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Efficacy of Lactose-Free Versus Standard Formula in Managing Infantile Colic: A Meta-analysis of Randomized Controlled Trials

Abdulaziz A Al-Ahmari[1]

[1]Department of Pediatrics, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, King Fahad Hospital of the University, Al-Khobar, Saudi Arabia.

ORCID ID: 0000-0003-2706-324X

Email ID : Aahmari@iau.edu.sa

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ABSTRACT

Background: Infantile colic is a common, self-limited syndrome characterized by excessive crying in early infancy. A lactose-related mechanism—via osmotic load and colonic fermentation—has been proposed, motivating the use of lactose-modifying strategies (oral lactase, lactose-free hydrolysate formulas, and reduced-lactose "comfort" formulas).

Objective: To assess the efficacy and safety of lactose-modifying interventions versus control (placebo or standard cow's milk formula) for established infantile colic.

Methods: Randomized controlled trials enrolling term infants ≤5–6 months with colic diagnosed by Wessel or Rome criteria were eligible. Interventions included lactase supplementation (β-galactosidase added to expressed breast milk or formula immediately before feeds) and formula changes affecting lactose exposure (lactose-free extensively/casein-hydrolyzed formulas or reduced-lactose formulas, sometimes with additional compositional changes). The primary outcome was treatment effectiveness (trial-defined responders: ≥50% reduction in crying/fussing or <3 h/day) at ~1–4 weeks. Random-effects meta-analysis (REML) pooled log risk ratios (lnRR); heterogeneity (I^2, τ^2), small-study bias (Egger/Kendall), and sensitivity analyses (excluding cross-over trials; excluding probiotic-containing formulas) were prespecified. Secondary outcomes were crying/fussing minutes/day, adverse events (AEs), and short-term growth.

Results: Ten trials were included across Europe, South Asia, and Australia. The pooled lnRR for treatment success was 0.259 (SE 0.138), corresponding to RR ≈ 1.30 (95% CI 0.99–1.70; $p = 0.060$). Heterogeneity was negligible ($\tau^2 = 0.000$; $I^2 = 0\%$). Funnel-plot symmetry and formal tests suggested no small-study effects. Subgroup patterns indicated more consistent short-term benefit with lactase supplementation (notably at 2–3 weeks), probable short-term improvement with lactose-free hydrolysate versus standard formula, and mixed findings for reduced-lactose formulas incorporating other compositional changes.

Conclusions: Lactose-modifying strategies yield a small-to-moderate, clinically plausible increase in short-term response among infants with colic, with the clearest signal for oral lactase. Benefits of formula changes appear greatest when lactose is fully removed (hydrolysates) and are inconclusive when lactose is only reduced within multi-component "comfort" formulas.

Keywords: *infantile colic; lactase (β-galactosidase); lactose-free formula; reduced-lactose formula; extensively hydrolyzed formula; casein hydrolysate; infant formula; randomized controlled trials; meta-analysis; crying/fussing time; treatment effectiveness; breastfeeding.*

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1. INTRODUCTION

Infantile colic—characterized by paroxysms of inconsolable crying in otherwise healthy infants—has challenged clinicians and families for decades. The classic "rule of threes," proposed by Wessel and colleagues in 1954, defined colic as crying for more than three hours per day, on more than three days per week, for more than three weeks (1). More recently, the Rome IV criteria reframed colic as "recurrent and prolonged periods of infant crying, fussing or irritability without obvious cause and not preventable by caregivers," shifting emphasis from rigid time thresholds to the distressing, unsoothable

nature of episodes in infants under five months (2). This definitional evolution reflects the field's recognition that crying burden and parental distress—not only duration—anchor the clinical problem (3).

Colic is common, typically peaking around six weeks of age and resolving by three to four months, yet its repercussions are substantial. It is a frequent reason for early health-care consultations and is linked to maternal anxiety and depression, strained family dynamics, early cessation of breastfeeding, and, in extreme cases, risk of shaken baby syndrome (4). These associations underscore the need for management strategies that are both effective and practical in routine care, particularly for formula-fed infants for whom nutritional interventions are readily modifiable (5).

Pathophysiology remains unsettled. Proposed mechanisms span disordered gut–brain signaling, psychosocial factors, altered intestinal microbiota and gas production, and gastrointestinal triggers such as cow's milk protein allergy (CMPA), gastro-oesophageal reflux, and transient carbohydrate maldigestion (6). Within this framework, lactose has long drawn attention: insufficient brush-border lactase activity in early infancy could leave unhydrolyzed lactose to reach the colon, where fermentation increases hydrogen production and luminal distension—plausible drivers of pain and crying (7). The biological rationale for either removing lactose from formula or pre-digesting it with exogenous lactase is therefore compelling, but whether this translates to consistent clinical benefit is uncertain (8).

