Associations of an Exclusive Human Milk Diet with Morbidity and Mortality in ELBW Infants Born ≤750 Grams: an Individual Participant Data Meta-Analysis

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Abstract

Background: Survival without major comorbidities remains low among extremely low birthweight (ELBW) infants. An exclusive human milk diet (EHMD) has shown clinical benefits among infants born weighing ≤1,250 g.

Methods: Our objective was to determine the associations between an exclusive human milk diet (EHMD) or a diet containing cow milk-based products (CMBD) and common morbidities and mortality among infants born weighing ≤750 g. We conducted a systematic review with individual participant data meta-analysis. After a PubMed search (Jan 2000 to Feb 2022), authors from eligible RCT and observational studies were invited to contribute their data. EHMD was compared to a CMBD, including formula (CMBD+f). Sensitivity analyses compared an EHMD and a base diet of human milk fortified with cow milk-based fortifiers (CMBD-f). Adjusted odds ratios (aOR) reported are from complete cases.

Results: Six studies were included, totaling 879 infants born between 2007-2015 and weighing ≤750 g. Infants fed an EHMD (n=449) had reduced odds of developing necrotizing enterocolitis (NEC), surgical NEC, and bronchopulmonary dysplasia (BPD) compared to those fed a CMBD+f (n=430). Similar reductions were observed when an EHMD was compared with CMBD-f (n=78). Additionally, an EHMD was associated with 50% lower odds of scoring affirmatively on a mortality and morbidity index (MMI) compared to CMBD+f.

Conclusions: In this study, infants born ≤750 g have reduced odds of developing several major comorbidities than those fed cows milk-based nutritional products, even with a base diet of human milk.

Registry Number: PROSPERO, identifier: CRD42022319031

Keywords: extremely low birth weight infant; human milk; infant, premature*; bronchopulmonary dysplasia; retinopathy of prematurity; necrotizing enterocolitis; exclusive human milk diet; sepsis; meta-analysis

KEY POINTS

Question: Does an exclusive human milk diet (EHMD) provide more benefit than diets containing cow milk products for infants born weighing ≤750 g?

Findings: Among six included studies, infants born between 2007-2015 and weighing ≤750 g (*n*=879) had reduced odds of developing several major comorbidities than those fed cow milk-based nutritional products even with a base diet of human milk. Results were strongest for death, NEC, and BPD.

Meaning: Avoiding cow milk-based fortifiers may be important in reducing mortality and major comorbidities, such as NEC and BPD, in infants weighing ≤750 g.

Introduction

Advances in medical interventions have lowered the viability age to include extremely low birthweight (ELBW) infants born as early as 22 weeks gestational age and ≤500 g. (1-3) Even so, survival without major comorbidities among these infants remains low. (4, 5) Many ELBW infants require longer hospital stays and high-cost health care interventions during early life and long term compared to infants born at higher birthweights. (6-10) Moreover, children born ELBW are more likely to suffer from parent-reported inattention, hyperactivity, and autistic symptoms and require additional resources such as special education. (11, 12) This creates a financial and emotional burden for families, hospitals, and society. Interventions to reduce major comorbidities are needed to improve the long-term quality of life for surviving ELBW infants.

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One of the main challenges in caring for ELBW infants is providing optimal nutrition. ELBW infants rely on the less efficient premature infant gastrointestinal tract instead of the placenta for nutrient transfer. (13) Total parenteral nutrition (TPN) is started soon after birth to ensure sufficient nutrient intake. However, long-term exposure to TPN without enteral feeding can delay the maturation of the GI tract and can lead to liver dysfunction. (14) Thus, achieving full enteral feeds promptly and safely is a primary goal of the healthcare team. (15)

ELBW newborns also require additional nutrients beyond what human milk, the preferred source of nutrition, can provide. (13, 16, 17) Fortifiers are added to the mother's own milk (MOM) or donor human milk (DHM) To provide these required nutrients. (16, 17) These fortifiers have traditionally been made from cow milk. Cow milk-based fortifiers, however, are not always well tolerated and have been associated with NEC, one of the primary causes of death among ELBW infants. (1, 2, 18) Thus, attaining full enteral feeding is a delicate balance between the risk of liver dysfunction and NEC or other morbidities.

Avoiding cow milk-based products using human milk-based versions allows exclusive human milk feeding, which is recommended for all infants with few exceptions. (16) An exclusive human milk

diet [(EHMD), MOM or DHM with added human milk-based human milk fortification] has shown promising results in clinical trials to reduce health complications of prematurity in infants weighing ≤1,250 g compared to diets containing cow milk products, including reduced incidences of NEC and feeding intolerance. (18-23) Given that infants weighing ≤750 g have a higher mortality and morbidity incidence than those born larger and more mature,(24) we hypothesized that the benefits of an EHMD were extended to these smallest ELBW infants, born weighing ≤750 g.

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To test our hypothesis, we conducted an individual participant data meta-analysis from existing EHMD clinical trials involving premature infants of any weight category, analyzing only data from those born weighing ≤750 g. We aimed to determine the associations between an EHMD or a diet containing cow milk-based products and common morbidities and mortality among infants weighing ≤750 g. Additional sensitivity analyses compared an EHMD with infants with a diet of MOM and/or DHM with cow milk-based fortifiers and excluded preterm infant formula.

Methods

All studies received hospital-specific ethical reviews that adhered to the Declaration of Helsinki (25), and parents or legal guardians provided written informed consent for all patients before enrollment. For this individual participant data (IPD) meta-analysis, we followed reporting guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for IPD. (26) This systematic review and IPD meta-analysis were prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under ID: CRD42022319031.

Search Strategy and Study Selection:

Search strategy:

We identified 34 EHMD studies using existing internal databases. We also performed a PubMed search to ensure that a comprehensive list of EHMD studies was captured (**Supplemental Table 1**). The search strategy included a combination of controlled vocabulary and keywords to create search concepts for HM, premature infants, clinical outcomes, and study designs of interest. Records were limited to articles published in 2000 or later as human milk-based human milk fortifiers were not commercially available before this time. For practical reasons, only articles published in English were included. Search results were transferred to Covidence (Veritas Health Innovation, Melbourne, Australia) and screened in duplicate by SMR and JRSM for relevance and eligibility. Conflicts were resolved through consensus.

Inclusion criteria:

All randomized, controlled trials and observational cohort studies with any design (e.g., prospective, retrospective, cross-sectional, or case-control) were eligible for inclusion. All cohorts were required to include infants weighing ≤1,500 g; compare an EHMD intervention diet to cow milk-based diets including cow milk-based fortifier with a base diet of human milk and/or preterm infant formula; and assess clinical outcomes of interest: mortality, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), surgical NEC, mortality and morbidity index (MMI), and sepsis, as defined by the study authors. Unpublished data from relevant RCTs and observational cohorts were also eligible for inclusion. Authors from eligible studies provided and consented to use their individual participant data.

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Non-human and preclinical studies were excluded, as were all other published articles (e.g., commentaries, reviews, and case studies). Also excluded were linked studies which would have resulted in duplicate entries per infant. For example, we did not include secondary analyses of trials already included. Finally, studies were excluded if they did not include infants born weighing ≤750 g or if data were not available after contact with study authors.

