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STATE-OF-THE-ART

Systematic review and meta-analysis of human milk intake and retinopathy of prematurity: a significant update

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OBJECTIVE: Two recent meta-analyses have studied the association of exclusive or mainly human milk intake (HMI) on retinopathy of prematurity (ROP). One of these meta-analysis found a protective effect of only or mainly HMI on Severe ROP but not on any stage ROP. However, both these meta-analyses did not find protection from any stage ROP or Severe ROP with any amount of HMI. The objective of this study was to study the association between any amount of HMI and the development of All ROP and Severe ROP in very-low birth weight infants (VLBWI) and extremely low birth weight infants (ELBWI) by systematic review using PRISMA-P guidelines and meta-analysis.

STUDY DESIGN: Exposure, controls and outcomes studied were any amount of HMI vs no HMI and All ROP/Severe ROP in VLBWI/ELBWI. All ROP was defined as all stages of ROP pooled together, and Severe ROP as ⩾ stage 3 ROP and ROP requiring intervention. Results and effect sizes are expressed as odds ratio (OR), relative risk (RR), risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals (95% CI). Data sources used were PubMed, MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials, Scopus and CINAHL until 24 April 2015. Extracted data were pooled using a fixed effects model. Heterogeneity was assessed. Sensitivity analysis was performed.

RESULTS: Five hundred nine of 1701 infants who received any amount of HMI developed All ROP vs 310 of 760 infants without HMI developed All ROP with a pooled OR 0.63* (0.51,0.78), RR 0.76* (0.67,0.86) and RD −0.09* (−0.13, −0.05). The NNT with any amount of HMI was 11* (8,20) (*$P < 0.0001$) to prevent one case of All ROP. 204 of 2465 infants who received any amount of HMI developed Severe ROP vs 85 of 764 infants without HMI developed Severe ROP with a pooled OR 0.74* (0.56,0.98), RR 0.77* (0.60,0.98) and RD −0.03* (−0.05, −0.00). The NNT with any amount of HMI was 33* (*$P = 0.04$) to prevent one case of Severe ROP.

CONCLUSION: Any amount of HMI is strongly associated with the protection from All ROP and Severe ROP.

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INTRODUCTION

With increased survival of very-low birth weight infants (VLBWI) (weighing < 1500 g at birth), the incidence of retinopathy of prematurity (ROP), a significant cause of blindness among children in the United States,[1] is also increasing. According to the World Health Organization, ROP is the third leading cause of avoidable blindness in the developed world.[2]

VLBWI have altered development of the retinal vascular system *ex utero* causing retinal traction and retinal detachment. They also have decreased abilities to handle oxidative stress and to synthesize long-chain polyunsaturated fatty acids.[3] All these factors put them at increased risk for ROP.

Clinical interventions to reduce the development of ROP have been limited because many identified risk factors for ROP are difficult to alter in clinical practice. The ability to limit supplemental oxygen administration is necessarily constrained by the need to safeguard the life and neurological status of the VLBWI and extremely low birth weight infants (ELBWI).

Not many clinical interventions have reduced the development of ROP. Vitamin E therapy trials have produced inconsistent findings although inositol administration to preterm infants has resulted in a lower incidence of ROP.[4]

Some studies are associated with a reduced incidence of ROP in human milk-fed preterm infants.[2,5-10]However, other studies have not demonstrated this protective effect.[11,12] Also, some studies demonstrate a clear dose-response effect on major morbidities of prematurity including ROP, particularly over the critical exposure period of the first 14 days of life.

The rates of exclusive breast-feeding in the VLBWI and ELBWI in the Neonatal Intensive Care Unit (NICU) in the United States are low and variable. There are estimates of breast-feeding initiation rates[13] of about 35% and rates of human milk feeding at NICU discharge of about 50-60% in the USA.[14] Also, there are important variations in exclusive breast-feeding rates between NICUs (20-90%), and across gestational ages and birth weights (30-70%). As per the Joint Commission on Accreditation of Hospitals, the performance on perinatal core measure PC-05: exclusive breast milk feeding continues to be below 50% at approximately half of Joint Commission accredited hospitals.[15] The CDC data[16] reveal rates of exclusive breast-feeding among all infants of 40.7% with rates varying between 25.3 and 60.5%.