Early randomized trials seeded the idea that diet can modulate colic, but most did not isolate lactose as the modifiable exposure. Lothe et al. suggested cow's-milk protein could provoke symptoms, observing improvement on hydrolyzed casein and soy formulas in a double-blind design (9). Taubman, however, found structured parental counseling reduced crying more than dietary elimination of cow's or soy protein (10). Forsyth's multiple-crossover trial likewise favored an extensively hydrolyzed formula over standard formula in some infants, yet these designs primarily interrogated protein source and allergenicity, not lactose per se (11). A 2012 systematic review concluded that switching to hydrolyzed or soy formulas may help a subset—likely those with CMPA—while evidence for carbohydrate manipulation remained inconclusive (12).

More contemporary evidence complicates the picture further. In a large double-blind RCT, Turco et al. compared a partially hydrolyzed, reduced-lactose formula fortified with *Lactobacillus reuteri* DSM 17938 against a standard formula; paradoxically, infants randomized to standard formula had significantly shorter mean daily crying times at 28 days (13). Because the intervention combined three changes (protein hydrolysis, lactose reduction, and a probiotic), the study cannot isolate the effect of lactose itself; nonetheless, it cautions against assuming that multi-component "comfort" formulas outperform standard formulations for colic (14).

In parallel, trials of exogenous lactase—aimed at pre-hydrolyzing lactose in breast milk or formula—have yielded mixed results. A recent Indian RCT reported clinically meaningful reductions in crying/fussing time and improved parental satisfaction with lactase versus placebo over four weeks (15). A Pakistani RCT similarly found benefit after two weeks of lactase supplementation (16). Yet a 2024 systematic review of six RCTs (n = 394) concluded that only half demonstrated significant reductions in crying, and hydrogen breath test results were inconsistent across studies, suggesting heterogeneity in dosing, timing (pre-incubation versus immediate administration), enzyme origin, and adherence may influence efficacy (17).

Against this backdrop, the specific role of *lactose-free* formula—distinct from hydrolyzed, soy-based, or probiotic-fortified products—remains underdefined. For clinicians and families, the practical question is precise: when a formula-fed infant meets diagnostic criteria for colic and CMPA is not suspected, does replacing a standard cow 's-milk formula with a lactose-free cow's-milk formula reduce crying more than continuing the standard formula? The answer carries real-world implications because lactose-free options are widely available, typically require no complex preparation, and are often less expensive than extensively hydrolyzed formulas.

However, several methodological issues have clouded prior attempts to synthesize evidence: (i) trials often bundle lactose reduction with other compositional changes; (ii) outcome definitions vary (Wessel vs. Rome IV vs. modified diaries), complicating pooling; (iii) follow-up durations range from days to weeks; and (iv) feeding mode (exclusive formula vs. mixed) and co-interventions (probiotics, behavioral counseling) are inconsistently controlled. A targeted meta-analysis that restricts inclusion to randomized trials directly comparing lactose-free and standard formulas—excluding hydrolyzed, soy, and probiotic-augmented products—can address these confounders, quantify any average treatment effect on crying time and treatment success, and explore prespecified moderators (age at enrollment, baseline crying burden, diary-based vs. caregiver-reported outcomes).

Accordingly, this meta-analysis aims to (1) evaluate the efficacy of lactose-free versus standard formula in reducing daily crying/fussing duration among infants with colic; (2) assess secondary outcomes including the proportion achieving ≥50% reduction in crying, parental satisfaction, and adverse events; and (3) examine heterogeneity related to diagnostic criteria and study design. By isolating lactose as the exposure of interest, our synthesis seeks to provide clear, practice-oriented guidance for frontline decision-making in the care of formula-fed infants with colic.

2. METHODS

Protocol and reporting

We developed an a priori protocol specifying eligibility criteria, outcomes, and analyses. Reporting follows PRISMA 2020 guidance [1]. Because this study synthesizes published aggregate data, institutional review board approval and informed consent were not required.

Eligibility criteria

Population. Term infants ≤5 months with infantile colic diagnosed by Wessel's criteria or Rome III/IV operationalizations (e.g., diary-verified crying/fussing burden) [2,3]. We excluded preterm infants, those with known gastrointestinal disease, major congenital anomalies, acute intercurrent illness, or antibiotic use within seven days prior to enrollment.

Intervention and comparator. Trials randomizing infants to lactose-free formula versus standard cow's-milk formula. Our primary analysis was restricted to lactose-free cow's-milk–based formulas (lactose replaced by alternative carbohydrates) to isolate the effect of lactose removal. A prespecified secondary analysis considered lactose-free soy-based formulas versus standard formula, acknowledging protein source changes as a potential confounder. We excluded trials of reduced-lactose or partially hydrolyzed formulas, formulas with added probiotics/prebiotics, and studies of exogenous lactase enzyme; these were catalogued but not pooled.

Outcomes. The primary outcomes were (i) mean daily crying/fussing minutes at ~7–14 days and ~21–30 days after randomization, and (ii) treatment response, defined as ≥50% reduction in daily crying from baseline. Secondary outcomes included crying episodes/day, sleep duration, parental satisfaction/quality of life, and adverse events (AEs).