IPD Integrity, Outcome Measures, and Data Harmonization

Data were assessed for consistency with previously published articles of the included studies, with any discrepancies resolved by communication with the respective study investigators. The primary outcomes of interest were mortality, BPD, ROP, NEC, NEC requiring surgery (surgical NEC), sepsis, and MMI. MMI was examined because individual morbidities with low prevalence limit the power to declare group differences statistically significant and because it has been used in at least one relevant study. (27) Additionally, neonatal morbidities often occur simultaneously. Thus using an MMI allows for a more comprehensive evaluation of nutritional interventions. (28, 29)

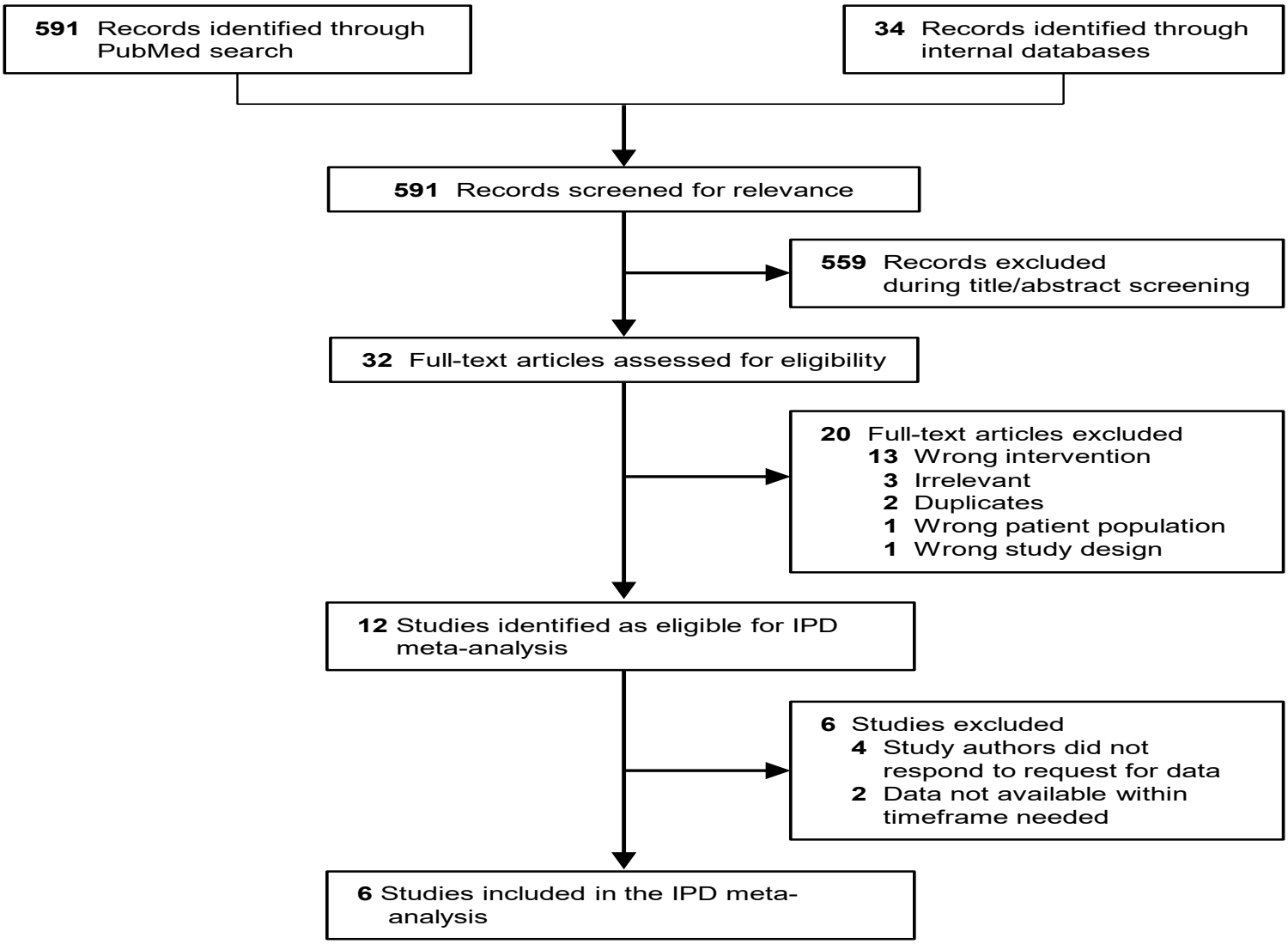


Figure 1. Flow diagram of studies included in the IPD meta-analysis. IPD, individual participant data.

"Outcome variables were re-coded as indicator variables to harmonize results. The definitions of ROP varied, with some studies defining ROP at any stage and some capturing all stages of ROP while others still only documented severe ROP (stage ≥3)."

Outcome variables were re-coded as indicator variables to harmonize results. The definitions of ROP varied, with some studies defining ROP at any stage and some capturing all stages of ROP while others still only documented severe ROP (stage ≥3). Primary analyses included all definitions of ROP (all ROP). Sensitivity analyses were conducted on the subset of cohorts for which severe ROP was reported. Similarly, the definitions of sepsis varied, with one study reporting only late-onset sepsis(30) and the rest reporting all episodes of sepsis. Although individual datasets classified NEC as "any NEC" or "medical NEC," the definitions of each of these variables were the same (Bell Stage ≥2) and were collapsed into one variable, defined as "NEC." NEC requiring surgery was a separate variable, defined as surgical NEC. No studies of interest reported an MMI, and one was calculated for this study, given the available information. Therefore, MMI was a binary outcome defined as an affirmative response for any of the following outcomes: death, severe ROP, sepsis, NEC, or BPD.

Neonatal data captured across studies included gestational age, birth weight, and infant sex. Additional data in a subset of studies included a 5-minute APGAR score, antenatal steroid use, and maternal race and ethnicity. Due to varied reporting practices, maternal race and ethnicity were harmonized using the latest recommendations from the *AMA Manual of Style* Committee(31) into White, Black, and Other.

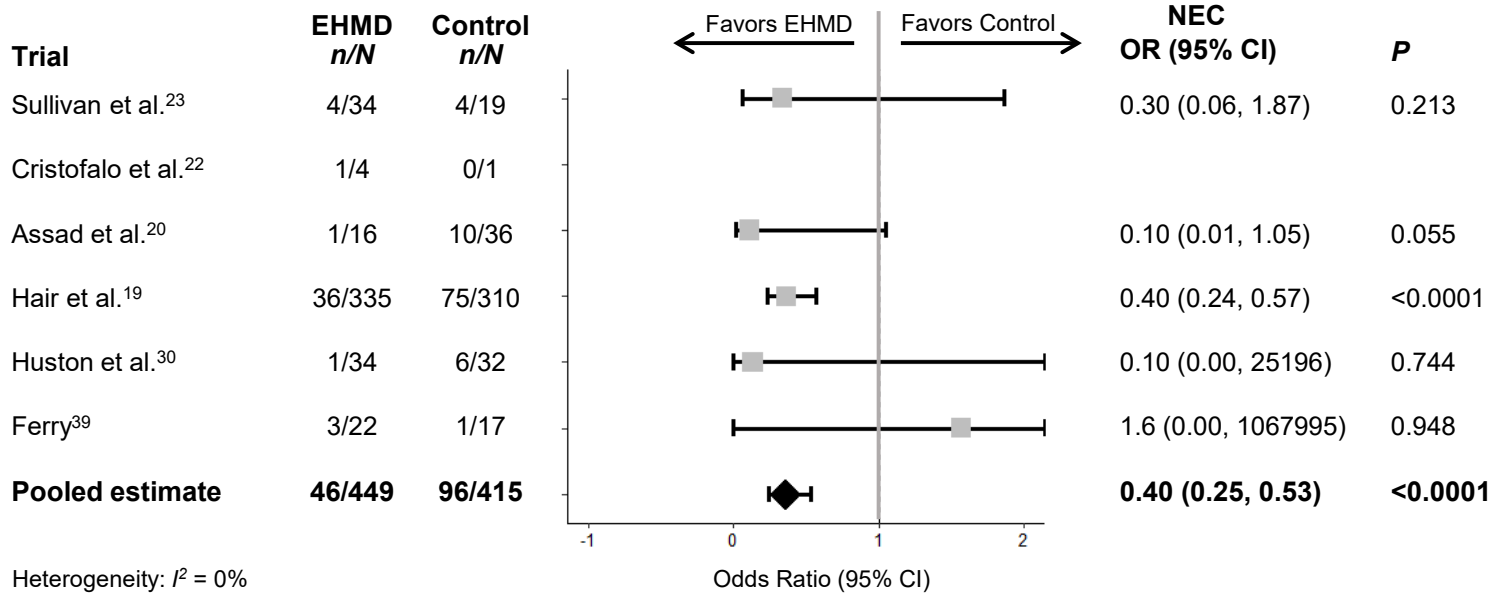


Figure 2. Associations of an EHMD with NEC among infants born ≤ 750 g (N = 860). Forest plots were generated using logistic mixed effects models—CI, confidence interval; EHMD, exclusive human milk diet; NEC, necrotizing enterocolitis.

"Included published studies were assessed for quality using a modified Newcastle-Ottawa scale (32) with a maximum possible score of 9."