Two recent meta-analyses[17,18] have studied the association of exclusive or mainly human milk intake (HMI) on ROP. One of these meta-analysis[18] found a protective effect of only or mainly HMI on

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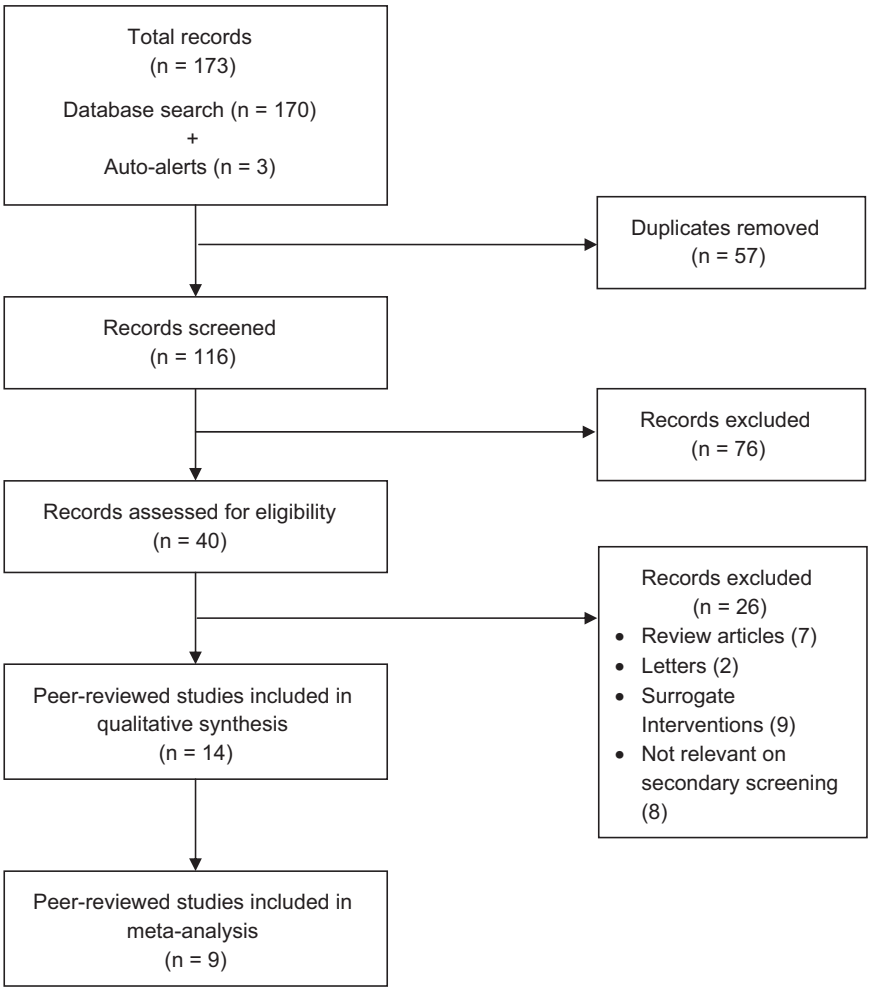

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow process for the selection of eligible studies.

severe ROP but not on any stage ROP. However, both these meta-analyses did not find protection from any stage ROP or severe ROP with any amount of HMI, which is the commonest scenario of maternal milk availability in the NICU. As the benefits of human milk for VLBWI and ELBWI restricts the option of randomized trials with human milk,[9] and as the majority of NICU infants generally do not exclusively receive maternal breast milk, we performed a meta-analysis in the commonest subset of NICU infants to try to answer the question whether any amount of HMI offers protection against the development of All ROP and Severe ROP and to quantify the magnitude of this association.

MATERIALS AND METHODS

Literature search

A comprehensive search of electronic databases since inception including PubMed and MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Clinical Trials and Scopus was done using Medical Subject Headings (MeSH) terms 'infant, very/extremely low birth weight', 'human milk', 'breast feeding', 'retinopathy of prematurity', 'retinal detachment', 'retrolental fibroplasia', and relevant keywords, 'low birth weight', 'extremely low birth weight', 'extreme prematurity', 'very low birth weight', 'ELBW', 'VLBW', 'human milk intake', 'human milk fed', 'breast milk intake', 'breast milk fed', 'ROP', 'severe ROP' or 'severe retinopathy of prematurity', 'threshold ROP', 'threshold retinopathy of prematurity'. Auto alerts were set for new articles. A quick search of PubMed was redone in April 2016.