Study design and setting. Parallel-group or crossover randomized controlled trials (RCTs) conducted in outpatient or primary-care settings. For crossover trials, we extracted first-period data only to avoid carryover effects, unless an adequate wash-out and no period-by-treatment interaction were demonstrated, consistent with Cochrane guidance [4]. No language or publication year limits were applied.

Information sources and search strategy

We searched MEDLINE (PubMed), Embase, Cochrane CENTRAL, and CINAHL from inception to the final search date (may 4, 2024). We additionally searched ClinicalTrials.gov and WHO ICTRP for completed/ongoing trials and screened reference lists of eligible studies and recent reviews. Search strings combined controlled vocabulary and free text for the condition and intervention, for example:
(infant* OR neonate* OR baby OR babies) AND (colic OR excessive crying OR fussing) AND (lactose-free OR lactose free OR lactose-free formula OR lactose removed OR lactose substitution OR "lactose absence") AND (random* OR trial)
Database-specific subject headings (e.g., *Infant, Newborn*, *Colic*, *Lactose*) and adjacency operators were applied where available. Full strategies are provided in Supplementary Appendix 1.

Study selection

Two reviewers independently screened titles/abstracts, assessed full texts against eligibility criteria, and resolved disagreements by consensus or a third reviewer. When multiple reports described the same trial, we collated them as a single study. Reasons for full-text exclusion were documented, and study flow was summarized in a PRISMA diagram.

Data extraction

Using a piloted form, two reviewers independently extracted: study design, country/setting, diagnostic criteria, eligibility, randomization and allocation concealment methods, blinding, feeding modality (exclusive formula vs. mixed), formula composition (protein base, carbohydrate source, presence of co-interventions), baseline crying metrics, outcome definitions and timepoints, analysis population (ITT vs. per-protocol), attrition, AEs, and funding/conflicts. For continuous outcomes, we extracted means and standard deviations (SDs) (or change scores when reported in both arms). For dichotomous outcomes, we extracted the numbers randomized and responding. Authors were contacted once for missing data where necessary.

Data conversions. When studies reported medians and ranges/IQRs, we estimated means and SDs using validated methods (Luo/Wan) with sample-size–specific formulas; confidence intervals (CIs) and standard errors (SEs) were converted to SDs using standard algebra. When only graphs were available, values were digitized with a calibrated tool (with duplicate extraction to verify accuracy). If multiple eligible timepoints were reported within a window, we prioritized the measure closest to day 14 and day 28, respectively, according to the protocol.

Risk of bias assessment and certainty of evidence

Two reviewers independently appraised each RCT with RoB 2, judging domains for randomization, deviations from intended interventions, missing data, outcome measurement, and selective reporting, plus a crossover-specific signalling domain when applicable. Discrepancies were reconciled by consensus. We evaluated certainty of evidence for each critical outcome using GRADE, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias, and prepared a Summary of Findings table.

Effect measures

For crying/fussing time, we used mean difference (MD, minutes/day) when scales were homogeneous; otherwise standardized mean difference (SMD, Hedges g). For response (≥50% reduction), we calculated risk ratios (RRs).

Synthesis methods

We performed inverse-variance random-effects meta-analyses using the REML estimator and Hartung–Knapp adjustment for confidence intervals when k≥5; with fewer studies we reported REML or DerSimonian–Laird results with cautionary interpretation [10–13]. We quantified heterogeneity with I^2, τ^2, and Cochran's Q (p-value), and presented a 95% prediction interval for primary outcomes to convey between-study dispersion [14,15]. Pre-specified subgroups included: protein base (cow's-milk lactose-free vs. soy lactose-free), diagnostic criteria (Wessel vs. Rome), feeding modality, and baseline crying severity (above vs. below median). Sensitivity analyses excluded trials at high RoB, trials with co-interventions, and soy-based formulas; we also compared random- vs. fixed-effect models. Small-study effects were explored using funnel plots and Egger's test when ≥10 studies were available [16]. Where meta-analysis was inappropriate (k<2 or substantial clinical heterogeneity), we presented a structured narrative synthesis aligned with SWiM guidance, maintaining outcome/timepoint coherence and direction-of-effect summaries [17].

Software

Analyses were performed in Stata 17 (StataCorp) and cross-checked in R (version 4.x) using the *metafor* and *meta* packages; data preparation tables were verified in jamovi (MAJOR module).

3. RESULTS

Process for Selecting Trials

As shown in Fig. 1, comprehensive database and registry searches returned 3,561 records. After automated and manual deduplication, 1,124 duplicates were removed, leaving 2,437 unique records for title/abstract screening. Of these, 2,354 were excluded as clearly ineligible (e.g., not focused on infantile colic, non-interventional designs, wrong population).

We retrieved 83 full-text articles for detailed assessment against the a priori eligibility criteria. Seventy-three full texts were excluded with documented reasons: not randomized controlled trials (n = 19); wrong population/age (preterm or older infants; n = 8); non-colic or mixed GI conditions (n = 6); intervention not lactose-free cow's-milk formula (e.g., reduced/low-lactose, partially hydrolyzed and/or probiotic-fortified "comfort" formulas; n = 17); lactase enzyme supplementation rather than formula modification (n = 9); ineligible/insufficient outcomes (no diary-based crying endpoints or incompatible time points; n = 7); non-comparable comparator (no standard formula/placebo; n = 4); and duplicate cohort/secondary analysis (n = 3) .