Quality Assessment

Included published studies were assessed for quality using a modified Newcastle-Ottawa scale (32) with a maximum possible score of 9. We designated 4 points for *diet exposure assessment*, including diet fed (e.g., MOM, DHM, formula) (1 point), fortification start (e.g., day of life) (1 point), fortification end (1 point), and days to full enteral feeds (1 point); 2 points for *consideration of confounders and potential effect modifiers* including protocol for holding feeds and/or withdrawals (1 point) and control for participant characteristics (e.g., gestational age, sex, race, congenital abnormalities, APGAR score, antenatal steroids, etc.) (1 point); and 3 points for *outcome assessment*, including assessment of the outcome (e.g., diagnosed by trained staff, collection from records) (1 point), the same method of ascertainment in all groups (1 point), and whether follow-ups were long enough for the outcome to occur (1 point). Articles scored >7 were considered high quality; 4-7 moderate quality; <4 low quality. Each article was assessed for quality in duplicate by SMR and JRSM. Conflicts were resolved through consensus.

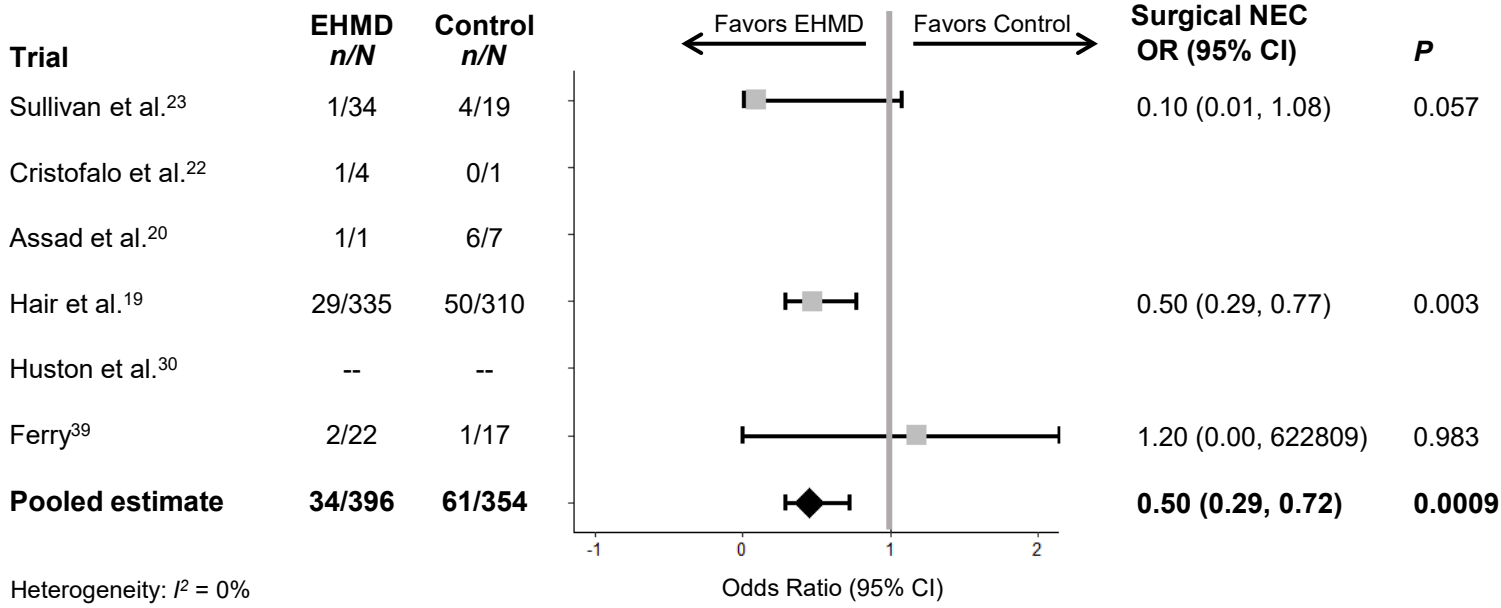
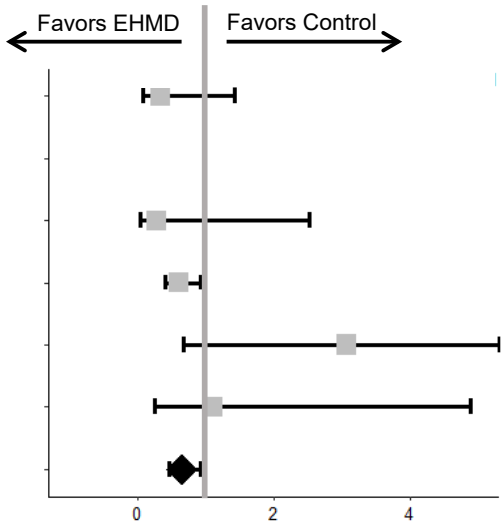


Figure 3. Associations of an EHMD with surgical NEC among infants born ≤ 750 g (N = 860). Forest plots were generated using logistic mixed effects models—CI, confidence interval; EHMD, exclusive human milk diet; NEC, necrotizing enterocolitis.

Trial	EHMD *n/N*	Control *n/N*	BPD OR (95% CI)	*P*
Sullivan et al.[23]	19/34	15/19	0.30 (0.08, 1.42)	0.137
Cristofalo et al.[22]	0/4	1/1		
Assad et al.[20]	8/16	21/36	0.30 (0.03, 2.52)	0.258
Hair et al.[19]	202/279	203/256	0.60 (0.40, 0.92)	0.018
Huston et al.[30]	26/32	16/28	3.10 (0.66, 14.14)	0.152
Ferry[39]	7/22	5/17	1.10 (0.25, 4.88)	0.898
Pooled estimate	**262/387**	**261/357**	**0.60 (0.46, 0.92)**	**0.015**



Heterogeneity: I^2 = 50%

Figure 4. Associations of an EHMD with BPD among infants born ≤ 750 g (N = 860). Forest plots were generated using logistic mixed effects models. BPD, bronchopulmonary dysplasia; CI, confidence interval; EHMD, exclusive human milk diet.

"Unpublished studies were evaluated using the Accuracy, Authority, Coverage, Objectivity, Date, Significance (AACODS) tool. (33) Each domain was assessed using and recorded with "Yes," "No," or "N/A" as applicable. Recording of 4 or more "Yes" responses were considered high quality."

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Statistical Analyses

All analyses were conducted following a complete-case, intention-to-treat framework between July 20 and September 29, 2022. (34) We used a two-stage approach. First, we harmonized all outcome variables to be binary, then calculated within-study estimates using logistic mixed effects models with gestational age and birthweight

Trial	EHMD *n/N*	Control *n/N*	MMI OR (95% CI)	*P*
Sullivan et al.[23]	30/34	19/19		
Cristofalo et al.[22]	1/4	1/1		
Assad et al.[20]	11/16	28/36	0.30 (0.05, 2.45)	0.283
Hair et al.[19]	282/339	296/325	0.40 (0.25, 0.69)	0.0007
Huston et al.[30]	29/34	24/32	1.00 (0.00, 769)	0.999
Ferry[39]	17/22	11/17	1.30 (0.27, 6.69)	0.728
Pooled estimate	**370/449**	**379/430**	**0.50 (0.33, 0.75)**	**0.001**

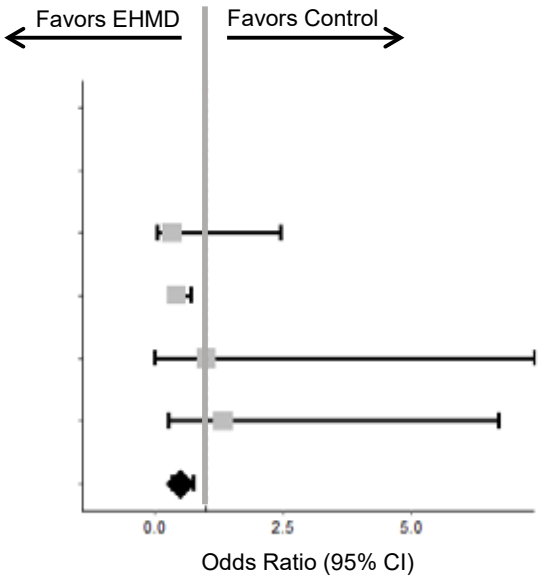

Figure 5. Associations of an EHMD with MMI among infants born ≤ 750 g (N = 860). Forest plots were generated using logistic mixed effects models—CI, confidence interval; EHMD, exclusive human milk diet; MMI, mortality, and morbidity index.