Our search identified 173 records. After 57 duplicates were removed, 116 records were screened and all but 40 were excluded after screening of the study title and abstracts. Forty records were assessed for eligibility. Of these, 26 records were excluded (there were 7 review articles, 2 letters, 9 reports with human milk surrogates, for example, inositol, carotenoids, lutein, zeaxanthin, insulin-like growth factor 1, Vitamin A and E, antioxidants as the intervention; the other 8 records were deemed not relevant after a complete review of the study on secondary screening). Finally, 14 peer-reviewed studies were included for the qualitative synthesis and 9 peer-reviewed studies were included for quantitative meta-analysis (Figure 1). Only peer-reviewed studies that used any amount of maternal milk were included. Studies using exclusive pasteurized donor human milk were not included in the meta-analysis.

Conference proceedings were searched. There were no efforts to identify unpublished studies. We did not check print versions of electronic databases, as these studies were generally done after the mid-1970s and should be covered by the electronic databases from 1966 onward. Only citations in the English language were chosen. Cross references of citations were checked. No hand searching was done. The systematic review is presented in the format suggested by the consensus statement of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group[19] and the PRISMA-P statement.[20]

Study selection

All studies considered were retrospective case control or cohort studies. Case series, case reports, review articles, ideas, opinions, letters and editorials were not considered, as they did not have control groups for comparison. Abstracts that were not published as full text articles were excluded as they were not peer-reviewed. Data extracted for the outcome of All ROP were the number of patients with/without All ROP in the any amount of HMI group and also the number of patients with/without All ROP in the non-HMI group. Similar data were extracted for the outcome of Severe ROP. The cases and control groups in each of the studies were closely matched and the studies were evaluated for internal validity (methodological quality) and external validity (generalizability or applicability) of the data.

Data extraction

A template of 2x2 contingency tables was constructed for data abstraction. Five authors (SKB, JCP, RD, SSB and SSB) independently abstracted the results and resolved disparities by consensus. The following information was abstracted from each included study: first author, total number of patients with any amount of HMI and no HMI, those that had the outcome of All ROP/Severe ROP vs those that did not have the outcome of All ROP/Severe ROP, the type of study and the year of publication.

Data transformation and analysis

Evidence synthesis was done by meta-analysis using a fixed effects model with Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Results and effect sizes analyzed are expressed as odds ratio (OR), relative risk or risk ratio (RR), risk difference (RD) and numbers needed to treat (NNT) with 95% confidence intervals (95% CI).

I^2 (inconsistency index)[21] and Cochran's Q statistic (χ^2) tests were performed to assess heterogeneity. The Q statistic indicates whether the individual effects are farther away from the common effect, beyond what is expected by chance. I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). An I^2 value $>75\%$ may be considered substantial heterogeneity. Tests for overall effect are expressed as *Z*-scores and *P*-values. There were not enough studies to test for publication bias using funnel plots.

RESULTS

A total of 40 citations were found after a comprehensive search of PubMed, MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Clinical Trials and Scopus. There were 14 eligible studies[2,5–12,22–26] for qualitative analysis. The authors made an extensive good faith effort to procure summary data from the original authors of six studies, as the data presented in their studies were not easily amenable to analyze in the format needed for a meta-analysis,[2,6,9,10,12,27] and three of them responded[6,7,9] with summary data. Other authors[2,12] responded but summary data were not accessible. Two authors were not contactable by phone[27] or e-mail.[10,27] The summary data of the cross-tabbed cell counts for any amount HMI vs All ROP/Severe ROP were not published in two studies.[2,12] These were estimated by inverse calculation from the published sample sizes and ORs by a biostatistician (JCP) of our team.

Of the 14 eligible records used for qualitative synthesis, only 9 could be used in the quantitative meta-analysis (as one of the studies[10] had all of the predictors analyzed as continuous numerical measures and hence did not have data that could be used in a 2x2 contingency table from the information given in the article; four other articles did not have data clearly available in the two intervention groups of this meta-analysis[22,24–26]). Finally, nine peer-reviewed studies, all retrospective, were found by the authors and were included for quantitative meta-analysis in this review.[2,5–9,11,12,23] The characteristics of these included studies are presented in Table 1.

There were many similarities and differences in the studies. The similarities were that all of the studies used the International Classification of ROP to stage the severity of ROP, and all were retrospective. There were also differences among studies. Patients included were only ELBW in some studies[6,9,12] but VLBW and ELBW in others.[2,5,7,8,11,23] Reporting of HMI was done differently by different studies. Some studies reported infants that received either exclusive human milk or exclusive formula,[8,23] four studies[2,6,9,11] reported HMI as mean dose of HMI vs no HMI, whereas other studies[2,5,7,8,23] defined HMI as any amount of human milk regardless of supplementation with formula. The outcomes studied were All ROP[2,5,7,8,11,23] and Severe ROP.[5,6,8,9,12,23] Studies with severe ROP differed in their definition of severe ROP as an outcome measure. A few studies defined severe ROP as stage 3 and 4 ROP,[23] others defined it as ROP treated surgically,[9,12] and yet others either used retinal detachment[10] or threshold ROP[8] to define severe ROP. Inclusion and exclusion criteria were available for all studies.