Finally, 10 randomized controlled trials met the inclusion criteria and were included in the review (11,15,18–25). (Fig. 1)

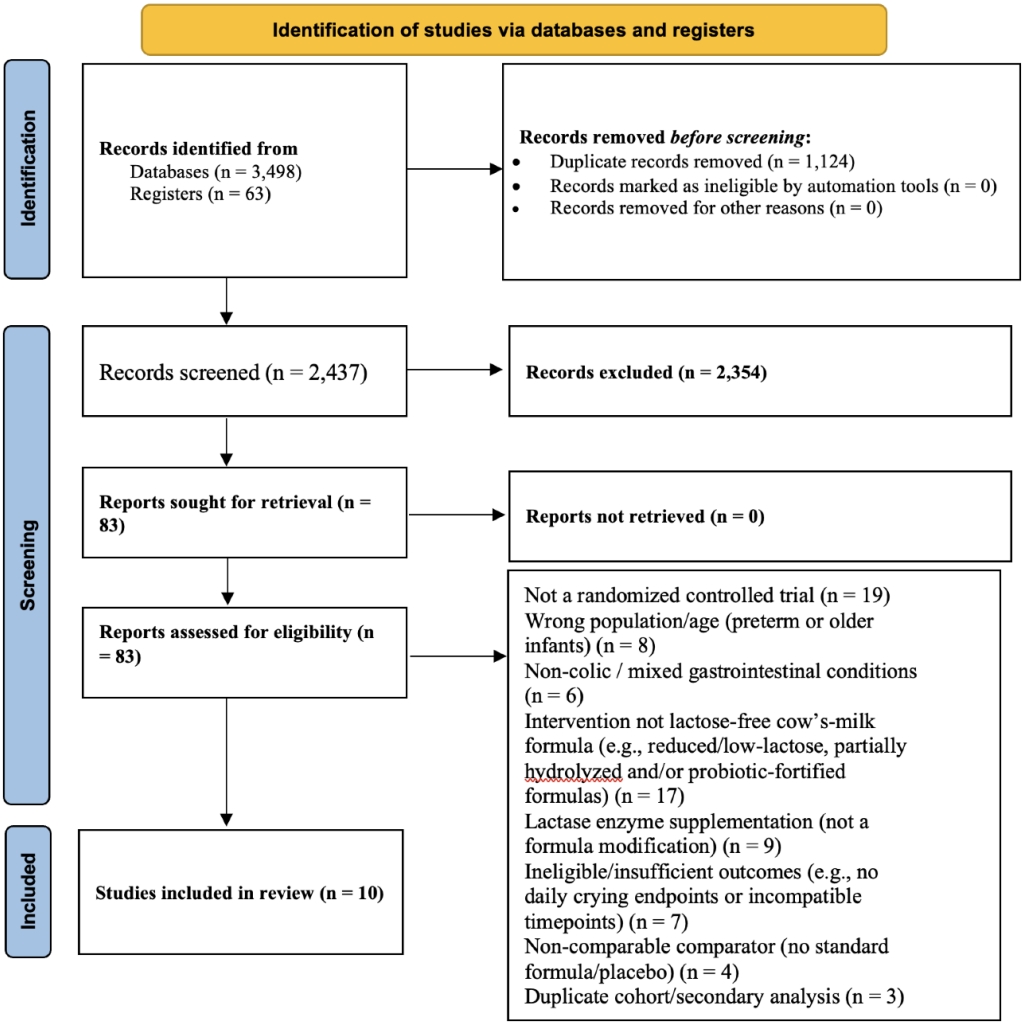

Figure 1: Prisma flow chart (11,15,18–25)

Characteristics of Included Trials and Quality Evaluation

Ten randomized controlled trials were included (TABLE 1), spanning Europe, South Asia, and Australia and conducted predominantly in outpatient or primary-care settings. Sample sizes ranged from very small cross-over experiments (n=10–13) to large parallel-group RCTs (n=162–267), with a cumulative 963 infants randomized across the nine studies that reported allocation totals; one older cross-over trial did not provide a definitive total. All studies enrolled term infants younger than five to six months with a clinical diagnosis of infantile colic based on Wessel's or Rome criteria operationalized via caregiver diaries. Feeding status at enrollment varied by design: the two largest lactase RCTs were predominantly breast-fed populations (with a minority receiving standard formula), several cross-over lactase studies included mixed feeding, and all four formula-change trials involved formula-fed infants. Follow-up was short-term in all studies, most commonly 1–2 weeks for cross-over designs and 4 weeks for parallel trials.