Table 1. Summary of studies included in the individual participant data meta-analysis and percentage of infants born ≤750 g

Publication	Location	Study Design	Participants Birth Year	Initial eligibility criteria	EHMD Fortification	Control Diet	Infants born ≤750 g No. / total No. (%)			Quality Score[a]
							EHMD	Control	Total	
Sullivan et al., 2009[23,b]	US, Austria	Multicenter RCT	2007-2008	BW 500 to 1250 g PN <48 h after birth EN <21 d after birth	Prolact+ $H_2MF^{®}$ @ 40 mL/kg/d or 100 mL/kg/d*	MOM + cow milk-based fortifier @ 100 mL/kg/d or preterm infant formula[c]	34/138 (24.6)	19/69 (27.5)	53/207 (25.6)	7
Cristofalo et al., 2013[22,b]	US, Austria	Multicenter RCT	2007-2008	BW 500 to 1250 g PN <48 h after birth EN <21 d after birth	Prolact+ $H_2MF^{®}$ @ 40 mL/kg/d or 100 mL/kg/d*[3]	Preterm infant formula[d]	4/29 (13.8)	1/24 (4.2)	5/53 (9.4)	6.5
Assad et al., 2015[20]	US	Single center retrospective cohort study	2009-2012 (Controls) 2012-2014 (Intervention)	GA ≤28 wk or BW ≤1500 g	Prolact+ $H_2MF^{®}$ @ 120-150 mL/kg/d	MOM + cow milk-based fortifier and/or preterm infant formula[c]	16/87 (18.4)	36/206 (7.8)	52/293 (17.7)	8
Hair et al., 2016[19]	US	Multicenter retrospective cohort study	2006-2008 (Control) 2009-2012 (Intervention)	BW <1250 g	Prolact+ $H_2MF^{®}$ @ 60 mL/kg/d or 100-120 mL/kg/d*	MOM+ cow milk-based fortifier and/or preterm infant formula[c]	339/819 (41.4)	325/768 (42.3)	664/1587 (41.8)	7
Huston et al., 2018[30]	US	Single center retrospective cohort study	2007-2015	BW 500 to 1250 g	Prolact+ $H_2MF^{®}$ @ 40-50 mL/kg/d	MOM+ cow milk-based fortifier and/or preterm infant formula[c]	34/127 (26.8)	32/252 (12.7)	66/379 (17.4)	7
Ferry et al., (unpublished)[39]	US	Single center retrospective cohort study	2012-2014	BW 440 to 2722 g	Prolact+ $H_2MF^{®}$ @ 40-80 mL/kg/d	MOM + cow milk-based fortifier @ 80-100 mL/kg/d[c]	22/138 (15.9)	17/113 (15)	39/251 (15.5)	--

*Pasteurized donor human milk–based HMF (Prolact+ H2MF®; Prolacta Bioscience)
[a]Study quality was assessed using a modified Newcastle-Ottawa Scale [32], maximum score of 9. See Supplemental Table 2 for detailed quality assessment results.
[b]Trial registered with ClinicalTrials.gov under study ID: NCT00506584. Note Sullivan et al., 2009 [23] and Cristofalo et al., 2013 [22] used the same protocol defined in this trial registry, but were separate studies.
[c]Infants in the control group received MOM + cow milk-based fortifier preferentially over preterm infant formula
[d]Study included only infants whose mothers did not intend on providing their own milk. Consequently, in this study, EHMD consisted of vat pasteurized donor human milk (20 kcal/oz Neo20; Prolacta Bioscience) and vat pasteurized donor human milk-based human milk fortifier (Prolact+ H^2MF; Prolacta Bioscience)
BW, birthweight; EHMD, exclusive human milk diet; GA, gestational age

Table 2. Participant characteristics at baseline according to infant diet (N=879)[a]

Factor	All participants (N=879)	Intervention	Controls		*P* value	
		EHMD (n=449)	(All controls) CMBD+f (n=430)	(No formula controls) CMBD-f (n=78)	EHMD vs. CMBD+f	EHMD vs. CMBD-f
Gestational age, wk	24.6 (3.2)*	24.4 (1.4)*	25.0 (2)*	25.0 (2.3)*	**0.019**	0.066
Birthweight (g)	650 (180)*	660 (115)*	645.0 (130)*	646.5 (101)*	0.055	0.594
Female sex	459 (52.2)*	238 (53.0)*	221 (51.4)*	38 (48.7)*	0.681	0.564
Antenatal steroids[b]	563 (64.1)	299 (66.6)	264 (61.4)	34 (43.6)	0.248	**0.007**
Race[c]					0.645	**<0.001**
Black	316 (35.9)	153 (34.1)	163 (37.9)	4 (5.1)		
White	249 (28.3)	133 (29.6)	116 (27.0)	2 (2.6)		
Other	198 (22.5)	102 (22.7)	96 (22.3)	27 (34.6)		

[a]Values are median (IQR)* for non-normally distributed continuous variables or n (%) for categorical variables. Student's *t* test and chi-squared tests were used to compare continuous and categorical variables, respectively. All tests were run with R (v. 4.1.3) package finalfit (v. 1.0.4).[37,38]
[b]Data available for 3 cohorts,[19,22,23] N=701
[c]Data available for 4 cohorts,[19,20,22,23] N=763
CMBD+f, cow milk-based diet including cow milk-based fortifier with base diet of human milk and/or preterm infant formula; CMBD-f, cow milk-based diet including cow milk-based fortifier with base diet of human milk, excluding preterm infant formula; EHMD, exclusive human milk diet.

as fixed effects and participant as the random effect. Second, pooled estimates were also calculated using logistic mixed effects models adjusted for gestational age and birthweight (fixed effects). Pooled models used the study as the random effect. These models were used to test the association between an EHMD and morbidity and mortality outcomes compared to CMBD+f. Sensitivity analyses evaluated these associations, comparing an EHMD and no formula controls (CMBD-f). We conducted analyses in R (v. 4.1.3). (35-38) Results were considered statistically significant at $p<0.05$. Study heterogeneity was measured using the I^2 statistic. We assessed publication bias using funnel plots with the trim and fill method.

Results

Description of Included Studies

In total, 591 unique records were identified and screened. Of these, 559 were excluded during the title and abstract screening, with 32 full-text articles screened for eligibility (**Figure 1**). After excluding 20 studies that did not meet eligibility criteria, 12 were identified as eligible for IPD meta-analysis, and authors were invited to contribute their data. Six of these 12 studies were excluded due to no response from authors (n=4) or the data being unavailable within the timeframe needed (n=2).

Overall, data from six unique studies were analyzed, totaling 879 infants born weighing ≤750 g between 2007-2015. (19, 20, 22, 23, 30, 39) Of these, 449 infants received an EHMD; 430 received a cow milk-based diet, including cow milk-based fortifier with a base diet of human milk and/or preterm infant formula (CMBD+f). Due to varied reporting practices related to formula feeding in some cohorts, medical records were reviewed as needed. A curated list was created, including only infants who, from their medical records, were confirmed not to have received any preterm infant formula. Consequently, of the 430 CMBD+f infants, only 78 were confirmed to have received a cow milk-based diet including cow milk-based fortifier with a base diet of human milk excluding preterm infant formula (CMBD-f).

Cohort-level characteristics

All included studies were based in the US, with two studies having a study center in Austria (**Table 1**). Included studies were a mix of multicenter RCTs and single or multicenter retrospective cohorts.

Each included study had an EHMD intervention group. In all studies, the EHMD intervention consisted of a base diet of human milk with added vat pasteurized human milk-based human milk fortifiers (Prolact+ H2MF; Prolacta Bioscience). For the base diet of human milk, MOM was almost always preferentially used over DHM. The only exception was Cristofalo et al., 2013 (22) because they only included infants whose mothers did not provide their own milk. Thus, in this study, all infants received vat pasteurized donor human milk (20 kcal/oz Prolacta Bioscience). (22)

Fortification initiation and advancement in the EHMD interventions varied greatly within and across studies (**Table 1**). The earliest initiation of fortification was 40 mL/kg/d. Additionally, weaning from the EHMD varied, with some studies transitioning to a diet including cow milk at 32 weeks and others at 34 weeks.