Quality assessment of observational studies

The nine observational studies included in the meta-analysis were subjected to a quality assessment score using the Newcastle–Ottawa Scale[28] for cohort studies (Supplementary Table 1). All studies were of good methodological quality[29] (defined as a score $\geqslant 7$ from a maximum score of 9) implying that there is a low risk of bias for all the three domains, that is, selection, comparability and outcome. These domains address selection bias, performance bias, detection bias, attrition bias and reporting bias. Thus, there is good internal validity (the extent to which the design and conduct of a study are likely to have prevented bias and likely to yield results that are closer to the truth) and good external validity (generalizability and applicability) of the data.

It should be noted that in Heller *et al.*,[12] data were missing on $141/1203 = 11.72\%$ of infants in the study which was not explained and hence did not score a * on the adequacy of follow up of cohorts on quality assessment. However, Hylander *et al.*[5] received a * on quality assessment despite $44/218 = 20.18\%$ of eligible infants not being included. This is because the proportion of infants excluded for not having received eye examinations to determine ROP status before discharge did not differ significantly between the two feeding groups (human milk: 19% excluded and formula: 17% excluded) and other valid reasons.

All ROP

Five hundred nine of 1701 infants who received any amount of HMI developed All ROP vs 310 of 760 infants without HMI developed All ROP with a pooled OR 0.63* (0.51,0.78), RR 0.76* (0.67,0.86) and RD −0.09* (−0.13, −0.05). The NNT with any amount of HMI was 11* (8,20) (*$P < 0.0001$) to prevent one case of All ROP. The risk of All ROP was significantly higher in the group that did not receive human milk compared with the group that received any amount of human milk (Table 1 and Figures 2–4).

Severe ROP

Two hundred four of 2465 infants who received any amount of HMI developed Severe ROP vs 85 of 764 infants without HMI developed Severe ROP, with a pooled OR 0.74* (0.56,0.98) and RR 0.77* (0.60,0.98). The diamond of pooled point estimate for RD −0.03* (−0.05, −0.00) does not cross the line of no effect and the test for overall effect for RD reveals a $P < 0.05$. The NNT with any amount of HMI was 33* (*$P = 0.04$) to prevent one

Table 1. Characteristics of included studies

Study	*Country*	*Setting*	*Study design*	*Sample size*	*Timeframe*	*BW(g)/GA(wk)*	*Other details*	*Feeding (n)*	*ROP diagnosis*	*Total ROP events (n)*	*No events (n)*
Johnson *et al.*[7]	USA	NICU, University Hospital	Cohort	216	1979–1981	⩽1500 g/not specified	Mean serum Vitamin E ± s.d. and mean ml blood received (as a marker for degree of illness) were similar between groups. >1500 to <2000 g = 169 infants not included, as they are larger/older infants where risk of ROP is lower.		All ROP		
Human milk								39		14	25
Formula								177		95	82
Hylander *et al.*[5]	USA	NICU, University Hospital	Cohort	174	January 1992 to September 1993		Maternal factors: prenatal care, health insurance, maternal smoking, alcohol and illegal drug use. Infant factors: mechanical ventilation and TPN days and supplemental oxygen days		Stages 1–4		
Human milk						1044 ± 251[a] g/28 ± 2.2[^] wk		100%-17;80–90%-28;20–79%-39: <20%-16 (total = 100)		41 (All ROP) 6 (Severe ROP)	59 94
Formula						948 ± 223[a] g/27.5 ± 2.4[a] wk		74		47 (All ROP) 9 (Severe ROP)	27 65
Furman *et al.*[11]	USA	NICU, University Hospital	Cohort	119	1 January 1997 to 14 February 1999		Ethnicity, ventilator dependence, effect of breast milk on ROP, sepsis, NEC, CLD and jaundice		All ROP		
Human milk						ml kg^{-1} per day: 1–24, 914 ± 205: 25–49, 988 ± 248; >50,1163 ± 225[a] g/28 ± 2[a] wk		ml kg^{-1} per day: 1–24, 29; 25–49, 18; >50,32 (total = 79)		44	35
Formula						1103 ± 260[a] g/28 ± 2[a] wk		40		16	24
Heller *et al.*[*12]	USA	NICU, Multicenter University Hospitals	Cohort	1057	October 1999 to September 2001		Ethnicity, pneumothorax, antenatal steroids, maternal hypertension, prenatal care, human milk proportion, day of first feeding.		Severe ROP (Surgical ROP)		
Human milk						775 ± 134[a] g/26 ± 2[a] wk	Not included after sensitivity analysis due to attrition bias	788		130	658
Formula						783 ± 140[^] g/26.2 ± 2[^] wk		269		33	236
Porcelli and Weaver[9]	USA	NICU, University Hospital	Cohort	77	01 January 2002 to 30 September 2003	867 ± 85[^] g/26.3 ± 1.2[a] wk	Human milk feeding, parenteral nutrition volume and vitamin E intake were predictors for ROP surgery. All infants received triweekly i.m. Vitamin A as chronic lung disease prophylaxis.		Severe ROP (Surgical ROP)		
Human milk								65		9	56
Formula								12		2	10
Kao *et al.*[2]	USA	NICU, University Hospital	Case control	132	2000–2009	960 ± 272[a] g/27 ± 2[^] wk	Study to explore the association of serum bilirubin level and breast milk feeding with ROP in preterm infants.		All ROP		
Human milk								67		30	37
Formula								65		36	29
Manzoni *et al.*[8]	Italy	NICU, Multicenter Hospitals	Cohort	498	2004 through 2008		Hyperglycemia		All ROP and Severe ROP (Threshold ROP)		
Human milk						1125 ± 247[^] g/29.4 ± 2.5[a] wk		314		11 (All ROP) 4 (Severe ROP)	303 310
Formula						1100 ± 272[^] g/29.2 ± 2.8[^] wk		184		29 (All ROP) 23 (Severe ROP)	155 161

