionine, taurine, and carnitine, and the electrolyte composition is assessed to avoid deficiencies in zinc, calcium, or phosphorus.[30]

Description of hydrolyzed rice formula

Hydrolyzed rice formula (HRF), similarly to SF, does not contain cow's milk proteins, and the rice proteins are either partially or extensively hydrolyzed in a similar fashion as those found in hydrolyzed milk protein formulas. Trial-based evidence shows that HRF is safe in patients with CMA and soy protein allergy.[31-33] Again, similarly to SF, HRFs are fortified with the amino acids lysine and threonine[34]

Description of probiotics addition to infant formulas

The optimal development of a healthy gut is crucial during infancy, playing a vital role in growth

and development. It facilitates the digestion and absorption of nutrients and fluids, while also serving as a key contributor to immune system development.[35]

A pivotal factor in fostering proper gut function and development is maintaining a balanced gut microbiota.[36] Various prenatal and perinatal factors, such as delivery method, antibiotic use, diet, and environmental influences, can impact microbial colonization in infants and subsequently affect immune system maturation.[37] Generally, consensus exists that the gold standard for a favorable microbial composition in early life is found in the gut microbiota of healthy, full-term, vaginally delivered, and breast-fed infants.[38] Given the significant role of human milk in shaping a balanced gut microbiota, it is imperative for infant formula to closely emulate its composition, providing bioactives that target both gut and immune health.[39]

To this end, formulas have started being fortified by incorporating bioactive agents from the "biotics" family, encompassing probiotics, prebiotics, synbiotics, and postbiotics. Probiotics are live microorganisms that, when administered within specified ranges, impart health benefits to the host.[40] Prebiotics are specific substrates intended to be taken up by the intestinal microbiota, contributing to health benefits.[41] Synbiotics represent a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host.[42,43] Meanwhile, postbiotics are preparations of inanimate microorganisms and/or their components that confers a health benefit.[44-46]

In this review, we focused only on "probiotics", and used the term to refer to the general addition of live bacteria or microorganisms to specialized formulas, specifying the specific stain in brackets. We did not make any distinction, with respect to inclusion criteria, between the addition of probiotics as pre-mixed in the formula and probiotics administered concomitantly with the formula in the form of pills or capsules.

METHODS

We developed and reported this systematic review in accordance with current PRISMA, GRADE (Grading of Recommendations Assessment, Development, and Evaluation), and Cochrane standards.[47-50] All decisions regarding the research question, analytic approach and risk of bias (RoB) assessment were defined *a priori*.

We registered the review's protocol on Open Science Framework (10.17605/OSF.IO/N8AD2).

Outcome measures

The WAO DRACMA guideline panel defined a set of outcomes of interest a priori. The panel members rated the relative importance of outcomes for decision-making as suggested by the GRADE Working Group, classifying the outcomes either as critical or important.[51,52] The critical outcomes the panel agreed upon were: acquisition of tolerance of cow's milk, failure to thrive, epinephrine use, vomiting, diarrhea, severe asthma, and development of food protein-induced enterocolitis syndrome (FPIES). The outcomes considered important to decision-making were sensitization to the administered formula, urticaria, eczema, and change or discontinuation

of therapy due to adverse effects. When examining the identified evidence, we accepted the authors' definitions for severity of adverse effects.

Search strategy and selection criteria

We searched the indexed literature from database inception to November 2018, and then updated it in April 2020, March 2021, September 2022, and January 2024. We employed separate strategies for systematic reviews and primary studies.

We searched for existing systematic reviews on PubMed, 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 (www.epistemonikos.org).

We ran the searches for individual studies on PubMed, Ovid Medline and Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). We searched for published and unpublished studies, including randomized controlled trials (RCTs) and nonrandomized studies (NRSs) with at least 5 patients, in any language either with a direct comparison of two or more among the eligible formulas (eHF-CM, AAF, HRF, and SF) or comparing a formula with probiotics vs the same formula without probiotics. We designed the search strategies with the assistance of an information scientist and clinical experts. We focused on RCTs to inform effect estimates while using NRS as a source of complementary, sequential or substitutive evidence as described by recent GRADE guidance.[53,54] Considering this, we used specific filters on Medline[55] and Embase.[56] Furthermore, we conducted citation analyses by reviewing the references of identified studies.

The search strategies and selection criteria are found respectively in the online Supp. Appendices 1-2.

Data collection

We performed title and abstract screening and subsequently assessed the full articles for inclusion. These steps were conducted independently and in duplicate using Covidence (www.covidence.org). We resolved conflicts at any stage through consensus or discussion with a third reviewer. WAO DRACMA guideline panel members reviewed the final list of included studies checking for potentially missing records.

We extracted data in duplicate and independently on pre-piloted excel spreadsheets. In addition to the pre-defined outcomes, we recorded studies' bibliographical information, design, setting, population characteristics, and intervention characteristics.

We considered extracted data from multiple records of a same study (eg, primary study, and follow-up analyses) as belonging to a single eligible entry. If a single record reported on more than one study, we extracted each as separate. In case of missing or unclear relevant data, we contacted the investigators of the primary studies.

Risk of bias assessment and critical appraisal of the evidence

We assessed the risk of bias (RoB) per individual study and outcome using Cochrane RoB 2.0 tool and Newcastle Ottawa Scale for RCTs and NRS respectively.[57,58] We considered the overall RoB of a study as equal to the highest risk-judgement across the appraised domains. We critically appraised the certainty of the evidence for each outcome following the current GRADE approach by considering RoB, imprecision, indirectness, inconsistency, publication bias, and factors for uprating the certainty in the evidence. Current GRADE guidance defines certainty in the evidence as follows: high certainty reflects a high confidence that the true effect lies close to the synthesized estimate; moderate certainty indicates moderate confidence that the true effect is likely close to the estimate, but there is a possibility that it might be substantially different; low certainty indicates limited confidence, hence the true effect might be substantially different from the synthesized estimate of effect; very-low certainty indicates a very little confidence in the estimate of effect and that the true effect is likely substantially different.

Data synthesis

We synthesized the treatment effects following the intention-to-treat principle.[48] We pooled the

effect estimates quantitatively, when appropriate, using random-effect meta-analysis. If pooling was not justifiable, we conducted a narrative synthesis of the evidence.

For dichotomous data, we quantitatively summarized the effect estimate as relative risk (RR), while as pooled incidence rate ratio for count data. The synthesized continuous data as mean difference (MD) or standardized mean difference (SMD), if different measurement scales were used among the studies.

If there were zero events for an outcome, we used continuity correction by using the reciprocal of the comparator group size.[59,60] For count variables we obtained the frequency measures by estimating person-time follow-ups and multiplied the number of participants by the reported duration of observation.

We conducted data analysis on Review Manager (v5.4.1)[61] and used GRADEpro (www.GRADEpro.org)[62] to create the summary of findings tables.

RESULTS

Included studies

After running the original search, we screened 1285 deduplicated records and reviewed 81 documents (Fig. 1). Throughout the subsequent search updates, we screened a total of 2273 records and evaluated 120 full-texts for eligibility (Supp. Figures 1-4). We included 21 reports[28,63-82] of 14 RCTs[63-65,68,69,72-77,80-82] and 8 reports[83-90] of 7 NRS[83-86,88-90] (Table 1).

In the last search update (January 2024), we identified the conference abstract of a potentially eligible RCT comparing eHF-CM and HRF,[91] but the limited reporting due to publication type did not allow for inclusion to the evidence synthesis. We reached out to the authors who provided some additional information but not enough for the inclusion of the study in this review. We will likely include this study in future iterations of the WAO DRACMA guidelines once it is published in a full-text format, including all required information.