Most published studies were rated as moderate (4-7 score on the modified Newcastle-Ottawa scale; maximum 9 points), with only 1 study being rated as high quality (>7) and no studies rated as low quality (<4) (**Table 1; Supplementary Figure 1**).

The only *unpublished* study included was rated as high quality. Four of the 5 AACODS criteria were recorded as "Yes," with the criteria for "Coverage" being deemed "Not Applicable" (**Supplementary Table 2**).

Participant characteristics

Among the included studies, infants born ≤750 g represented between 9.4% and 42.3% of the total infants enrolled in original study cohorts (**Table 1**). Overall, these ≤750 g infants were born at a median (IQR) of 24.6 (3.2) weeks gestational age with a birthweight of 650 (180) g (**Table 2**). About 52% of infants were female, ~64% were exposed to antenatal steroids, and nearly 36% were Black. These characteristics were similar across intervention and control groups, except that compared to all controls (CMBD+f), infants in the EHMD group were born slightly younger [gestational age at a birth median (IQR): 24.4 (1.4) vs. 25.0 (2.0), EHMD vs. CMBD+f, respectively; p=0.019, **Table 2**]. Additionally, compared to no formula controls (CMBD-f), more infants in the EHMD group were exposed to antenatal steroids, and a lower percentage was reported to be a race other than Black or White (p≤0.007 for both, **Table 2**).

Associations of an EHMD with Infant Morbidity and Mortality

Mortality

Five studies reported infant mortality. Although adjusted OR in all five studies indicated that an EHMD lowered the odds of death, none of these associations were statistically significant in primary analyses (**Table 3**). Similarly, the pooled estimate indicated a 20.6% reduction in odds of death (aOR: 0.79, 95% CI, 0.56, 1.13, p=0.20; I^2 22%; 838 participants). Although not statistically significant, these results are clinically meaningful.

In subgroup analyses, however, an EHMD was associated with a statistically significant reduction in the odds of death compared to CMBD-f (aOR: 0.39, 95% CI, 0.15, 0.997; p=0.049).

NEC and Surgical NEC

NEC was reported in all 6 included studies. In these cohorts, the incidence of NEC ranged from 10-21% and averaged 17% in pooled data (**Table 3**). The average incidence of NEC in infants fed an EHMD was 10% compared to 23% in those fed cows milk-based nutritional products (CMBD+f). This reduction attributed to an EHMD equated to a 60% decrease in the odds of developing NEC in pooled analyses (aOR: 0.40, 95% CI, 0.25, 0.53; p<0.0001; I^2 0%; 860 participants, **Figure 2, Table 3**). Subgroup analysis showed a similar significant reduction in an EHMD compared to CMBD-f (527 participants, **Table 4**).

NEC requiring surgery (surgical NEC) was reported in 5 studies. In pooled analyses, an EHMD was associated with a 54% decrease in the odds of developing surgical NEC compared to CMBD+f (aOR: 0.50, 95% CI 0.29, 0.73; p=0.0009; I^2 0%; 750 participants, **Figure 3, Table 3**). Subgroup analysis showed a 61% reduction in surgical NEC attributed to an EHMD compared to CMBD-f, though likely due to the small sample size in the control group, this was not statistically significant (aOR: 0.39, 95% CI 0.13, 1.16; p=0.09, 446 participants, **Table 4**).

Table 3. Associations between an EHMD and clinical outcomes among all infants born ≤750 g (N=879)[a]

		Intervention	All Controls	EHMD vs. All controls (CMBD+f)	
Outcomes	All Participants	EHMD n/N (%)	CMBD+f n/N (%)	Adjusted Odds Ratio (95% CI)	*P* value
Mortality					
Sullivan et al.[23]	5/53 (9.4)	2/34 (6)	3/19 (16)	0.30 (0.04, 2.30)	0.242
Cristofalo et al.[22]	0/5 (0)	0/4 (0)	0/1 (0)	--[b]	--[b]
Assad et al.[20]	5/52 (9.6)	1/16 (6)	4/36 (11)	0.62 (0.06, 6.48)	0.691
Hair et al.[29]	150/664 (22.6)	73/339 (22)	77/323 (24)	0.91 (0.63, 0.91)	0.634
Huston et al.[30]	7/66 (23)	1/34 (3)	6/32 (19)	0.09 (0, 16430)	0.697
Ferry et al.[39]	--[c]	--[c]	--[c]	--[c]	
Pooled estimate	167/838 (20)	77/427 (18)	90/411 (22)	0.79 (0.56, 1.13)	0.195
NEC					
Sullivan et al.[23]	8/53 (15)	4/34 (12)	4/19 (21)	0.30 (0.06, 1.87)	0.213
Cristofalo et al.[22]	1/5 (20)	1/4 (75)	0/1 (0)	--[b]	--[b]
Assad et al.[20]	11/52 (21)	1/16 (6.3)	10/36 (2.8)	0.10 (0.01, 1.05)	0.055
Hair et al.[29]	111/645 (17)	36/335(11)	75/310(23)	0.40 (0.24, 0.57)	<0.0001
Huston et al.[30]	7/66 (11)	1/34 (2.9)	6/32 (19)	0.10 (0, 25206)	0.744
Ferry et al.[39]	4/39 (10)	3/22 (14)	1/17 (5.9)	1.60 (0, 1067995)	0.948
Pooled estimate	**142/860 (17)**	**46/449 445 (10)**	**96/415 (23)**	**0.40 (0.25, 0.53)**	**<0.0001**
Surgical NEC					
Sullivan et al.[23]	5/53 (9)	1/34 (2.9)	4/19 (21)	0.10 (0.01, 1.08)	0.057
Cristofalo et al.[22]	1/5 (20)	1/4 (25)	0/1 (0)	--[b]	--[b]
Assad et al.[20]	7/8 (88)	1/1 (100)	6/7 (86)	--[b]	--[b]
Hair et al.[29]	79/645 (12)	29/335 (8.7)	50/310 (16)	0.50 (0.29, 0.77)	0.003
Huston et al.[30]	--[c]	--[c]	--[c]	--[c]	--[c]
Ferry et al.[39]	3/39 (8)	2/22 (9.1)	1/17 (5.9)	1.20 (0, 6228088)	0.983

Pooled estimate	**95/750 (13)**	**34/396 (9)**	**61/354 (17)**	**0.50 (0.29, 0.72)**	**0.0009**
BPD					
Sullivan et al.[23]	34/53 (64)	19/34 (56)	15/19 (26)	0.30 (0.08, 1.42)	0.137
Cristofalo et al.[22]	1/5 (20)	0/4 (0)	1/1 (100)	--[b]	--[b]
Assad et al.[20]	29/52 (56)	8/16 (50)	21/36 (58)	0.30 (0.03, 2.52)	0.258
Hair et al.[29]	405/535 (76)	202/279 (73)	203/256 (79)	0.60 (0.40, 0.92)	0.018
Huston et al.[30]	42/60 (70)	26/32 (81)	16/28 (57)	3.10 (0.662 14.14)	0.152
Ferry et al.[39]	12/39 (31)	7/22 (32)	5/17 (29)	1.10 (0.25, 4.88)	0.898
Pooled estimate	**523/744 (70)**	**262/387 (68)**	**261/357 (73)**	**0.60 (0.46, 0.92)**	**0.015**
All ROP					
Sullivan et al.[23]	35/53 (66)	22/34 (65)	13/19 (68)	0.69 (0.19, 2.48)	0.574
Cristofalo et al.[22]	3/4 (75)	2/4 (50)	1/1 (100)	--[b]	--[b]
Assad et al.[20]	27/52 (52)	5/16 (31)	22/36 (61)	0.23 (0.05, 1.05)	0.574
Hair et al.[29]	80/635 (13)	34/329 (10)	46/306 (14)	0.61 (0.60, 0.61)	<0.0001
Huston et al.[30]	41/60 (68)	25/32 (74)	16/28 (50)	2.41 (0.63, 9.30)	0.200
Ferry et al.[39]	20/39 (51)	13/22 (59)	7/17 (41)	1.89 (0.45, 7.92)	0.386
Pooled estimate	206/844 (24)	101/437 (23)	105/407 (26)	0.69 (0.47, 0.70)	0.055
Severe ROP					
Sullivan et al.[23]	10/53 (19)	7/34 (21)	3/19 (16)	0.90 (0.01, 3687)	0.981
Cristofalo et al.[22]	0/5 (0)	0/4 (0)	0/1 (0)	--[b]	--[b]
Assad et al.[20]	--[c]	--[c]	--[c]	--[c]	
Hair et al.[29]	80/635 (13)	34/329 (10)	46/306 (15)	0.61 (0.60, 0.61)	<0.0001
Huston et al.[30]	3/63 (4.8)	2/32 (6.3)	1/31 (3.1)	1.76 (1.75, 1.78)	<0.0001
Ferry et al.[39]	18/39 (46)	12/22 (55)	6/17 (35)	2.15 (0.50, 9.20)	0.301
Pooled estimate	111/684 (16)	55/421 (13)	56/374 (15)	0.71 (0.46, 1.09)	0.120
Sepsis					
Sullivan et al.[23]	21/53 (40)	15/34 (44)	6/19 (32)	1.66 (0.43, 6.38)	0.458