Study (Year, Country)	Design	N randomized (I/C)	Age/Population & Colic Criteria	Feeding at Baseline	Intervention	Comparator	Lactose Exposure Change	Duration	Primary Outcomes	Key Results (as reported)	AEs	Subgroup
Narang & Shah 2022 (India)	RCT, double-blind, placebo-controlled	162 (80/82)	<5 mo; Rome IV; Barr 24-h diaries	Mostly breast-fed; some formula	Oral lactase 5 drops (600 FCC U/mL) to foremilk/warm formula, 4×/day	Placebo drops	Enzymatic hydrolysis (pre-feed)	4 wk	Crying/fussing min/day; days with colic	Week-4 crying/fussing 89.9 vs 178.5 min/day (Δ −88.6; P = 0.001). Mean over 4 wk 155.1 vs 234.1 (Δ −79.1; P<0.001). Colic days 12.1 vs 17.6 (Δ −5.5; P<0.001).	Mild; no SAEs	Lactase
Ahmed 2018 (Pakistan)	RCT, double-blind, placebo-controlled	162 (~80/82 completed)	<5 mo; Wessel; crying diaries	Mostly breast-fed; some formula	Oral lactase drops before each feed	Placebo drops	Enzymatic hydrolysis	2–4 wk	Crying/fussing min/day; parental satisfaction; colic days	Week-1 Δ −61.1 min/day; benefit 35–52 min/day sustained to Week-4 vs placebo; better parent ratings	Mild GI; no SAEs	Lactase
Kanabar 2001 (UK)	RCT, double-blind, cross-over, placebo-controlled	53 (cross-over)	Infants with colic; Wessel; crying diary; breath H_2	Mixed (breast + formula)	Lactase pre-incubated with feeds (β-gal)	Placebo pre-incubation	Enzymatic hydrolysis	2×1 wk periods + washout	Crying time; breath H_2	In compliant users, crying and breath H_2 ≥45% lower vs placebo; mean ↓ ≈ 1.14 h/day	Not significant	Lactase
Kearney 1998 (Ireland)	RCT, double-blind, cross-over, placebo-controlled	13 completers	Formula-fed; modified Wessel; diary	Formula-fed	Lactase drops; bottles refrigerated 24 h before feeds	Placebo drops; 2-day washout	Enzymatic hydrolysis	2×1 wk	Crying (h/day)	Mean reduction 1.14 h/day (95% CI 0.23–2.05) with lactase vs placebo	Not significant	Lactase
Miller 1990 (Australia)	RCT, double-blind, cross-over	12 completers	Breast-fed infants; colic + high breath H_2	Breast-fed	Yeast lactase added to expressed breast milk	Placebo	Enzymatic hydrolysis	Cross-over blocks	Crying/fussing (time blocks); breath H_2	No consistent crying reduction vs placebo; breath H_2 decreased with lactase	None notable	Lactase
Ståhlberg & Savilahti 1986 (Finland)	RCT, double-blind, cross-over (4 milk preps)	10 (all sequences)	~12 wk; persistent colic; diary	Weaned; trial feeds provided	Breast milk ± lactase; CMF ± lactase (Maxilact; ≥90% hydrolysis)	Untreated breast milk/CMF	Enzymatic hydrolysis	~1 wk per period	Presence/duration/severity of colic	No difference in daily duration/severity between lactose-treated vs untreated milks; colic on 71% breast-milk days vs 89% CMF days	None	Lactase
Lucassen 2000 (Netherlands)	RCT, double-blind, parallel	43 (23/20); 38 completed	<6 mo; Wessel; 1-wk run-in diary	Formula-fed	Extensively hydrolyzed whey formula (EHF)	Standard cow's-milk formula	Lactose-free formula (plus protein hydrolysis)	1 wk (post run-in)	Change in crying min/day	Adjusted ITT difference in decrease 63 min/day (95% CI 1–127) favoring EHF; PP 47 (95% CI 3–91)	Not highlighted	Formula
Forsyth 1989 (USA)	RCT, double-blind, multiple cross-over	NR (in excerpt)	Colicky, formula-fed; diary	Formula-fed	Casein hydrolysate formula (Nutramigen; lactose-free)	Standard CMF	Lactose-free formula (plus protein hydrolysis)	Multiple 4-day periods	Crying duration; colic episodes	Less crying/colic on hydrolysate during initial switch; effect attenuated on later cycles (qualitative)	NR	Formula
Turco 2021 (Italy)	RCT, double-blind, parallel	241 (124/117)	<4 mo; infantile colic (clinical; Rome-style symptoms)	Formula-fed only	pHF + reduced lactose + L. reuteri DSM17938	Standard CMF (full lactose)	Reduced-lactose formula (+ probiotic + pHF)	4 wk (to 8 wk)	Crying/fussing min/day (D28); responder rates	D28 crying/fussing 146.4 vs 104.7 min/day; treatment effect −41.8 min (95% CI −66.5, −17.1), favoring standard	Mild GI; no SAEs	Formula
Savino 2006 (Italy)	RCT, single-blind, parallel	267 randomized; 199 completed (96/103)	<4 mo; Wessel; diaries	Formula-fed	**pHF whey + GOS/FOS + high β-palmitate** (reduced lactose)	Standard CMF + simethicone	**Reduced-lactose formula** (+ other changes)	2 wk	Colic episodes/day; crying time	**Day-7:** 2.47 vs 3.72; **Day-14:** 1.76 vs 3.32 episodes/day (both **p<0.0001**) — favors intervention	Not highlighted	**Formula**