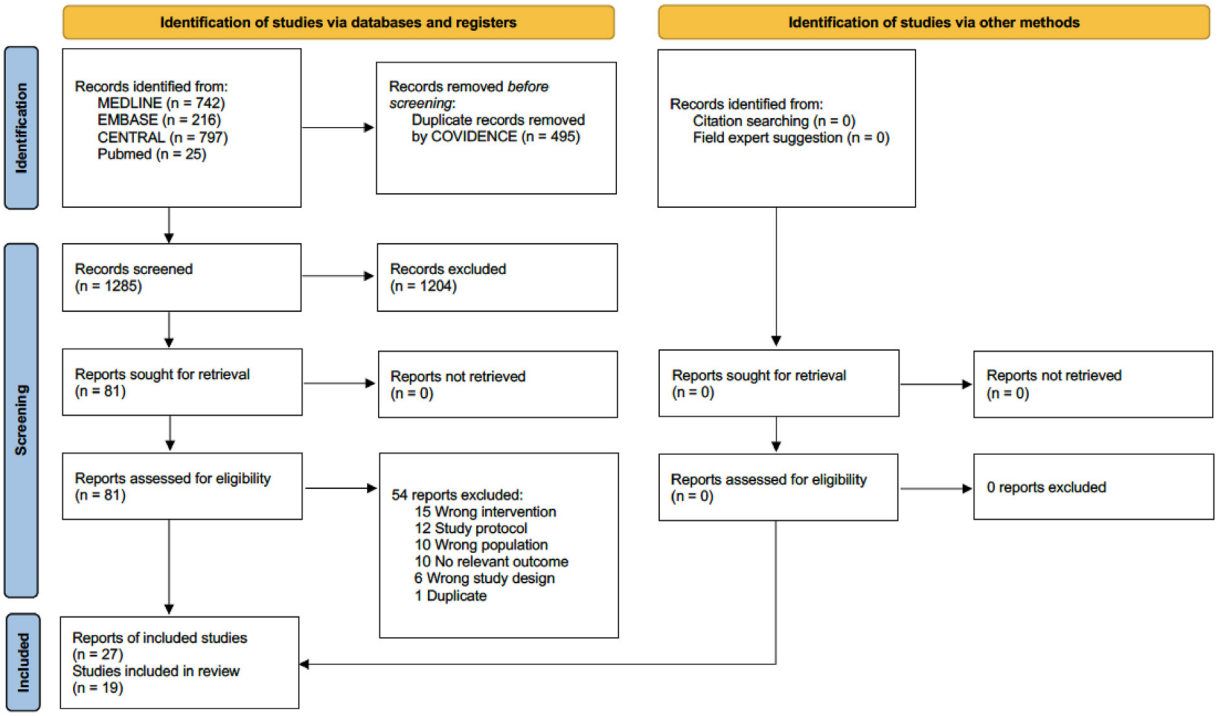

Fig. 1 PRISMA diagram of the evidence selection process from the original search (Nov 2018)

The included randomized trials enrolled 1132 participants (mean across trials: 81, range: 16 to 220), mean age 5.9 months (range of means, 2.4–11 months) with an average follow-up of 11.9 months (range of means, 1–36 months), receiving formula supplementation compared with each other, with 5 trials investigating the use of probiotics as adjuvant to milk formulas (*Lacticaseibacillus rhamnosus* GG (formerly known as *Lactobacillus rhamnosus* GG): 4 trials, *Lacticaseibacillus casei* CRL431 (formerly known as *Lactobacillus casei* CRL431) and *Bifidobacterium lactis* Bb-12: 1 trial). A total of 1298 participants was enrolled in the NRSs (median 92; range 14–412), with a median age of 5.4 months (range of medians, 4.1 months–14.1 months). Most of the studies presented a mixed patient population with both IgE and non-IgE mediated CMA, with only 3 RCTs and 4 NRSs having entirely IgE-CMA patients, and 1 trial focusing solely on non-IgE CMA.

We rated 10 of the included trials[63,69,73–77,80–82] to be with "Some concerns" of RoB, due to issues with the random sequence generation, missing data, and outcome measurement and reporting. No study was deemed to be at high RoB. Since we considered the RoB to be similar across the different outcomes, we reported the judgements at study level (Supp. Table 1). The observational studies used for evidence synthesis presented several limitations with respect to patient selection, comparability of the study groups and outcome measurement (Supp. Table 2).

Effects of interventions

The evidence profiles for the different pairwise comparisons among formula supplements, as well as formulas with probiotics vs. formulas without probiotics, are presented in the Supp. Tables 3 to 12. The evidence profiles summarize the information about the effect estimates for the critical, and important health outcomes, (as defined by the WAO DRACMA guideline panel members), including the time of measurements, and the ratings of the certainty of the supporting evidence (ie, CoE) following the GRADE approach.

Note about indirect evidence: Where possible, we used data for children with IgE-mediated and non-IgE-mediated CMA separately to estimate the effects in those populations. Several studies reported results for both groups together; in such situations, we used the combined populations' data as indirect evidence for each group

Study ID	Same study as	Duration (months)	Interventions	Population size	Age (mean/ median)	Gender (% Female)	CMA Type (% IgE-CMA)
Randomized Controlled Trials							
Reche 2010	NA	24	eHF vs. HRF	81	4.3 m	50.0%	100.0%
Berni Canani 2012	Nocerino 2010 (abstract)Berni Canani 2011 (abstract)	12	eHF + LGG vs. eHF	55	3.6 m	32.7%	38.2%
Berni Canani 2017 (probiotics)	Berni Canani 2016 (abstract) Berni Canani 2018 (abstract)	36	eHF + LGG vs. eHF	220	5 m	33.0%	100.0%
Berni Canani 2017 (formulas)	NA	12	eHF vs. AAF	50	6.7 m	38.0%	56.0%
Hol 2008	Dupont 2015	12	eHF + L. Casei, B. lactis vs. eHF	119	4.2 m	44.5%	0.0%
Isolauri 1995	NA	9	eHF vs. AAF	45	NR	NR	NR
Agostoni 2007	NA	12	eHF vs. HRF vs. SF	108	5 m	30.1%	100.0%
Salpietro 2005	NA	6	eHF vs. SF	26	6.8 m	50.0%	23.1%
D'Auria 2003	NA	6	HRF vs. SF	16	11 m	43.8%	NR
Niggemann 2001	Dupont 1999	6	eHF vs. AAF	73	5.6 m	32.9%	48.0%
Niggemann 2008	NA	6	eHF vs. AAF	62	8.1 m	59.7%	NR
Klemola 2002	Klemola 2005	24	eHF vs. SF	170	7 m	41.8%	41.8%
Majamaa 1997	NA	1	eHF + LGG vs. eHF	31	2.4 m	NR	NR
Viljanen 2005	NA	1	eHF + LGG vs. eHF	76	6.4 m	38.0%	57.9%
Observational Studies							
Berni Canani 2013	Nocerino 2011 (abstract)	12	eHF + LGG vs. eHF vs. AAF vs. HRF vs. SF	260	5.7 m	35.8%	42.7%
Nocerino 2021	NA	36	eHF vs. AAF vs. HRF vs. SF	365	5 m	34.2%	100.0%
Terracciano 2010	NA	18	eHF vs. HRF vs. SF	72	14.1 m	NR	100.0%

(continued)

Study ID	Same study as	Duration (months)	Interventions	Population size	Age (mean/ median)	Gender (% Female)	CMA Type (% IgE-CMA)
Ovcinnikova 2015	NA	12	eHF vs. AAF vs. eHF + LGG	412	<6 m	NR	NR
Mehr 2008	NA	24	eHF vs. AAF vs. SF	14	4.8 m	NR	100.0%
Aguiar 2013	NA	24	eHF vs. AAF	83	9 m	41.6%	100.0%
Trakulpark 2021	NA	12	eHF vs. AAF vs. SF	92	4.1 m	45.7%	21.1%

Table 1. (Continued) Characteristics of included studies

separately, and we noted that in the evidence profiles (Supp. Tables 3 to 12).

Fig. 2A and B summarize the effect estimates across the pairwise comparisons of interventions with respect to the identified health outcomes in IgE and non-IgE mediated CMA respectively.