Cristofalo et al.[22]	1/5 (20)	1/4 (25)	0/1 (0)	--[b]	--[b]
Assad et al.[20]	22/52 (42)	7/16 (43)	15/36 (42)	0.90 (0.26, 3.14)	0.862
Hair et al.[29]	138/664 (21)	69/339 (20)	69/325 (21)	0.96 (0.65, 1.41)	0.822
Huston et al.[30]	10/66 (15)	7/34 (21)	3/32 (9.3)	2.52 (0.56, 11.2)	0.227
Ferry et al.[39]	10/39 (26)	2/22 (9.1)	8/17 (47)	0.05 (0.01, 0.44)	0.007
Pooled estimate	202/879 (23)	101/449 (22)	101/430 (23)	0.94 (0.68, 1.30)	0.694
MMI					
Sullivan et al.[23]	49/53 (92)	30/34 (88)	19/19 (100)	--[b]	--[b]
Cristofalo et al.[22]	2/5 (40)	1/4 (25)	1/1 (100)	--[b]	--[b]
Assad et al.[20]	39/52 (75)	11/16 (69)	28/36 (78)	0.30 (0.05, 2.45)	0.283
Hair et al.[29]	578/664 (87)	282/339 (83)	296/325 (91)	0.40 (0.25, 0.69)	0.0007
Huston et al.[30]	53/66 (80)	29/34 (85)	24/32 (75)	1.00 (0.00, 769.22)	0.999
Ferry et al.[39]	28/39 (72)	17/22 (77)	11/17 (65)	1.30 (0.27, 6.69)	0.728
Pooled estimate	**749/879 (85)**	**370/449 (82)**	**379/430 (88)**	**0.50 (0.33, 0.75)**	**0.001**

[a]Values are means ± SD for continuous variables or n (%) for categorical variables. CMBD+f, cow milk-based diet including cow milk-based fortifier with base diet of human milk and/or preterm infant formula; EHMD, exclusive human milk diet. Within-study estimates were calculated using logistic mixed effects models with gestational age and birthweight as fixed effects and participant as the random effect. Pooled estimates were also calculated using logistic mixed effects models adjusted for gestational age and birthweight (fixed effects), and study as the random effect. All tests were run with R (v4.1.3) package lme4 (v1.1-30) and emmeans (v.1.8.1-1).[35-37]

[b]Model did not converge due to low sample size

[c]Outcome was not measured

Table 4. Pooled associations between an EHMD cow milk-based diet without formula supplementation clinical outcomes among infants born ≤750 g (N=527)

		Intervention	Cow milk-based diet: no formula	EHMD vs. CMBD-f	
Outcomes	Total n/N (%)	EHMD n/N (%)	CMBD-f n/N (%)	Odds Ratio (95% CI)	p-value
Mortality	**89/428 (21)**	**77/427 (18)**	**12/61 (20)**	**0.39 (0.15, 1.00)**	**0.049**
NEC	**62/527 (12)**	**46/445 (10)**	**16/78 (21)**	**0.41 (0.22, 0.78)**	**0.006**
Surgical NEC	45/446 (10)	34/396 (9)	11/50 (22)	0.39 (0.13, 1.16)	0.09
BPD	309/459 (67)	262/387 (68)	47/72 (65)	0.64 (0.33, 1.23)	0.18
Severe ROP	72/483 (15)	55/421 (13)	17/62 (27)	0.47 (0.19, 1.13)	0.091
Sepsis	120/527 (23)	101/449 (22)	19/78 (24)	0.94 (0.48, 1.82)	0.851
MMI	406/496 (82)	370/449 (82)	36/47 (77)	0.89 (0.41, 1.94)	0.765

CMBD-f, cow milk-based diet including cow milk-based fortifier with base diet of human milk, excluding preterm infant formula, EHMD, exclusive human milk diet. Pooled estimates were calculated using logistic mixed effects models adjusted for gestational age and birthweight (fixed effects), and study as the random effect. All tests were run with R (v4.1.3) package lme4 (v1.1-30) and emmeans (v.1.8.1-1).[35-37]

"BPD was reported in all six studies included. The odds of developing BPD attributed to an EHMD compared to a cow milk-based diet (CMBD+f) varied across individual studies. In pooled analyses, we found that an EHMD was associated with a significant (40%) reduction in odds of developing BPD compared to a CMBD+f (aOR: 0.60; 95% CI, 0.46, 0.92; p=0.02; I2 50%; 744 participants, Figure 4, Table 3)."

Bronchopulmonary Dysplasia

BPD was reported in all six studies included. The odds of developing BPD attributed to an EHMD compared to a cow milk-based diet (CMBD+f) varied across individual studies. In pooled analyses, we found that an EHMD was associated with a significant (40%) reduction in odds of developing BPD compared to a CMBD+f (aOR: 0.60; 95% CI, 0.46, 0.92; *p*=0.02; I^2 50%; 744 participants, **Figure 4, Table 3**). Subgroup analysis showed a similar reduction attributed to an EHMD compared to no formula controls (CMBD-f), though again likely due to the small sample size in the control group, this was not statistically significant (aOR: 0.64; 95% CI, 0.33, 1.23; *p*=0.18, 459 participants, **Table 4**).

"An EHMD was associated with a 31% decrease in the odds of developing any ROP and a 29% decrease in the odds of developing severe ROP compared to CMBD+f (Table 3). Although these reductions were not statistically significant, the reduction in any ROP attributed to an EHMD bordered on significance (aOR: 0.69, 95% CI, 0.47, 0.70; p=0.055, 844 participants,Table 4). "

Retinopathy of Prematurity

Five studies reported stages of ROP or only reported severe ROP (stages ≥3). The remaining study reported any ROP without information about the stage. Consequently, we analyzed ROP data in two ways: *all ROP*, representing all incidences of ROP, regardless of the stage using all available information, and *severe ROP,* which only included stages ≥3. An EHMD was associated with a 31% decrease in the odds of developing *any ROP* and a 29% decrease in the odds of developing *severe ROP* compared to CMBD+f (**Table 3**). Although these reductions were not statistically significant, the reduction in *any ROP* attributed to an EHMD bordered on significance (aOR: 0.69, 95% CI, 0.47, 0.70; *p*=0.055, 844 participants, **Table 4**).

The effect size of an EHMD on *severe ROP* was even greater when compared against no formula controls (CMBD-f). That is, compared to infants fed a base diet of human milk with added cow milk-based fortifier (CMBD-f), those fed an EHMD had a 53% decrease in the odds of developing *severe ROP* (aOR: 0.47, 95% CI, 0.19, 1.13; *p*=0.09, 483 participants, **Table 4**).

Sepsis

Sepsis was reported in all 6 included studies. There was no consistent direction of association between an EHMD and the odds of developing sepsis compared to CMBD+f across studies. Pooled estimates indicated that an EHMD slightly reduced the odds of developing sepsis compared to CMBD+f (aOR: 0.94, 95% CI, 0.68, 1.30; *p*=0.69; I^2 41%; 879 participants, **Table 3**). Subgroup analyses excluding the formula showed a similar result associated with an EHMD diet. Compared to no formula controls (CMBD-f), infants fed an EHMD had 6.1% decreased odds of developing sepsis (aOR: 0.94, 95% CI 0.48, 1.82; *p*=0.85, 527 participants, **Table 4**).