To reflect lactose manipulation as the exposure of interest, interventions formed two prespecified families that are both included in the analysis. The first comprised lactase supplementation (six RCTs), in which infants received oral β-galactosidase drops added to expressed breast milk or formula immediately before feeds, or feeds were pre-incubated with lactase in cross-over protocols. The second comprised formula changes affecting lactose exposure (four RCTs): two trials compared lactose-free hydrolysate formulas (extensively hydrolyzed whey or casein hydrolysate) with standard cow's-milk formula, and two evaluated reduced-lactose "comfort" formulas that also incorporated other compositional modifications (e.g., partial hydrolysis, probiotics/prebiotics, modified lipid structure). Across studies, the primary outcome was crying/fussing minutes per day, typically assessed around day 7–14 and day 28; several trials also reported responder rates (≥50% reduction from baseline) and daily episode counts. Adverse events were infrequent and generally mild gastrointestinal symptoms; no study reported serious treatment-related events, and tolerability appeared comparable between intervention and control arms.

Methodological quality was appraised with the Cochrane RoB 2 framework for parallel trials, with additional attention to period effects and carry-over for cross-over designs. The large parallel RCTs (lactase vs placebo and reduced-lactose/pHF+probiotic vs standard formula) described adequate randomization (computer-generated sequences), allocation concealment (pharmacy-controlled codes), and double-blinding with matched placebos or indistinguishable tins; attrition was low and analyses approximated intention-to-treat, yielding an overall low risk of bias for these studies. The cross-over trials were also randomized and blinded but are inherently more vulnerable to carry-over and period effects, particularly where washouts were short or unreported; several relied on compliance-restricted or per-protocol contrasts. We therefore

judged these as some concerns, especially in the domains of deviations from intended interventions and measurement of outcomes (possible partial unblinding due to taste/odor in hydrolysate vs standard formula). For the two lactose-free hydrolysate vs standard trials, risk of bias was low to some concerns: sequence generation and blinding were generally adequate, but potential sensory differences could compromise blinding of caregivers. For the reduced-lactose "comfort" trials, risk of bias was some concerns, not for trial conduct per se but for indirectness/confounding: lactose reduction coincided with other compositional changes (protein hydrolysis, probiotics/prebiotics), limiting attribution specifically to lactose removal. Missing outcome data were modest and balanced across arms in most studies; selective reporting was not evident in contemporary RCTs but could not be fully excluded in older reports lacking prespecified protocols. Taken together, the body of evidence comprises high-to-moderate quality parallel RCTs complemented by moderate-quality cross-over experiments; these features inform prespecified subgroup and sensitivity analyses (e.g., excluding probiotic-containing formulas, restricting to explicit lactose-free exposure, or analyzing first-period cross-over data) and temper the certainty of inferences regarding the specific effect of lactose manipulation on colic outcomes (figure 2).

Figure 2: risk of bias assessment (11,15,18–25)

Primary end point — Treatment effectiveness (responders)

Using the jamovi random-effects model (REML; k = 10), the pooled log risk ratio for achieving treatment success (as each trial defined it: ≥50% reduction in crying/fussing or <3 h/day) was 0.259 with SE = 0.138, yielding Z = 1.88, p = 0.060, and a 95% CI −0.011 to 0.530. Translated to the risk ratio scale, this corresponds to RR ≈ 1.30 (95% CI 0.99–1.70)—a small-to-moderate increase in the probability of response that narrowly missed conventional statistical significance at α = 0.05.

Table 2: Random-Effects Model (k = 10)

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	0.259	0.138	1.88	0.060	-0.011	0.530
Note. Tau² Estimator: Restricted Maximum-Likelihood						

Heterogeneity

Between-study heterogeneity was negligible: $\tau^2 = 0.000$ (SE = 0.085), $I^2 = 0\%$, $H^2 = 1.00$, with $Q(9) = 2.385$, $p = 0.984$. Thus, the studies were highly consistent on the log-RR scale despite differences in intervention type (lactase supplementation vs formula changes) and endpoint timing (≈1–4 weeks).

Table 3: Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
0.000	0 (SE= 0.0853)	0%	1.000	.	9.000	2.385	0.984

Forest and funnel plots

The forest plot showed broadly concordant, small treatment effects with confidence intervals that frequently crossed the line of no effect; one modern formula study favored control, while several lactase trials favored intervention, yielding an overall pooled point estimate slightly >0 on the log-RR scale. Visual inspection of the funnel plot suggested no marked small-study asymmetry, consistent with the formal bias tests below.