Table 1. (Continued)

Study	*Country*	*Setting*	*Study design*	*Sample size*	*Timeframe*	*BW(g)/GA(wk)*	*Other details*	*Feeding (n)*	*ROP diagnosis*	*Total ROP events (n)*	*No events (n)*
Patel *et al.*[6]	USA	NICU, University Hospital	Cohort	101	2003–2004	770[b] g/26.1[b] wk	Mean dose (ml kg^{-1}per day) of HMI over different exposure periods; neonatal morbidities of NEC, CLD, ROP, IVH, PVL and LOS studied		Severe ROP (Stage 3 and above)		
Human milk								96		6	90
Formula								5		2	3
Spiegler *et al.*[23]	Germany	NICU, Multicenter including University Hospitals	Cohort	1322	2013	1080 (805–1340)[c] g/28.7 (26.6–30.1)[c] wk	Study the association of breast milk with reduced risk of BPD. Secondary outcomes analyzed were ROP and NEC		All ROP and Severe ROP (Stages 1–4)		
Human milk								1102		369 (All ROP)	733
										49 (Severe ROP)	1053
Formula								220		87 (All ROP)	133
										16 (Severe ROP)	204

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CLD, chronic lung disease; GA, gestational age; HMI, human milk intake; i.m, intramuscular; IVH, intraventricular hemorrhage; LOS, length of stay; NEC, necrotizing enterocolitis; NICU, Neonatal Intensive Care Unit; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; TPN, total parenteral nutrition; Wk, week. [a]Mean ±1s.d. [b]Mean . [c]Median (Q1–Q3). *Excluded after sensitivity analysis due to attrition and performance bias.

case of Severe ROP. (Table 1 and Figure 5, Supplementary Figures 1 and 2).

One study[12] had some major methodological limitations as acknowledged by the authors in their discussion that human milk feeds were initiated after the first week of life, and had an attrition bias as the data on ROP findings after discharge were not collected in majority of patients and >10% of patients were lost to follow up. On sensitivity analysis, this study[12] was excluded for performance bias and attrition bias. In the new meta-analysis, 74 of 1677 infants who received any amount of HMI developed Severe ROP vs 52 of 495 infants without HMI developed Severe ROP, with a pooled OR 0.35* (0.24,0.53), RR 0.38* (0.26,0.56) and RD −0.06* (−0.09, −0.04). The NNT with any amount of HMI was 17* (11,25) (*$P < 0.00001$) to prevent one case of Severe ROP. The risk of Severe ROP was significantly higher in the group that did not receive human milk compared with the group that received any amount of human milk (Supplementary Figures 3–5).