Mortality and Morbidity Index

As commonly conducted due to the low prevalence of individual comorbidities, we evaluated the association between infant enteral feeding strategy and the binary mortality and morbidity index (MMI), representing death and/or development of severe ROP, sepsis, NEC, or BPD. We found that the odds of scoring affirmatively on the MMI were reduced by 50% in infants fed an EHMD compared to those fed a CMBD+f (aOR: 0.50, 95% CI, 0.33, 0.75; *p*=0.001; 879 participants, **Figure 5, Table 3**). In subgroup analyses, the odds of scoring affirmatively on the MMI were also reduced with an EHMD vs. no formula controls; however, likely due to the small number of patients in the control group, these results were no longer statistically significant (aOR: 0.89, 95% CI, 0.41, 1.94; *p*=0.77, 496 participants, **Table 4**).

Publication bias

Publication bias could not be conducted for all outcomes because of the limited number of studies. For example, MMI is not reported in all studies, and the definitions of MMI vary based on outcomes investigated in individual cohorts. Funnel plots indicated no publication bias for other outcomes (**Supplementary Figure 2**).

Discussion

This IPD meta-analysis examined the associations between an exclusive human milk diet (EHMD) or a diet containing cow milk-based products (CMBD) and mortality and morbidity among infants at highest risk for mortality or morbidity, those born weighing ≤750 g. Among the six contributing cohorts with a total sample size of 879 infants (19, 20, 22, 23, 30, 39), those fed an EHMD had 60% reduced odds of developing NEC and 50% reduced odds of developing surgical NEC compared to infants fed a CMBD. These reductions in NEC and surgical NEC were similar to those reported in previous EHMD studies conducted among larger preterm infants born weighing ≤1,250 g. (19, 20, 22, 23, 27, 30) NEC is one of the primary causes of death in extremely premature infants. (1) Mounting evidence suggests that cow milk protein may cause intestinal inflammation, leading to feeding intolerance and NEC.(18, 20, 40-43) Considering that infants in the EHMD group

Figure S1. Quality Assessment of studies included in IPD meta-analysis

Study	Quality Score[1] (Max 9)	Exposure Assessment (Max 4)	Comparability (Max 2)	Outcome Assessment (Max 3)
Sullivan et al., 2009[1]	7	***	*	***
Cristofalo et al., 2013[2]	6.5	**	*ǂ	***
Assad et al., 2015[3]	8	***	**	***
Hair et al., 2016[4]	7	***	*	***
Huston et al., 2018[5]	7			
Ferry et al., (unpublished)[6]	--			

Yellow = moderate quality (4-7); Green = high quality (8-9); Grey = no score assessed
*represents 1 point; ǂ represents 0.5 points

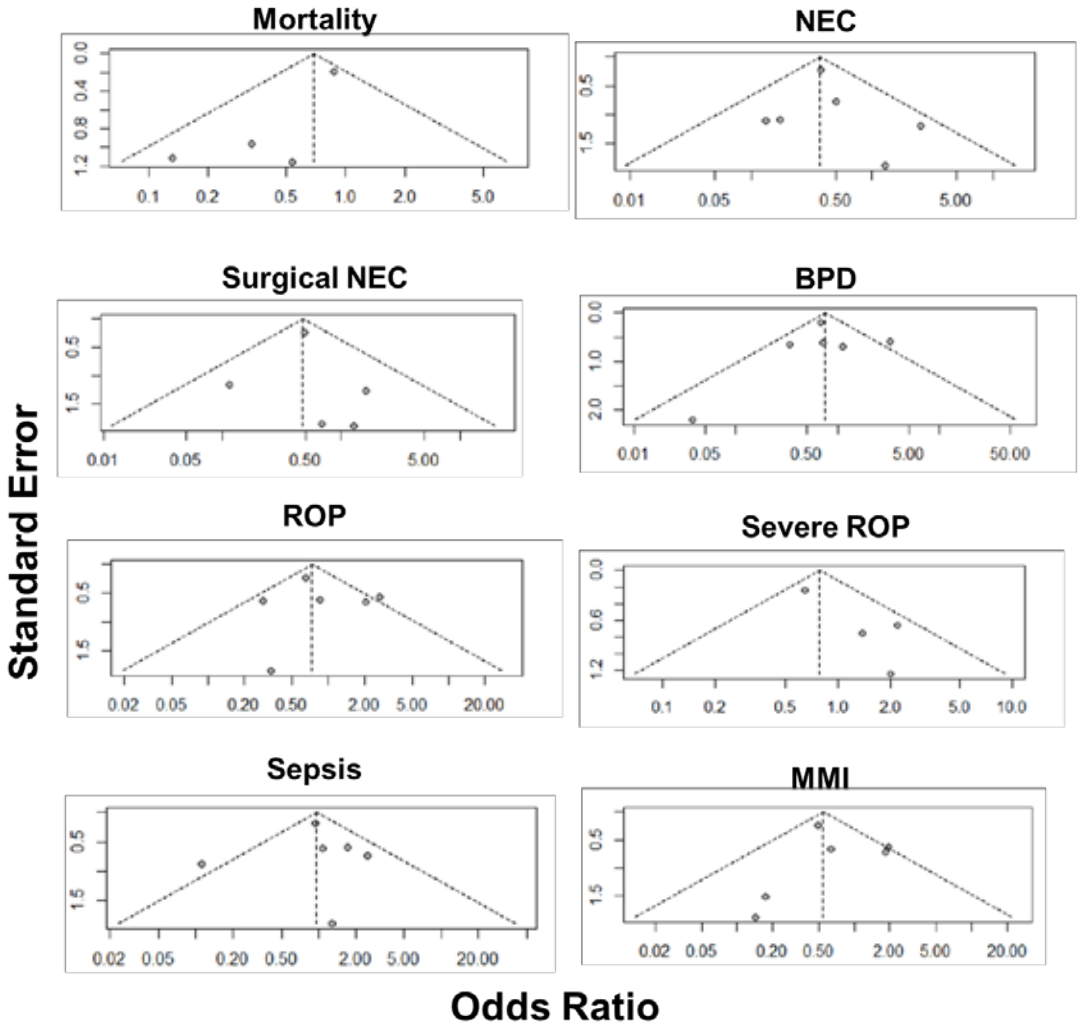

Figure S2. Funnel plots of studies included in the IPD meta-analysis. BPD, bronchopulmonary dysplasia; MMI, mortality and morbidity index; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity

Table S1. Search Strategy for PubMed

Number	Search terms	Filters	Results
1	"Milk*"[Mesh] OR "Milk, Human"[Mesh] OR "Infant Food"[Mesh] OR "Infant Formula"[Mesh] OR "Food, Fortified*"[Mesh] OR "human milk"[tiab] OR "breast milk"[tiab] OR breastmilk[tiab] OR "donor human milk"[tiab] OR "human milk fortifier"[tiab] OR "exclusive human milk*"[tiab] OR "enteral feeding"[tw]		152,498
2	"Infant, Premature, Diseases"[Mesh] OR "Mortality"[Mesh]" OR "Lung Diseases/epidemiology"[Mesh]" OR "Lung Diseases/diet therapy"[Mesh] OR "Retinopathy of Prematurity"[Mesh] OR "Ductus Arteriosus, Patent"[Mesh] OR "Enterocolitis, Necrotizing"[Mesh] OR "Neonatal Sepsis"[Mesh] OR "mortality"[tiab], "bronchopulmonary dysplasia"[tiab] OR "retinopathy of prematurity"[tiab] OR "patent ductus arteriosus"[tiab] OR "necrotizing enterocolitis" OR "surgical NEC" OR "mortality/morbidity index" OR "sepsis"[tiab] OR "late onset sepsis"[tw]		131,879
3	"Humans"[Mesh] OR "Female"[Mesh] OR "Male"[Mesh] OR "Infant, Premature"[Mesh] OR "Infant, Extremely Low Birth Weight"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh] OR "Infant, Newborn"[Mesh] OR "premature infant*"[tw] OR "preterm infant*"[tw] OR "low birthweight"[tw]		22,372,934
4	#1 AND #3 AND #2		2,114
5	#1 AND #3 AND #2	from 2000 - 3000/12/12	1,813
6	"Retrospective Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Published Erratum" [Publication Type] OR "retrospective stud*"[tiab] OR "controlled trial"[tiab] OR "randomized clinical trial"[tiab] OR "observational study"[tiab] OR "multi-center retrospective cohort study"[tiab]		3,822,783
7	#1 AND #3 AND #2 AND #6		667
8	#1 AND #3 AND #2 AND #6	from 2000 - 3000/12/12	591

Search strategy conducted in PubMed on February 22, 2022

Table S2. Quality Assessment of unpublished studies included in IPD meta-analysis.