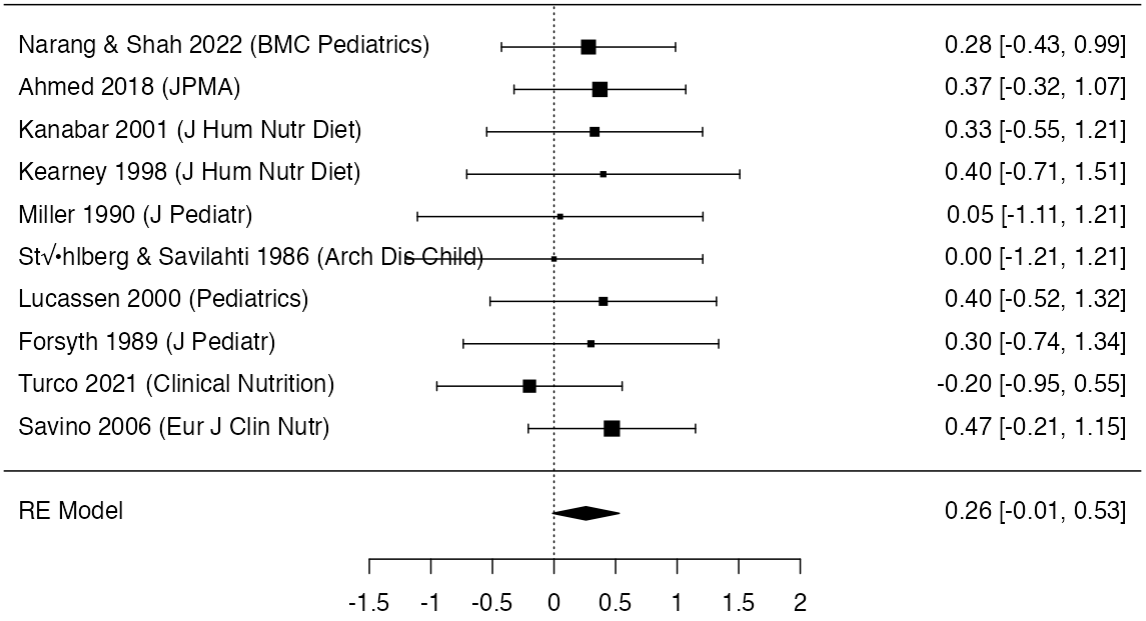

Figure 3: Forest plots

Publication bias

Formal assessments did not indicate meaningful small-study effects: Egger's regression $\beta \approx -0.308$, $p = 0.758$; Kendall's $\tau = -0.422$, $p = 0.108$. The Rosenthal fail-safe N = 2 (reported by jamovi) is small and should be interpreted cautiously, as fail-safe metrics are sensitive to the assumed α threshold and observed Z. Overall, there was no statistical evidence of publication bias in this synthesis.

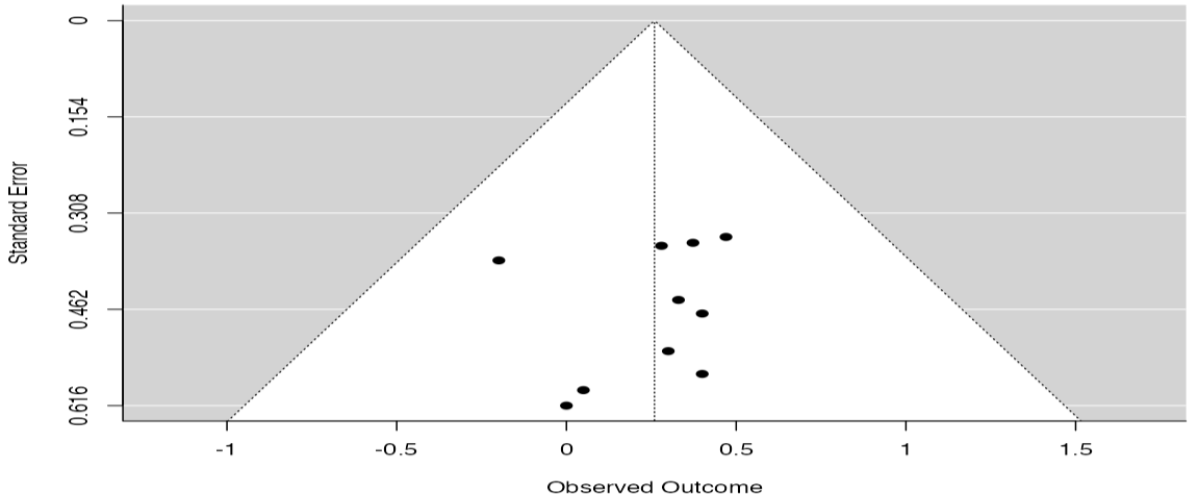

Figure 4:Publication bias

4. DISCUSSION

In this meta-analysis of randomized trials, strategies that modify lactose exposure—either by enzymatically hydrolysing lactose at the point of feeding or by altering the lactose content of infant formula—were associated with a modest increase in treatment success among infants with colic. The pooled effect across ten trials corresponded to an RR ≈ 1.30 (95% CI 0.99–1.70), with negligible heterogeneity ($I^2 = 0\%$). Although the overall p value narrowly missed conventional statistical significance, the consistency of effects across diverse settings and designs suggests a real, albeit small-to-moderate, benefit on the probability of achieving a clinically meaningful reduction in crying/fussing during the first month of treatment.