Extensively hydrolyzed formula vs amino acid formula

The evidence profiles in Supp. Tables 3 and 4 summarize the information about this comparison in children with IgE-mediated and non-IgE-mediated CMA. The forest plots are shown in Supp. Figures 5 to 22.

IgE-mediated cow's milk allergy

We identified 3 randomized trials[73,76,77] (180 participants) and 6 observational studies [83-86,88,90] (673 participants) reporting the effects of eHF-CM compared with AAF in children with IgE-mediated CMA. The evidence for all health outcomes below is of very low certainty.

Anaphylaxis. We found no study directly reporting anaphylaxis but we assumed that the use of epinephrine may be a reasonable surrogate for anaphylaxis (1 observational study, 353 participants).[88] We did not find a difference in the use of epinephrine between children receiving eHF-CM and AAF. However, the results also do not exclude the possibility that such a difference exists (RR: 0.56, 95% CI: 0.24 to 1.29; RD: 4 fewer per 100 patients, 95% CI: 7 fewer to 3 more per 100).

Moderate to severe gastrointestinal symptoms. For most outcomes, the studies reported gastrointestinal symptoms without providing their severity. We acknowledged the indirectness in this context. One randomized trial (62 patients)[77] showed that eHF-CM might reduce the risk of moderate to severe vomiting, compared with AAF (RR: 0.12, 95% CI: 0.02 to 0.88; RD: 23 fewer per 100 patients, 95% CI: 3 to 26 fewer per 100), while possibly increasing the risk of severe diarrhea (RR: 1.41, 95% CI: 0.89 to 2.22; RD: 19 more per 100 patients, 95% CI: from 5 fewer to 57 more per 100), but the evidence is very uncertain due to concerns about the RoB, indirectness and imprecision.

Severe asthma/wheezing. We found one observational study (146 patients)[86] reporting that the difference in wheezing of any severity between eHF-CM and AAF is unlikely (RR: 1.05, 95% CI: 0.61 to 1.80; RD: 1 more per 100 patients, 95% CI: from 10 fewer to 21 more per 100).

Moderate to severe urticaria or eczema. One observational study (146 patients)[86] did not find a difference in the risk of urticaria between eHF-CM and AAF, however, the results also do not exclude the possibility that such a difference exists (RR: 0.76, 95% CI: 0.43 to 1.34; RD: 7 fewer per 100 patients, 95% CI: from 16 fewer to 10 more per 100). The same study[86] reported the risk of eczema with eHF-CM compared with AAF (RR: 0.70, 95% CI: 0.44 to 1.10; RD: 12 fewer per 100 patients, 95% CI: from 23 fewer to 4 more per 100). Three randomized trials with a total of 180 patients[73,76,77] measured the severity of eczema using SCORAD (scale from 0 to 103 points; minimal important difference is considered to be ~8 points). The mean difference in the severity

Experimental Intervention	Comparison Intervention	Critical Outcomes									Important Outcomes		
		CMA tolerance	Failure to thrive (weight)	Failure to thrive (lenght)	Epinephrine Use	Vomiting (moderate/severe)	Diarrhea (moderate/severe)	Asthma or wheezing (moderate/severe)	Urticaria (moderate/severe)	FPIES	Secondary Sensitization	Change/Stop of Formula	Eczema
eHF-CM	AAF	**RR 2.32** (1.36, 3.94) **RD 25%** (6%, 44%)	**MD -5.5%** (-9.5%, -1.5%)	**MD -0.7 SD** (-1.15, -0.25)	**RR 0.56** (0.24, 1.29) **RD -4%** (-7%, 3%)	**RR 0.12** (0.02, 0.88) **RD -23%** (-26%, -3%)	**RR 1.41** (0.89, 2.22) **RD 19%** (-5%, 57%)	**RR 1.05** (0.61, 1.80) **RD 1%** (-10%, 21%)	**RR 0.76** (0.43, 1.34) **RD -7%** (-16%, 10%)	**RR 0.15** (0.03, 0.82) **RD -34%** (-39%, -7%)	**RR 5.44** (0.33, 89.00) **RD 38%** (-0%,75%)	**RR 2.88** (0.0, >100) **RD 3%** (ne, 100%)	**RR 0.70** (0.44, 1.10) **RD -12 %** (-23, 4%)[a]
	HRF	**RR 1.20** (0.76, 1.88) **RD 9%** (-11%,39%)	**MD -0.04 SD** (-0.53, 0.45)	**MD 0.33 SD** (-0.13 ,0.79)				**RR 1.05** (0.61, 1.80) **RD 1%** (-10%, 21%)	**RR 0.80** (0.45, 1.42)* **RD -5%** (-15%,12%)			**RR 0.69** (0.21, 2.22)° **RD -5%** (-13%, 20%)	**RR 0.91** (0.56, 1.50) **RD -3%** (-14%, 16%)
	SF	**RR 0.96** (0.63, 1.46) **RD -2%** (-16%, 20%)	**MD 0.23 SD** (0.01, 0.45)	**MD 0.27 SD** (-0.19, 0.73)				**RR 0.95** (0.57, 1.60) **RD -1%** (-12%, 17%)	**RR 0.89** (0.49, 1.60)* **RD -3%** (-13%, 15%)	**RR 1.57** (0.08, 30.32)* **RD 6%** (-9%, 21%)	**RR 0.15** (0.01, 2.82) **RD -7%** (-8%, 15%)	**RR 0.86** (0.38, 1.96) **RD -2%** (-9%, 13%)	**RR 0.83** (0.58, 1.20) **RD -7%** (-17%, 8%)
HRF	SF	**RR 1.11** (0.88, 1.39) **RD 5%** (-5%, 17%)	**MD 0.25** (-0.11, 0.6)	**MD 0.01** (-0.37, 0.39)				**RR 0.90** (0.53, 1.54) **RD -3%** (-14%, 16%)	**RR 1.11** (0.64, 1.92)* **RD 3%** (-9%, 23%)		**RR 0.15** (0.01, 2.82) **RD -7%** (-8%, 15%)	**RR 1.27** (0.43, 3.78) **RD 3%** (-6%, 31%)	**RR 0.85** (0.54, 1.34) **RD -6%** (-17%, 13%)
Formula & Probiotics	Formula alone	**RR 2.47** (1.03, 5.93) **RD 27%** (1%, 91%)			**RR 0.33** (0.04, 2.62) **RD -3%** (-5%, 8%)			**RR 0.12** (0.02, 0.95) **RD -7%** (-8%, -0%)	**RR 0.97** (0.14, 6.74)* **RD -0%** (-2%, 12%)			**RR 0.77** (0.26, 2.28) **RD -2%** (-7%, 11%)	**See EP** (Supp. Table 11)

Classification of the intervention (color)			Certainty of the evidence (CoE)
Relatively most beneficial	No clear direction of effect (Minimally Contextualized Approach)	No data (blank)	The CoE for all outcomes was judged to be ''Low'' or ''Very low''
Relatively least beneficial			

Fig. 2a Summarized effect estimates across the pairwise comparisons of interventions, together with CoE rating for infants with IgE mediated CMA Abbreviations eHF-CM: extensively hydrolyzed cow's milk formula; AAF: aminoacid formula; HRF: hydrolyzed rice formula; SF: soy formula;CMA: Cow's milk allergy; FPIES: Food protein-induced enterocolitis syndrome; RR: risk ratio (relative risk); RD: risk difference (absolute risk difference); MD: mean difference; SD: standard deviations; EP: evidence profile; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; CoE: certainty of evidence Explanations * This outcome was considered to be "Important" for Decision making by the WAO DRACMA guidelines panel for this pairwise comparison of interventions This outcome was considered to be "Critical" for Decision making by the WAO DRACMA guidelines panel for this pairwise comparison of interventions a We also synthesized evidence on the severity of eczema (atopic dermatitis) (follow-up: range 6 to 9 months; assessed with: SCORAD; MID ~ 8 points; Scale from: 0 to 103): 1.39 points higher (1.08 lower to 3.86 higher) GRADE certainty levels High certainty - reflects a high confidence that the true effect lies close to the synthesized estimate Moderate certainty - indicates a moderate confidence that the true effect is likely close to the estimate, but there is a possibility that it might be substantially different Low certainty - indicates a limited confidence, hence the true effect might be substantially different from the synthesized estimate of effect Very-low certainty - indicates a very little confidence in the estimate of effect and that the true effect is likely substantially different.

of eczema with eHF-CM compared with AAF was 1.39 points (95% CI: 1.08 to 3.86).