AACODS		Ferry et al., [6]		
		Yes	No	?
Authority	Identifying who is responsible for the intellectual content Individual author: • Associated with a reputable organization? • Professional qualifications or considerable experience? • Produced/published other work (grey/black) in the field? • Recognised expert, identified in other sources? • Cited by others? (use Google Scholar as a quick check) • Higher degree student under "expert" supervision? Organization or group: • Is the organization reputable? (e.g., WHO) • Is the organization an authority in the field? In all cases: • Does the item have a detailed reference list or bibliography?	X		
Accuracy	Does the item have a clearly stated aim or brief? • If so, is this met? • Does it have a stated methodology? • If so, is it adhered to? • Has it been peer-reviewed? • Has it been edited by a reputable authority? • Supported by authoritative, documented references or credible sources? • Is it representative of work in the field? • If No, is it a valid counterbalance? • Is any data collection explicit and appropriate for the research? • If an item is secondary material (e.g., a policy brief of a technical report) refer to the original. Is it an accurate, unbiased interpretation or analysis?	Yes		
Coverage	All items have parameters that define their content coverage. These limits might mean that a work refers to a particular population group or excludes certain types of publication. A report could be designed to answer a particular question or be based on statistics from a particular survey. • Are any limits clearly stated?			N/A
Date	For the item to inform your research, it needs to have a date that confirms The relevance • Does the item have a clearly stated date related to the content? No easily discernible date is a strong concern. • If no date is given but can be closely ascertained, is there a valid reason for its absence? • Check the bibliography: have key contemporary material been Included?	X		
Significance	This is a value judgment of the item in the context of the relevant research area • Is the item meaningful? (this incorporates feasibility, utility, and relevance) • Does it add context? • Does it enrich or add something unique to the research? • Does it strengthen or refute a current position? • Would the research area be lesser without it? • Is it integral, representative, or typical? • Does it have an impact? (in the sense of influencing the work or behavior of others)	Yes		

were not exposed to cow milk proteins, our findings support this hypothesis. Our findings suggest that an EHMD is better tolerated in ≤750 g infants than a CMBD, as shown previously in larger preterm infants. (20, 40, 44, 45)

"For subgroup analyses, we observed nearly the same magnitude of reduction in NEC (59% lower odds) when an EHMD was compared to a base diet of only human milk with added cow milk-based fortifiers (no formula controls, CMBD-f, p=0.006)."

For subgroup analyses, we observed nearly the same magnitude of reduction in NEC (59% lower odds) when an EHMD was compared to a base diet of only human milk with added cow milk-based fortifiers (no formula controls, CMBD-f, *p*=0.006). Due to the small sample size of infants, we could confirm through medical records did not receive formula, this comparison did not reach statistical significance for surgical NEC (*p*=0.09), but the magnitude of the decrease was similar to infants who received some formula (61% lower odds). These findings serve as an important reminder that effect sizes and measures of association cannot be interpreted by their *P* values alone. (46) The clinical meaningfulness of effect sizes should be considered when evaluating the results of nutrition interventions.

BPD is one of the major comorbidities affecting ELBW infants (5, 47), and BPD severity is linked to their long-term health. (48, 49) Our results attributed an EHMD to a 35% reduction in the odds of developing BPD among infants born weighing ≤750 g. Due to differences in analytical techniques, it is difficult to directly compare our results to those reported previously for larger preterm infants born weighing ≤1,250 g. (19-21)

Nevertheless, the percent difference in incidences of BPD between an EHMD and CMBD was smaller in our study than previously reported, suggesting that an EHMD has a larger effect size in larger infants. One potential reason for this is that the overall incidence of BPD is inversely correlated with birthweight and gestational age at birth; moreover, younger infants are more likely to suffer from more severe forms of BPD than infants born later and with higher birthweights. (28, 47, 50) It is plausible that BPD severity may be differentially impacted based on enteral nutrition. BPD severity should be investigated in future research on the enteral nutrition of ELBW infants.

Research on the effectiveness of small baby units (SBUs) in reducing mortality and comorbidities supports the assertion that standardized care is important for ELBW infants. (51-53) Optimizing nutrition is one of the core tenants used in SBUs that have adopted an infant-driven model of care. (54) We found a 10% lower incidence of death (*p*=0.049) in infants receiving an EHMD than those receiving cow milk-based fortifier without formula. We also found significant reductions in many of the most common major comorbidities, including NEC, BPD, and MMI. These findings suggest that feeding an EHMD to these smallest babies may be safer than feeding cow milk-based products.

Strengths and Limitations:

This study had several strengths. Data harmonization and IPD meta-analysis allow for reliable comparison across cohorts and improved statistical power to declare observed differences statistically significant compared to what aggregate meta-analysis would have allowed. In addition, many of the outcomes reported here have not been previously published. Thus, IPD allowed for a more comprehensive analysis than only existing published data.

"This study also had some limitations. The first is related to availability bias. Importantly, although all authors were invited to contribute their data, 33% did not respond to our request. Not all the data from all eligible studies were able to be collected. In some cases, this was due to timing issues. However, some authors did not respond to our invitation to contribute their data."

This study also had some limitations. The first is related to availability bias. Importantly, although all authors were invited to contribute their data, 33% did not respond to our request. Not all the data from all eligible studies were able to be collected. In some cases, this was due to timing issues. However, some authors did not respond to our invitation to contribute their data. Another limitation was that we could not fully adjust models for all clinically meaningful covariates, including antenatal steroid use, because these data were unavailable in all cohorts. There is also some potential misclassification bias because some cohorts lacked sufficient nutrition data to confirm formula intake. Consequently, we may have underrepresented the number of infants who did not receive formula. However, we remain confident in our findings because undercounting infants would bias estimates toward the null. Additionally, data on the quantity of cow milk-based vs. human milk-based fortifiers consumed in each group were unavailable for analysis. Nevertheless, our results suggest the control group received relatively great amounts of cow milk-based fortifier, and the EHMD group received none. Previous research has shown that for every 10% increase in the volume of milk containing cow milk protein, the increased risk of developing NEC is 12%, surgical NEC is 21%, and sepsis is 18%. (18) Finally, our results may have underestimated the measures of association attributed to an EHMD because the EHMD group was analyzed as a homogeneous group. This is potentially problematic because EHMD feeding protocols varied greatly within studies (e.g., across study sites) and between studies. Previous research has suggested that earlier EHMD fortification protocols may be advantageous in reducing several comorbidities in infants born weighing ≤1250 g (55) and should be the subject of research for smaller ELBW infants. Future studies should carefully consider standardized feeding protocols, including the timing of feeding, the timing of fortifi-

cation, feed advancement rates, and the timing of transitioning off fortifiers. (30, 55)

"Our findings improve the scientific premise that an EHMD reduces the odds of developing several major comorbidities, including a 60% reduction in NEC, a 50% reduction in surgical NEC, and a 40% reduction in BPD, compared to a CMBD in the smallest preterm infants born weighing ≤750 g. These results support our hypothesis that compared to a CMBD, an EHMD reduces comorbidities in ELBW infants born weighing ≤750 g."

Conclusions:

Feeding the smallest infants remains a critical challenge for healthcare teams, who must balance providing the appropriate nutrition while avoiding feeding intolerance and other common feeding-related issues. Our findings improve the scientific premise that an EHMD reduces the odds of developing several major comorbidities, including a 60% reduction in NEC, a 50% reduction in surgical NEC, and a 40% reduction in BPD, compared to a CMBD in the smallest preterm infants born weighing ≤750 g. These results support our hypothesis that compared to a CMBD, an EHMD reduces comorbidities in ELBW infants born weighing ≤750 g. Our results build upon previous findings that human milk has significant clinical advantages over a CMBD when taken together (15, 56-59) and provide new evidence that replacing cow milk-based fortifiers with human milk-based fortifiers reduces mortality and morbidity in ELBW infants born weighing ≤750 g.

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