Sensitivity analysis

To investigate whether the protective association of any amount of HMI on All ROP and Severe ROP in our meta-analysis was mainly the effect of studies in which infants were exclusively human milk fed, we performed a sensitivity analysis. A new meta-analysis was performed after excluding studies in which infants were exclusively human milk fed. In the new meta-analysis there was a significant association of any amount of HMI with the protective effect in preventing All ROP[2,5,7,11,23] with an OR 0.72* (0.57,0.90), RR 0.82* (0.72,0.94), RD −0.08* (−0.13, −0.03) and NNT 13* (8,33) (*$P = 0.004$). It also showed a significant association of any amount of HMI with the protective effect in preventing Severe ROP[5,6,9,23] with an OR 0.58* (0.36,0.93), RR 0.60* (0.39,0.93), RD −0.04* (−0.07, −0.00) and NNT 25* (*$P = 0.04$).

In the meta-analysis of All ROP as the outcome, two of the studies[2,23] used either maternal or donor milk. The proportion of the use of either of these is unavailable. Kao *et al.*[2] showed a RR of developing any ROP to be 0.81 (0.57,1.14) and Spiegler *et al.*[23] showed the RR of developing any ROP to be 0.85 (0.70,1.02). Even if these studies[2,23] are excluded on the grounds of some infants receiving donor milk, the new meta-analysis with four studies[5,7,8,11] that used only maternal milk still demonstrates a significant association of any amount of HMI with the protective effect in preventing All ROP with an OR 0.49* (0.35,0.68), RR 0.65* (0.53,0.80), RD −0.12* (−0.17, −0.06) and NNT 8* (6,17) (*$P < 0.0001$). Similarly, the new meta-analysis with four studies[5,6,8,9] also showed a significant association of any amount of HMI with the protective effect in preventing Severe ROP with an OR 0.22* (0.12,0.40), RR 0.25* (0.14,0.43), RD −0.10* (−0.14, −0.06) and NNT 10* (7,17) (*$P < 0.00001$).

DISCUSSION

Our results clearly indicate that any amount of HMI is significantly associated with protection (compared with no HMI) from the risk of developing All ROP (all stages of ROP pooled together) and Severe ROP (⩾ stage 3 and ROP requiring intervention).

The broad literature search and extensive efforts to minimize information bias and inclusion/selection bias by contacting six authors yielded a larger number of studies and infants for the meta-analysis. This may have helped significantly change the conclusions of two recently published meta-analyses[17,18] that did not show a protective association for All ROP and Severe ROP with any amount of HMI in VLBWI and ELBWI.

The other strengths of this systematic review and meta-analysis are: (1) the methodological rigor and the appropriate reporting of the review based on the PRISMA-P guidelines, and (2) it addresses a very important, practical and relevant question about the

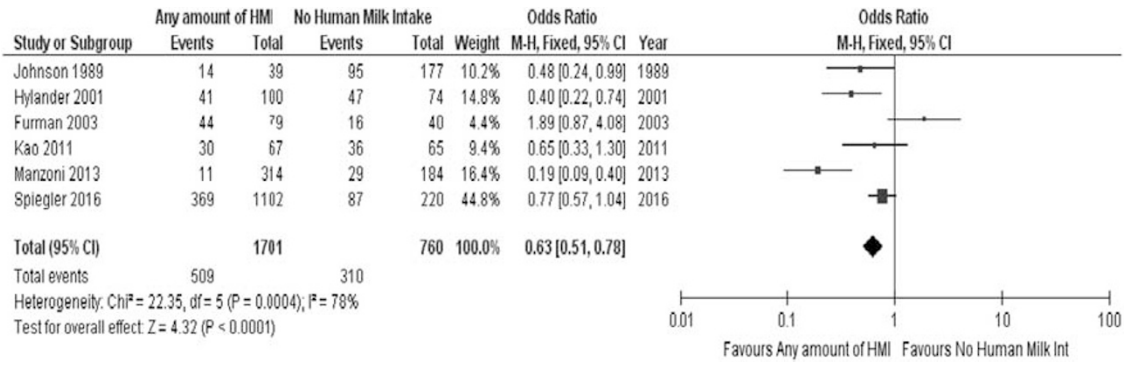

Figure 2. Outcome—All ROP—odds ratio. ROP, retinopathy of prematurity.