Development of FPIES. One observational study with 39 patients (only 5 in the AAF group)[90] suggested that eHF-CM might reduce the risk of developing FPIES compared with AAF (RR: 0.15, 95% CI: 0.03 to 0.82; RD: 34 fewer per 100 patients, 95% CI: 7 to 39 fewer per 100 patients), but the evidence was very uncertain.

Sensitization to or discontinuation of the formula. One observational study with only 14 patients[85] suggested that more patients may get sensitized to the formula with eHF-CM compared with AAF. However, it is necessary to interpret this apparently increased risk with caution because of very few patients and events observed (3/8 patients with eHF-CM and 0/6 patients with AAF). The best estimate based on these numbers is a relative risk 5.44 (95% CI: 0.33 to 89.0) with an estimated risk difference of 38 more per 100 patients (95% CI: from 1 fewer per 1000 patients to 75 more per 100 patients). The risk of discontinuing or changing the formula due to any reason was reported in 2 observational studies. In one study[83] 7/37 children receiving eHF-CM and 4/5 children receiving AAF (19% vs 80%) had their formula changed or discontinued. In another study[88] 12/136 children receiving eHF-CM and 0/217 receiving AAF (9% vs 0%) had their formula changed. In such a case it is debatable whether a meta-analysis should be attempted. However, we found little clinical difference between those populations and the best estimate based on both studies would be a relative risk of 2.88 (95% CI: 0.00 to 16,709.44).

Experimental Intervention	Comparison Intervention	Critical Outcomes									Important Outcomes		
		CMA tolerance	Failure to thrive (weight)	Failure to thrive (lenght)	Epinephrine Use	Vomiting (moderate/severe)	Diarrhea (moderate/severe)	Asthma or wheezing (moderate/severe)	Urticaria (moderate/severe)	FPIES	Secondary Sensitization	Change/Stop of Formula	Eczema
eHF-CM	AAF	**RR 1.84** (0.89, 3.80) **RD 27%** (- 3%, 88%)	**MD -5.5%** (-9.5%, -1.5%)	**MD -0.7 SD** (-1.15, -0.25)	**RR 0.56** (0.24, 1.29) **RD -4%** (-7%, 3%)	**RR 0.12** (0.02, 0.88) **RD -23%** (-26%, -3%)	**RR 1.41** (0.89, 2.22 **RD 19%** (-5%, 57%)			**RR 0.15** (0.03, 0.82) **RD -34%** (-39%, -7%)	**RR 5.44** (0.33, 89.00) **RD 38%** (-0%, 75%)	**RR 2.47** (0.00, >100) **RD 3%** (ne, 100%)	**MD 1.39** (-1.08, 3.86)[a]
	HRF	**RR 1.03** (0.64, 1.64) **RD 2%** (-20%, 36%)											
	SF	**RR 1.86** (1.03, 3.37) **RD 27%** (1%, 74%)	**MD 0.19 SD** (-0.07, 0.45)							**RR 1.57** (0.08, 30.32)* **RD 6%** (-9%, 21%)		**RR 0.61** (0.09, 4.17) **RD -5%** (-11%, 40%)	**RR 0.93** (0.52, 1.68) **RD 4.2%** (-29%, 41%)
HRF	SF	**RR 1.81** (0.97, 3.38) **RD 25%** (-1%, 74%)	**MD 0.07** (-0.47, 0.61)	**MD 0.25** (-0.57, 1.07)								See EP (Supp Table 10)	
Formula & Probiotics	Formula alone	**RR 1.32** (0.70, 2.52) **RD 24%** (-22%, 100%)	**MD 0.1 kg** (-0.34, 0.54)	**MD 0.2 cm** (-1.07, 1.47)								**RR 0.77** (0.26, 2.28) **RD 2%** (-7%, 11%)	See EP (Supp. Table 12)

Classification of the intervention (color)			Certainty of the evidence (CoE)
Relatively most beneficial	No clear direction of effect (Minimally Contextualized Approach)	No data (blank)	The CoE for all outcomes was judged to be ''Low'' or ''Very low''
Relatively least beneficial			

Fig. 2b Summarized effect estimates across the pairwise comparisons of interventions, together with CoE rating for infants with Non-IgE mediated CMA Abbreviations eHF-CM: extensively hydrolyzed cow's milk formula; AAF: aminoacid formula; HRF: hydrolyzed rice formula; SF: soy formula;CMA: Cow's milk allergy; FPIES: Food protein-induced enterocolitis syndrome; RR: risk ratio (relative risk); RD: risk difference (absolute risk difference); MD: mean difference; SD: standard deviations; EP: evidence profile; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; CoE: certainty of evidence Explanations * This outcome was considered to be "Important" for Decision making by the WAO DRACMA guidelines panel for this pairwise comparison of interventions ° This outcome was considered to be "Critical" for Decision making by the WAO DRACMA guidelines panel for this pairwise comparison of interventions a Severity of eczema (atopic dermatitis) (follow-up: range 6 to 9 months; assessed with: SCORAD; MID ~ 8 points; Scale from: 0 to 103) GRADE certainty levels High certainty - reflects a high confidence that the true effect lies close to the synthesized estimate Moderate certainty - indicates a moderate confidence that the true effect is likely close to the estimate, but there is a possibility that it might be substantially different Low certainty - indicates a limited confidence, hence the true effect might be substantially different from the synthesized estimate of effect Very-low certainty - indicates a very little confidence in the estimate of effect and that the true effect is likely substantially different.

Failure to thrive. One trial with 45 patients[73] reported a lower weight gain in children receiving eHF-CM compared with AAF (mean difference 5.5% lower weight change from baseline, 95% CI: 1.5%–9.5% lower) and lower length gain (mean difference: 0.7 SD lower z-score change from baseline, 95% CI: 0.25 SD to 1.15 SD lower). However, we deemed the evidence to be of very low certainty due to concerns about RoB, indirectness in how the outcome was measured, and excessively small sample size.

Outgrowing CMA. Two observational studies with altogether 184 patients[84,86] found that eHF-CM might increase the probability of outgrowing CMA compared with AAF (RR: 2.32, 95% CI: 1.36 to 3.94; RD: 25 more per 100 patients, 95% CI: 6 to 44 more per 100 patients), but the evidence was considered as very uncertain.

Non IgE-mediated cow's milk allergy

Three trials[73,76,77] (180 participants) and 5 observational studies[83–85,88,90] (539 participants) provided information on the effect of eHF-CM compared with AAF in non-IgE-mediated CMA. We judged the evidence on all outcomes to be of very low certainty, except for severity of eczema (low CoE).

Epinephrine use. One observational study (353 participants)[88] found evidence suggestive that eHF-CM, compared with AAF, might reduce the risk of eliciting reactions requiring epinephrine, but could not exclude entirely the possibility of

relative harm (RR 0.56, 95%CI 0.24 to 1.29; RD 4 fewer per 100 patients, 95%CI 7 fewer to 3 more per 100 patients).