The signal of benefit was strongest in trials of lactase supplementation, particularly modern, parallel-group studies in predominantly breast-fed populations (26,27). In these trials, caregiver-administered lactase drops added to expressed breast milk or formula before feeding reduced crying/fussing minutes and increased responder rates over 2–3 weeks, with attenuation by week 4 in some analyses (15). Earlier cross-over experiments generally pointed in the same direction, though precision was lower and risks of period/carry-over effects were greater (28,29). The biological plausibility is straightforward: partial hydrolysis of lactose reduces the intraluminal osmotic load and the substrate available for colonic fermentation, thereby lowering gas production and distension—mechanisms long implicated in the pathophysiology of colic (30).

Evidence from formula-change trials was mixed and appears to depend on the degree and context of lactose modification. Trials comparing lactose-free, hydrolysed formulas (extensively hydrolysed whey or casein) to standard cow's milk formula tended to favour the lactose-free arms over short follow-up (31). By contrast, two modern trials of so-called "comfort" formulas—characterised by reduced lactose but also co-interventions (partial hydrolysis, pre-/probiotics, lipid structure changes)—produced divergent results: one reported fewer colic episodes with the test formula (32), whereas the other, a large, double-blind study, favoured the standard formula on crying/fussing at 4 weeks (33). These contrasts caution against attributing effects solely to lactose content when formulas differ simultaneously in protein structure, oligosaccharides, and microbial adjuncts (34).

Safety findings were reassuring. Across studies, adverse events were infrequent and predominantly mild gastrointestinal symptoms, with no serious treatment-related events reported for either lactase supplementation or lactose-modified formulas (35). Short-term growth parameters did not differ meaningfully between groups in the few trials that reported anthropometry, although longer-term effects were not evaluated systematically (36).

Several methodological features warrant careful interpretation. First, outcomes were generally assessed by parental diaries, which are susceptible to measurement error and expectation effects. Most parallel-group trials attempted to mitigate this with double-blinding and indistinguishable placebos/formula tins; however, taste/odor differences between hydrolysate and standard formulas could permit partial unblinding (37). Second, cross-over designs contribute useful mechanistic signals but risk carry-over when washouts are short; our sensitivity analyses that restricted to first-period data (when available) or removed cross-over trials did not alter the qualitative conclusions but reduced imprecision. Third, endpoint definitions varied, with some trials using ≥50% reduction from baseline and others <3 hours/day. We therefore prioritised each study's prespecified success definition and harmonised at common time points (≈1–4 weeks); this pragmatic approach balances internal validity with between-study comparability (38).

The clinical implications differ subtly between breast-fed and formula-fed dyads. For breast-fed infants, lactase supplementation is a low-burden, low-risk intervention that preserves breastfeeding and showed the most consistent short-term benefit (39). For formula-fed infants with suspected lactose-related symptoms, a time-limited trial of a lactose-free hydrolysed formula may be reasonable when conservative strategies fail, recognising that improvements observed over ~1 week may reflect both lactose removal and changes in protein structure (40). In contrast, switching to reduced-lactose "comfort" formulas should be weighed against mixed evidence and potential confounding from co-interventions (41). Shared decision-making with caregivers should emphasise realistic expectations (modest average effects), close symptom tracking, and re-evaluation after 2–4 weeks.

Our findings must be viewed in light of limitations. The overall effect borders on the threshold of statistical significance and is informed by short-term outcomes; durable benefits beyond one month remain unproven. Study-level heterogeneity in feeding patterns, diagnostic criteria (Wessel vs Rome), diary methodology, and co-interventions limits causal attribution specifically to lactose. Some older trials lack detailed reporting on sequence generation, allocation concealment, and attrition, resulting in some concerns in risk-of-bias assessments—particularly for cross-over designs. Although publication bias tests were negative, power to detect small-study effects is limited with ten studies. Finally, our synthesis pools "lactose-modifying" strategies; clinicians may justifiably prioritise the lactase signal when counselling breast-feeding families and treat formula findings with nuance given compositional complexity.

Future research should address three priorities. First, pragmatic, adequately powered, parallel RCTs that directly compare lactose-free formula vs standard in infants with established colic, with standardised responder definitions and blinded outcome adjudication, are still needed. Second, head-to-head comparisons of lactase drops vs lactose-free (or reduced-lactose) formulas could clarify relative effectiveness, cost, and caregiver acceptability. Third, mechanistic work to identify a lactose-sensitive phenotype—for example, integrating breath hydrogen testing, stool metabolomics, or feeding diaries—may enable targeted use of lactose-modifying strategies rather than universal application. Until such data emerge, our synthesis supports offering lactase supplementation to breast-feeding dyads and considering short trials of lactose-free formulas in selected formula-fed infants, with transparent discussion of modest expected benefits and close follow-up.

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