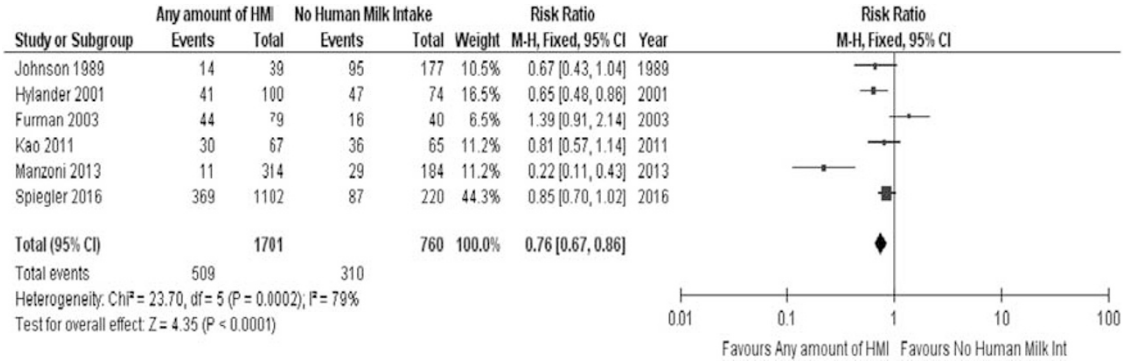

Figure 3. Outcome—All ROP—risk ratio. ROP, retinopathy of prematurity.

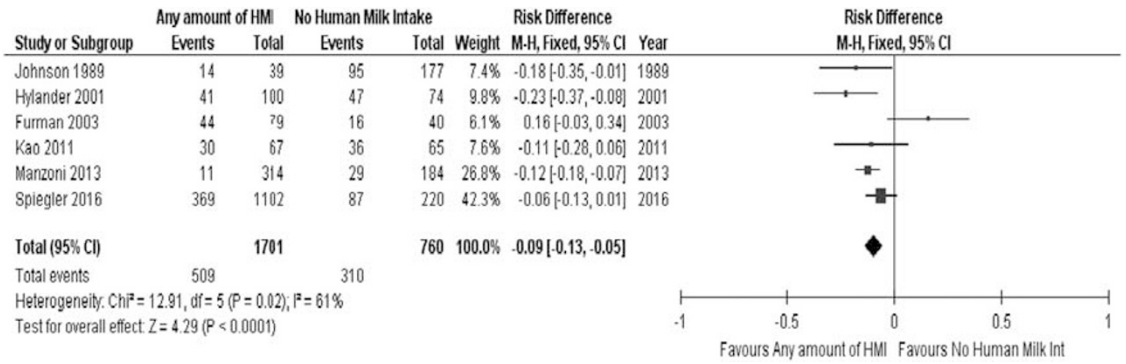

Figure 4. Outcome—All ROP—risk difference. ROP, retinopathy of prematurity.

commonest scenario in the NICU 'does any amount of HMI offer protection from ROP?'

This review has certain limitations. The review may be incomplete because of language bias. We cannot rule out publication bias, as we are unable to access any negative studies that did not get published. The number of current studies in each meta-analysis is < 10, which makes the power of the funnel plot for publication bias too low to distinguish chance from real asymmetry. Furthermore, it should be noted that not All ROP/Severe ROP studies necessarily report the use of HMI and similarly not all studies of HMI include All ROP/Severe ROP incidence.

The heterogeneity in our meta-analysis may be explained in part by variable definitions for 'human milk feeding' and for severe ROP among different studies used for the meta-analysis. Also, the definitions usually do not specify when the infant received human milk and if there were periods of exclusive or high doses of human milk feeding. Indeed, the current literature has many reports that suggest that there are relatively short, critical exposure periods postnatally when exclusive or high amounts of human milk are especially important in optimizing health outcomes for premature infants[25,30] and reducing the risk of enteral feeding intolerance, nosocomial infection and inflammation-based morbidities such as NEC.[6,11] Thus, an exclusively human milk-fed infant in the first month after birth may have better health outcomes compared with an infant who received low doses of human milk throughout the NICU stay.

We also explored heterogeneity by graphical methods in the Forest plots and by conducting a sensitivity analysis. Subgroup analysis and meta-regression to explore heterogeneity could not be performed due to the limited number of studies.

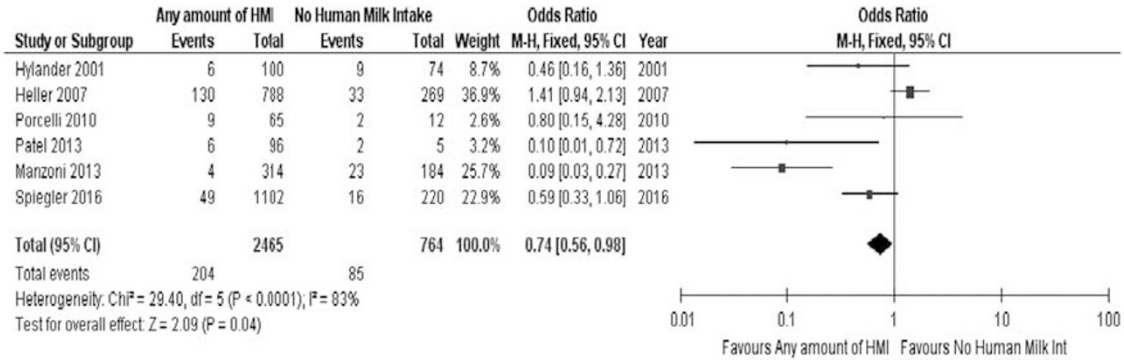

Figure 5. Outcome—Severe ROP—odds ratio. ROP, retinopathy of prematurity.