Moderate to severe gastrointestinal symptoms. We used the same trial informing on this outcome for IgE CMA. The study (62 participants)[77] showed that eHF-CM, compared with AAF, might reduce the risk of moderate to severe vomiting (RR: 0.12, 95% CI: 0.02 to 0.88; RD: 23 fewer per 100 patients, 95% CI: 3 to 26 fewer per 100 patients), while possibly increasing the risk of severe diarrhea (RR: 1.41, 95% CI: 0.89 to 2.22; RD: 19 more per 100 patients, 95% CI: from 5 fewer to 57 more per 100 patients). However, the informing evidence was very uncertain due to limitations in reporting, choice of outcome measurement, and imprecise effect estimates.

Severity of eczema. We used the data from the same 3 trials informing the outcome in IgE CMA (180 patients).[73,76,77] The studies used SCORAD to measure the severity of (scale from 0 to 103 points; minimal important difference: ~8 points). The pooled mean difference in the severity of eczema was suggestive of no important relative effect between eHF-CM and AAF (1.39 points, 95% CI: 1.08 to 3.86).

Development of FPIES. One observational study (96 participants, only 16 in AAF groups)[90] showed that eHF-CM might reduce the risk of developing FPIES compared with AAF (RR: 0.15, 95% CI: 0.03 to 0.82; RD: 34 fewer per 100 patients, 95% CI: 7 to 39 fewer), but the evidence was very uncertain.

Sensitization to or discontinuation of the formula. Only one small study with 14 patients[85] showed that eHF-CM was associated with a higher rate of secondary sensitization to the administered formula, compared with AAF. However, the very limited number of events and the minute sample size (3/8 patients with eHF-CM vs. 0/6 patients with AAF), greatly impair the certainty in this finding (RR: 5.44, 95% CI: 0.33 to 89.0; RD: 38 more per 100 patients, 95% CI: from 1 fewer per 1000 patients to 75 more per 100 patients). The discontinuation or changing of the formula was reported in 2 observational studies. In the first study[83] 7/37 children receiving eHF-CM and 4/5 children receiving AAF (19% vs 80%) changed or discontinued the formula they were receiving, while in the second study[88] 12/136 children receiving eHF-CM and 0/217 receiving AAF (9% vs 0%) changed or stopped therapy. The pooled estimate based on both studies would be a relative risk of 2.88 (95% CI: 0.00 to 16,709.44).

Failure to thrive. One randomized trial with 45 patients[73] showed that eHF-CM might be less efficient, compared with AAF at supporting physiological growth with respect to both weight gain (mean difference 5.5% lower weight change from baseline, 95% CI: 1.5%–9.5% lower) and length gain (mean difference: 0.7 SD lower z-score change from baseline, 95% CI: 0.25 SD to 1.15 SD lower). Still, we considered the evidence to be of very low certainty due to concerns about the RoB, indirectness and imprecision.

Outgrowing CMA. One observational study (50 participants)[84] showed no difference between eHF-CM and AAF with respect to the probability of outgrowing CMA (RR: 1.84, 95% CI: 0.89 to 3.80; RD: 27 more per 100 patients, 95% CI: 3 fewer to 88 more per 100 patients).

Extensively hydrolyzed formula vs hydrolyzed rice formula

The evidence profiles with information on the effect estimates and the judgments on the certainty in the evidence for this comparison in IgE and non-IgE CMA are shown in Supplementary Tables 5 and 6. The forest plots are available in Supp. Figures 23 to 30.

IgE-mediated cow's milk allergy

We identified 2 trials[63,80] (152 participants) and one observational study[86] (146 participants) comparing eHF-CM with HRF in people with IgE-mediated CMA. The certainty in the evidence was rated as very low for all outcomes across this comparison.

Severe asthma/wheezing. One observational study (146 participants)[86] showed eHF-CM might be equal to HRF with respect to the risk for an infant to have wheezing of any severity (RR: 1.05, 95%CI: 0.61 to 1.80; RD: 1 more per 100 patients, 95%CI: 10 fewer to 21 more per 100 patients), but the evidence was very uncertain.

Moderate to severe urticaria or eczema. Nocerino et al (146 patients)[86] did not find a difference in the risk of urticaria between eHF-CM and HRF,

without excluding however that such a difference might be present (RR: 0.80, 95%CI: 0.45 to 1.42; RD: 5 fewer per 100 patients, 95%CI: 15 fewer to 12 more per 100 patients). The same study[86] showed a comparable risk of eczema between eHF-CM and HRF (RR: 0.91, 95%CI: 0.56 to 1.50; RD: 3 fewer per 100 patients, 95%CI 14 fewer to 16 more per 100 patients), but the evidence is uncertain.

Sensitization to or discontinuation of the formula. One trial with 71 patients[63] suggested with very low certainty that eHF-CM might not differ, compared with HRF, in affecting the probability of requiring a stop or change of formula due to adverse effects (RR: 0.69, 95%CI: 0.21 to 2.22; RD: 5 fewer per 100 patients, 95%CI: 13 fewer to 20 more per 100 patients).

Failure to thrive. The same trial with 71 patients[63] showed, also with very low certainty, that eHF-CM might have no appreciable relative effect, compared with HRF on sustaining infants' growth [weight (−0.04 z-score change, 95%CI -0.53 to 0.45); length (0.33 z-score change, 95%CI -0.13 to 0.79)]. Like for the other comparisons, we acknowledged here the issue with indirectness in outcome measurements, as the change in growth parameters does not properly reflect the failure in catch-up growth due to CMA.

Outgrowing CMA. The trial by Reche et al (81 participants)[80] suggested eHF-CM might have no appreciable benefit, compared with HRF, on inducing tolerance to milk proteins at 12 month follow-up (RR: 1.2, 95%CI: 0.76 to 1.88; RD: 9 more per 100 patients, 95%CI: 11 fewer to 39 more per 100 patients). The same study followed up the participants for this outcome up to 24 months with no attrition, showing consistent findings of no appreciable difference between the two formulas (RR: 1.02, 95%CI: 0.81 to 1.3; RD: 2 more per 100 patients, 95%CI: 14 fewer to 23 more per 100 patients). Another trial published only as a conference abstract[92] reported that infants receiving eHF-CM (n = 70) acquired tolerance faster than those with HRF (n = 35) (p 0.0075), failing however to disclose the number of events per group. Furthermore, three reports[78,84,89] of 2 observational studies (166 participants) showed RR: 0.99, 95% CI: 0.48 to 2.03.

We found no evidence informing on the relative effect of eHF-CM vs HRF on the need for epinephrine administration due to allergic reactions, the development of gastrointestinal symptoms, and FPIES.

Non IgE-mediated cow's milk allergy

We only found 1 observational study[84] (54 participants) with relevant data on the effect of eHF-CM vs HRF in people with non-IgE CMA.

Even in this population, very low certainty evidence suggested that eHF-CM might have no relative effect, compared with HRF, on favoring tolerance acquisition (RR: 1.03, 95%CI: 0.64 to 1.64; RD: 2 more per 100 patients, 95%CI: 20 fewer to 36 more per 100 patients).

We could not identify relevant data informing the effect estimates for the other pre-specified outcomes.

Extensively hydrolyzed formula vs. soy formula

We created evidence profiles, available as Supp. Tables 7 and 8, providing extensive information on the effect estimates and the judgments on the evidence appraisal for this comparison in IgE and non-IgE mediated CMA. The forest plots with pooled estimates of effects for individual outcomes are available as Supp. Figures 31 to 44.

IgE-mediated cow's milk allergy

We found 3 trials[63,74,81] (169 participants) and four observational studies[84,86,89,90] (284 participants) with data comparing eHF-CM and SF in IgE CMA. The evidence for all predetermined outcomes in this population was judged to be of very low certainty.

Severe asthma/wheezing. We found 1 observational study (146 patients)[86] possibly showing no difference in wheezing of any severity between eHF-CM and SF, yet the pooled estimate was imprecise, not excluding the possibility of neither benefit or harm (RR: 0.95, 95% CI: 0.57 to 1.60; RD: 1 fewer per 100 patients, 95% CI: from 12 fewer to 17 more per 100 patients). Furthermore, the evidence was drawn from data on mild wheezing, hence presenting issues of indirectness and leading to a CoE judgment of very low.

Moderate to severe urticaria or eczema. The same study (146 patients)[86] also found no apparent difference in the risk of urticaria between the formulas, but the evidence was very uncertain and could not exclude the possibility of sizeable benefit or harm (RR: 0.89, 95% CI: 0.49 to 1.60; RD: 3 fewer per 100 patients, 95% CI: from 13 fewer to 15 more per 100). Nocerino et al. (146 patients)[86] and another observational study (44 patients)[90] found that children receiving eHF-CM might present an equal risk of developing the risk of eczema than the ones with SF, without excluding either an appreciable benefit or harm (RR: 0.83, 95% CI: 0.58 to 1.20; RD: 7 fewer per 100 patients, 95% CI: from 17 fewer to 8 more per 100 patients).

Development of FPIES. One study with 44 patients (only 10 in the SF group)[90] suggested there might be no difference between eHF-CM and SF in the risk of causing FPIES, yet the CI was very imprecise, not excluding major harm or possibly minor benefit (RR: 1.57, 95% CI: 0.08 to 30.32; RD: 6 more per 100 patients, 95% CI: 9 fewer to 21 more per 100 patients).

Sensitization to or discontinuation of the formula. One trial with only 72 patients[63] suggested that more patients may get sensitized to SF compared with eHF-CM, however, the synthesized estimate could not suggest a single direction of effect, plus the very limited number of events (0/35 in the eHF-CM arm, and 3/37 in the SF arm) makes the evidence very imprecise leading to a very low CoE. Despite these limitations, the best estimate of effect corresponds to a RR of 0.15 (95% CI: 0.01 to 2.82) with an estimated risk difference of 7 fewer per 100 patients (95% CI: from 8 fewer to 15 more per 100 patients). Still, this finding should be interpreted carefully, especially when considering that an identified observational study with 37 participants[85] showed opposing evidence (3/8 in eHF-CM arm vs 0/29 in SF arm developed secondary sensitization). The same study and 2 other trials (169 participants)[63,74,81] also reported data concerning the discontinuation or changing of the formula. All three studies reported few events, raising serious concerns of imprecision and leading to a very low confidence in our finding, which suggested no difference between eHF-CM and SF in the risk of discontinuing the formula or requiring a change (RR: 0.86, 95%CI: 0.38 to 1.96; RD: 2 fewer per 100 patients, 95%CI: 9 fewer to 13 more per 100 patients).

Failure to thrive. Two studies (89 participants)[63,81] showed a larger weight gain in children receiving eHF-CM compared with SF (0.23 z-score change, 95% CI: 0.01 to 0.45 z-score), while only Agostoni et al[63] reported the change in length, showing no difference across the 2 formulas (0.27 z-score change, 95%CI -0.19 to 0.73).

Outgrowing CMA. Three randomized trials (240 participants)[84,86,89] possibly found no noticeable difference between eHF-CM and SF at 12 months in the probability of favoring acquisition of tolerance to CMA (RR: 0.96, 95% CI: 0.63 to 1.46; RD: 2 fewer per 100 patients, 95% CI: 16 fewer to 20 more per 100 patients), but the evidence was considered as very uncertain.

We found no evidence informing the effect of eHF-CM vs SF on the probability of developing reactions requiring epinephrine administration, or gastrointestinal manifestations of any severity.

Non IgE-mediated cow's milk allergy

We identified 2 trials[74,81] (125 participants) and two observational studies[84,90] (107 participants) informing the estimates for eHF-CM vs SF in non-IgE CMA patients, but the certainty in the evidence was rated as very low for all the outcomes concerning this pairwise comparison in this population.

Moderate to severe urticaria or eczema. One observational study (44 participants)[90] showed that the hydrolysate formula possibly appeared to have no relative effect on the risk of developing eczema (RR: 0.93, 95% CI: 0.52 to 1.68; RD 4 fewer per 100 patients, 95%CI: 29 fewer to 41 more per 100 patients).

Development of FPIES. The same study by Trakulpark[90] showed comparable risks of developing FPIES between eHF-CM and SF (RR: 1.57, 95% CI: 0.08 to 30.32; RD 6 more per 100 patients, 95%CI: 9 fewer to 21 more per 100 patients), yet the evidence was very uncertain.

Sensitization to or discontinuation of the formula. Two trials (125 participants)[74,81] showed no clear difference and did not discriminate any direction of effect between eHF-CM and SF on the risk of discontinuing or changing the formula

(RR: 0.61, 95%CI: 0.09 to 4.17; RD: 5 fewer per 100 patients, 95%CI: 11 fewer to 40 more per 100 patients). One observational study[83] also provided very low certainty evidence that, despite showing no difference as well, was suggestive of the opposite direction of effect (RR: 2.15, 95% CI: 0.84 to 5.51).

Failure to thrive. One trial with only 26 participants[81] showed that eHF-CM and SF might be equally effective at supporting physiological weight gain (0.19 z-score change, 95%CI -0.07 to 0.45), yet the synthesized evidence was very uncertain due to serious concerns on the quality of the trial conduction, as well as of imprecision and indirectness of measured outcome.

Outgrowing CMA. One observational study (63 participants)[84] reported data suggestive that eHF-CM, compared with SF, might increase the probability of achieving tolerance to CM, even though did not allow to discriminate the effect size (RR: 1.86, 95%CI: 1.03 to 3.37; RD: 27 more per 100 patients, 95%CI: 1 to 74 more per 100 patients).

No identified evidence informed the effect of eHF-CM vs SF in non-IgE CMA on the probability of developing gastrointestinal manifestations.

Hydrolyzed rice formula vs soy formula

The evidence profiles in Supplementary Tables 9 and 10 summarize all the synthesized information about this comparison in children with IgE-mediated and non-IgE-mediated CMA.

The forest plots illustrating the individual studies' and pooled effect estimates for each outcome are available as Supp. Figures 45 to 55.

IgE-mediated cow's milk allergy

We identified 2 trials[63,69] (88 participants) and 3 observational studies[84,86,89] (246 participants) with relevant data eligible for synthesizing evidence on HRF vs SF in IgE CMA. We rated the certainty of the evidence informing on all outcomes as very low.

Severe asthma/wheezing. One observational study by Nocerino et al (146 patients)[86] showed that the 2 formulas might be at equal risk of eliciting wheezing of any severity (RR: 0.90, 95% CI: 0.53 to 1.54; RD: 3 fewer per 100 patients, 95%CI: 14 fewer to 16 more per 100 patients). We accounted for the concerns of indirectness due to the lack of a standardized definition for the severity of the outcomes.

Moderate to severe urticaria or eczema. The same study (146 patients) did not find a difference between HRF and SF in the risk of developing urticaria (RR: 1.11, 95%CI: 0.64 to 1.92; RD: 3 more per 100 patients, 95%CI: 9 fewer to 23 more per 100 patients), or eczema (RR: 0.85, 95%CI: 0.54 to 1.34; RD: 6 fewer per 100 patients, 95%CI: 17 fewer to 13 more per 100 patients) however, for both outcomes, the evidence was very uncertain and did not exclude the possibility that such a difference exists.

Sensitization to or discontinuation of the formula. Two trials (88 participants)[63,69] reported data suggestive of no appreciable difference in the risk of changing or stopping the formula due to lack of tolerance (RR: 1.27, 95%CI: 0.43 to 3.78; RD: 3 more per 100 patients, 95%CI: 6 fewer to 31 more per 100 patients). Agostoni et al (73 participants) also reported information on the rate of secondary sensitization to the administered formulas throughout the duration of the trial, possibly showing no superiority of HRF over SF (RR: 0.15, 95% CI: 0.01 to 2.82; RD: 7 fewer, 95%CI: 8 fewer to 15 more per 100 patients). The evidence was very uncertain as a result of the small number of events and lack of blinding for the trial.