Human milk has many antioxidants like inositol, vitamin E, catalase,[31] glutathione peroxidase, taurine and carotenoids that combat oxidative stress from free radicals.[32] Of these antioxidants, carotenoids (lutein, b-carotene, zeaxanthin, lycopene) are found in human milk but not in most formulae,[33] and are preferentially accumulated in the eyes. By combating oxidative stress, these antioxidants downregulate vascular endothelial growth factor which in turn halts neovascular proliferation implicated in the pathogenesis of ROP. Superoxide dismutase[34] found in human milk also neutralizes free radicals. Oxygen-induced retinopathy is reduced in newborn mice that overexpress superoxide dismutase[35] or are exogenously given the enzyme. Interestingly, oxygen toxicity is also reduced in infants fed human milk as compared with infants fed formula, supported by the finding that urinary 8-hydroxydeoxyguanosine, a marker for oxidative DNA damage, is significantly lower in infants fed human milk compared with infants fed formula.[36] Vitamin E prophylaxis also reduces the incidence of Severe ROP.[37]

Docosahexaenoic acid (DHA) in human milk has been found to improve visual acuity in preterm infants and may contribute to normal visual development.[38] DHA supplementation decreases the severity of ROP in VLBWI.[39] Deficits in DHA in combination with underdeveloped antioxidant protection may contribute to the neurovisual developmental disorders, including ROP. The retina has the highest concentration of DHA of all tissues where it regulates angiogenesis and has a cytoprotective and neuroprotective role.[40] Because DHA cannot be synthesized *de novo*, the developing fetus is dependent on a maternal source. Most DHA accretion occurs during the period of rapid growth and brain development during the third trimester of pregnancy. This transplacental transfer is interrupted by preterm birth. In ELBWI, this deficit persists or worsens due to decreased adipose stores and ineffective conversion from precursor fatty acids. Postnatally, human milk provides the much needed DHA.

Human milk also increases the levels of IGF-I, which is required for normal vascularization of the retina.[41] During the postmenstrual ages of 30 to 33 weeks, a critical period for the maturation of retinal blood vessels, lower levels of circulating IGF-I have been shown to correlate with more severe stages of ROP.

At the present time, premature infant formulae come fortified with vitamin E, inositol, taurine and DHA (2002 to 2003). Beta carotenoids are a recent addition since 2012 to only one of the three major commercial formulae. In addition, certain antioxidants present in human milk are difficult, if not impossible, to supplement in formulae (superoxide dismutase, catalase, glutathione peroxidase and insulin-like growth factor 1) and neither can the effect that human milk has on normal retinal development be replicated by formulae. Thus, human milk is the only natural elixir that has all the protective components suitable to prevent ROP.

Preterm infants diagnosed with ROP during the perinatal period are at a higher risk for ocular abnormalities and deficits in visual function including myopia[42] and strabismus during later years, even if the ROP later resolves. Infants with ROP have a greater degree of myopia that persists, whereas the myopia experienced by infants without ROP tends to decrease in degree during the first year of life.[43] Decreasing the risk of ROP by any means would reduce health-care costs, save the vision of many infants and immeasurably improve their quality of life.

The evidence presented in this meta-analysis strongly suggests that providing any amount of human milk, even if not exclusive, has immense clinical significance and economic benefits based on its association with a lower incidence of All ROP and Severe ROP.

SUMMARY

Based on the Guideline Recommendation and Evidence Grading (GREG)[44] system, this review provides a grade A recommendation (that is, there is robust evidence to recommend a pattern of care) for the use of any amount of human milk in the prevention of All ROP and Severe ROP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Reproducible literature search strategy: BFG, SKB and RD. Collection and assembly of the data: SKB, SSB, SSB and RD. Analysis and interpretation of the data: SKB, JCP, SSB, SSB and RD. Conception and design, drafting of the article, critical revision of the article for important intellectual content and final approval of the article: SKB, BFG, JCP, SSB, SSB and RD.

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