Failure to thrive. The same 2 trials (88 participants)[63,69] reported data possibly showing no difference in growth rates between children assuming HRF and others receiving SF, both with respect to weight gain (0.25 z-score change, 95% CI -0.11 to 0.60) and length increase (0.01 z-score change, 95%CI -0.37 to 0.39).

Outgrowing CMA. We synthesized evidence from three observational studies (246 participants)[84,86,89] suggesting no superiority between HRF and SF in affecting the probability of growing tolerant to milk proteins (RR: 1.11, 95% CI: 0.88 to 1.39; RD: 5 more per 100 patients, 95%CI: 5 fewer to 17 more per 100 patients), but the evidence was very uncertain.

We could not identify relevant data informing on the risk of developing anaphylaxis or reactions

requiring epinephrine administration, gastrointestinal manifestations of any severity, and FPIES.

Non IgE-mediated cow's milk allergy

Only one trial[69] (16 participants) and one observational study[84] (55 participants) were found with relevant data comparing HRF and SF in non-IgE CMA infants. We rated the certainty in the synthesized evidence as very low for all outcomes.

Sensitization to or discontinuation of the formula. We found very little information in the trial conducted by D'Auria et al (16 participants),[69] which reported no patient developing secondary sensitization to the administered formula, neither in the HRF or the SF group. This finding should be interpreted carefully, due to the ample limitations in the identified evidence, therefore any conclusion of equivalence should be further investigated in the future.

Failure to thrive. The same trial[69] provided very low certainty evidence, suggesting no difference in effect between the two formulas with respect to supporting infants' growth [weight (0.07 z-score change, 95%CI -0.47 to 0.61); length (0.25 z-score change, 95%CI -0.57 to 1.07)], although the findings were very uncertain.

Outgrowing CMA. One observational study (55 participants)[84] showed that HRF, compared with SF, might possibly increase the probability of tolerance to milk, still the pooled estimate could not exclude the chance of no difference between the two formulas (RR: 1.81, 95%CI: 0.97 to 3.38; RD: 25 more per 100 patients, 95%CI: 1 fewer to 74 more per 100 patients) and the evidence was deemed too uncertain to support a definite conclusion.

We could not identify relevant data informing on the risk of developing gastrointestinal or cutaneous manifestations of any severity, and FPIES.

Formulas supplemented with probiotics vs. formulas without probiotics

The evidence profiles with information on the effect estimates and the judgments on the certainty in the evidence for this comparison in IgE and non-IgE CMA are shown in Supplementary Tables 11 and 12. The forest plots for all the outcomes of this comparison are available as Supp. Figures 56 to 66.

IgE-mediated cow's milk allergy

We included 4 trials[64,65,75,82] (343 participants) and one observational study[88] (195 participants) for synthesizing the evidence on this pairwise comparison. We found low-certainty evidence

informing on the relative probability of outgrowing CMA and developing eczema following formula assumption, while for the remainder of outcomes, the evidence was rated to be of very low certainty.

Anaphylaxis. There was no study directly measuring the rate of anaphylaxis across the intervention arms; therefore, also in this case, we deemed appropriate the use of "epinephrine use" as a surrogate outcome. One study (195 participants)[88] found no difference in effect between formulas with probiotics (LGG) and formulas alone (RR: 0.33, 95%CI: 0.04 to 2.62; RD: 3 fewer per 100 patients, 95%CI 5 fewer to 8 more per 100 patients).

Severe asthma/wheezing. One trial by Berni Canani et al (193 participants)[64] reported a lower risk of wheezing of any severity in children receiving formulas supplemented with probiotics (LGG) rather than unsupplemented formula (RR: 0.12, 95%CI: 0.02 to 0.95; RD: 7 fewer per 100 patients, 95%CI: 8 fewer per 100 to 4 fewer per 1000 patients). However, the evidence was very uncertain and did not allow to discriminate the effect size.

Moderate to severe urticaria or eczema. One trial (203 patients)[64] showed the might not be any sizable difference in the risk of urticaria between formulas with probiotics (LGG) and formulas alone, without excluding however the possibility of either benefit or harms (RR: 0.97, 95%CI: 0.14 to 6.74; RD: 1 fewer per 1000 patients, 95%CI: 2 fewer to 12 more per 100 patients). The same study by Berni Canani,[64] together with 2 additional trials[75,82] (total 322 participants) also investigated the effect on the risk of developing eczema, as well as the severity of this cutaneous manifestation. However, the data could not be quantitatively synthesized due to inconsistent reporting and outcome measurement modalities. The trials by Majama[75] and Viljanen[82] reported the SCORAD severity, yet in one case, it was measured as an "end-of-study" value, while in the other, it was reported as a change from baseline. The differences between groups were on average small (1–4 points in SCORAD) and unlikely to be clinically important (MID ~8 points). Another trial,[64] on the other hand, reported the number of children presenting eczema at the end of 36 months observation period, also showing no sizeable difference in effect (RR: 0.16, 95% CI: 0.02 to 1.32; RD: 5 fewer per 100 patients, 95%CI: 6 fewer to 2 more per 100 patients).

Sensitization to or discontinuation of the formula. We identified 1 observational study (195 participants)[88] with relevant information on formula discontinuation. It showed that the supplementation with probiotics (LGG), compared with unsupplemented formula, might not increase the need of discontinuing treatment due to lack of tolerance (RR: 0.77, 95%CI: 0.26 to 2.28; RD: 2 fewer per 100 patients, 95%CI: 7 fewer to 11 more per 100 patients).

Outgrowing CMA. Two trials with altogether 236 patients[64,65] found adding probiotics (LGG) to formulas, compared with formulas alone, could favor tolerance acquisition (RR: 2.47, 95%CI: 1.03 to 5.93; RD: 27 more per 100 patients, 95%CI: 1 to 91 more per 100 patients).

We found no evidence informing on the probability of developing gastrointestinal symptoms, FPIES, or secondary sensitization to administered formulas. We also could not identify studies investigating the effect of probiotic supplementation to formulas, as compared to formulas alone, on supporting IgE CMA children's physiological growth.

Non IgE-mediated cow's milk allergy

We identified 5 trials[65,70,72,75,82] (366 participants) and 1 observational study[88] (195 participants) investigating formulas supplemented with probiotics (LGG or L. casei CRL431, and B. lactis Bb-12) vs formulas alone in non-IgE CMA children.

Moderate to severe urticaria or eczema. Four trials reported severity of eczema measured with the SCORAD tool, finding, on average, small differences across groups (0.1–4 points) that are unlikely to have clinical relevance (MID ~8 points). Two studies (186 participants)[70,82] reported the scores as a change from baseline with a pooled mean difference of −0.71, 95% CI: 4.07 to 2.66. Two other studies (137 participants)[72,75] instead measured the final scores, with a pooled mean difference of −1.48, 95% CI: 4.59 to 1.64. The study by Dupont et al[70] also reported the

number of events in the 36 months observation period (4/59 in the formulas and *L. casei* CRL431, *B. lactis* Bb-12 arm vs 6/60 in the formulas alone arm; RR:0.68, 95% CI: 0.20 to 2.28; RD: 3 fewer per 100 patients, 95% CI: 8 fewer to 13 more per 100 patients).

Sensitization to or discontinuation of the formula. The study by Ovcinnikova et al. (195 participants)[88] showed that probiotics (LGG) supplementation to formulas, as compared with formulas alone, might imply the same risk of discontinuing treatment due to safety concerns (RR: 0.77, 95%CI: 0.26 to 2.28; RD: 2 fewer per 100 patients, 95%CI: 7 fewer to 11 more per 100 patients).

Failure to thrive. One RCT (104 participants)[70] showed no difference in effect by supplementing formulas with probiotics (*L. casei* CRL431 and *B. lactis* Bb-12), compared to unsupplemented formulas, with respect to supporting children's growth [weight gain (0.1 kg, 95%CI -0.34 to 0.54); length increase (0.2 cm, 95%CI -1.07 to 1.47)], yet the evidence was very uncertain.

Outgrowing CMA. Two trials (140 participants)[65,72] showed that adding probiotics (LGG, and *L. casei* CRL431/*B lactis* Bb12) to formulas, compared to administering formulas alone, might not affect the probability of acquiring tolerance to milk, still, the pooled estimate was very imprecise, hence could not exclude the possibility of a treatment effect (RR: 1.32, 95%CI: 0.70 to 2.52; RD: 24 more per 100 patients, 95% CI: 22 fewer to 100 more per 100 patients).

We could not identify relevant data informing on the risk of developing general gastrointestinal manifestations, or FPIES.

DISCUSSION

This systematic review with multiple pairwise meta-analyses of 14 trials and 7 NRS including 2430 participants (1132 from trials) and 5 different interventions currently represents the most comprehensive assessment on the use of specialized formula for managing CMA in infants.

We found very low certainty evidence that eHF-CM, compared to AAF, might increase the probability of outgrowing milk allergy, while also reducing the risk of severe vomiting and developing FPIES for IgE CMA patients. On the other hand, very low certainty evidence also suggested that eHF-CM, compared to AAF, might be associated with a higher risk of impaired growth for IgE-mediated CMA infants, even though the effect estimates suggested the effect to be trivial in size. We found the effect by eHF-CM, compared with AAF, to be consistent also for non-IgE-mediated CMA with respect to failure to thrive and risk of vomiting, as supported by very low certainty evidence.

Furthermore, compared with SF, eHF-CM might reduce the risk of growth impairment, with respect to weight decrease, for IgE CMA patients and favor acquisition of CM tolerance for non-IgE CMA populations (both very low CoE). The pairwise comparisons between eHF-CM vs HRF, and HRF vs SF, showed equivalent effect on the investigated outcomes for both IgE and non-IgE mediated CMA, as supported by very low CoE.

Lastly, for IgE CMA patients, we found low certainty evidence that the addition of probiotics (LGG) to formula supplements (casein eHF-CM) might favor tolerance acquisition, while very low certainty evidence suggested that they might also reduce the risk of severe wheezing, still the uncertainty in the evidence did not allow to draw a definite conclusion. Contrastingly, in non-IgE-mediated CMA infants, the addition of probiotics (LGG) may have no significant effect, as supported by low to very low CoE.

This systematic review with meta-analyses informed the WAO DRACMA Guidelines recommendations on the use of formulas without or with probiotics for the management of children with CMA. The guidance paper[18] was accepted before we conducted the last update of the systematic search (January 2024), therefore presenting slight variations with respect to the timing of the search and number of screened references. Any update to this review that was done after the guideline was published did not affect the evidence used in the guidelines and, according to the WAO DRACMA guideline panel members, did not warrant any changes to the recommendations.

Strengths and limitations

The strengths of this review include the most updated and comprehensive evidence on the use of formula supplements and probiotics for CMA patients, the wide comparison of multiple clinically available interventions, and the rigorous process critical appraisal of the evidence using the GRADE approach.

In a methodological perspective, the major study limitation consists in the use of the Newcastle-Ottawa Scale (NOS) tool rather than the Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) to assess the RoB for observational studies. We opted to use the NOS for consistency with the previous systematic reviews done for the DRACMA guidelines.

Similar to other evidence syntheses,[93,94] we found several limitations in the identified evidence, primarily concerning the studies' quality, limited population size, poor definition and reporting of patient populations, most notably with respect to the type of CMA, inconsistent quality of outcome reporting, and limited variety and standardization of investigated interventions, both with respect to compared formulas and probiotics. These inconsistencies in the researched populations and outcome measures (intransitivity of the evidence), together with the narrow set of formulas compared in studies, and the paucity of publications reporting the same outcomes made it impossible to perform any network meta-analyses allowing only for cautious pairwise comparisons.

We minimized the issues with reporting by contacting authors for clarifications and by having a dedicated evaluation domain when assessing the studies' quality and critically appraising the identified body of evidence.

Research implications

The critical revision of the evidence done for this study highlighted several items that should be addressed by future researchers in this field, in order to achieve better quality scientific evidence to inform policy making and clinical practice:

A) Researchers should investigate values and preferences of those affected with CMA, their caregivers, and other stakeholders in this field to improve the understanding of the importance of particular health outcomes which would allow for more personalized decision-making.

B) Future studies should focus on proper standardization of interventions, their doses and administration modalities so to minimize inconsistency and facilitate evidence synthesis.

C) More high-quality trials should be conducted focusing on appropriately defining and reporting the patient disease status as either IgE or non-IgE CMA, severity of sensitization, and reactions while ensuring that study results are correctly stratified.

D) Investigators should opt for a better quality of outcome measurement and reporting, prioritizing outcomes important for patients and their caregivers and – if possible – continuous rather than binary outcomes.

E) Future studies should consider comparing a wider sample of the currently available interventions, possibly having more than two study arms at the time to achieve more precise and higher-quality effect estimates. Particular efforts should be made in investigating AAF, HRF, SF, and the addition of probiotics. This would allow for network meta-analyses to compare all available management options, better representing clinical practice.

F) Additional, rigorously conducted studies, should investigate the resource requirements for formulas' supplements and probiotics.

Clinical implications

Several specialized formulas can be offered to patients undergoing an avoidance diet from dairy products. While appearing mostly equally effective, eHF-CM appears to be the overall most beneficial with respect to patient important outcomes.

Abbreviations

AAF: Aminoacid formula; AHRQ: Agency for Healthcare Research and Quality; CADTH: Canadian Agency for Drugs and Technologies in Health; CENTRAL: Central Register of Controlled Trials; CI: Confidence interval; CMA: Cow's milk allergy; CoE: Certainty of the evidence; DRACMA:

Diagnosis and Rationale for Action against Cow's Milk Allergy; eHF-CM: Extensively hydrolyzed cow's milk-based formula; FPIES: Food protein-induced enterocolitis syndrome; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HRF: Hydrolyzed rice formula; LGG: Lacticaseibacillus rhamnosus GG; MD: Mean difference; MID: Minimally important difference; NICE: National Institute for Health and Care Excellence; NRS: Nonrandomized study; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT: Randomized controlled trial; RD: Risk difference; RoB: Risk of bias; RR: Risk ratio (Relative risk); SF: Soy formula; SMD: Standardized mean difference; WAO: World Allergy Organization.

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Contributions
JLB, AF, HJS originally conceived this work. AB and JB wrote the first draft. SW, AB and JLB did the literature search. AB, RF, SA and JLB screened records, evaluated full texts, and extracted data. AB, JB, RF, AC evaluated risk of bias. JLB and AB did the statistical analyses. HJS, DKC, SA, and SW provided critical methodological input. All other authors reviewed the manuscript and provided critical intellectual contributions to the analysis and interpretation of the data, and the revision of the manuscript.

Ethics statement
This systematic review did not require ethic approval.

Authors' consent for publication
All authors reviewed the final version and consented to publication of this work in the World Allergy Organization Journal.

WAO DRACMA guideline group – COI declarations
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Y Vandenplas – Abbott Nutrition, Alba Health, Arla, Ausnutria, Biogaia, Biocodex, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Hero, Hypocrata, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Orafti, Phacobel, Phathom Pharmaceuticals, Pileje, Sanulac, Sari Husada, United Pharmaceuticals (Novalac), Wyeth, Yakult.
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Declaration of competing interest
HJS and JLB, on behalf of McMaster University, received a research grant from the World Allergy Organization to conduct this review that was deposited into the university research account. RS participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott, Else, and Nestlé. HS serves as a board member of the International Scientific Association for Probiotics and Prebiotics (ISAPP), an unpaid and voluntary role. They have participated as a clinical investigator, advisory board member, consultant, and speaker for several companies, including Arla, BioGaia, Biocodex, Danone, Dicofarm, Nestlé, NNI, Nutricia, Mead Johnson, and Novalac.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100947.

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