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REVIEW OPEN ACCESS

Mapping the Evidence on Human Milk Fortification and Cardiovascular Risk Factors and Outcomes among Low Birth Weight Infants: A Scoping Review

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Abstract

Introduction: Preterm and low birth weight infants receiving a diet of human milk require fortification with protein, carbohydrates, vitamins, and minerals due to missed growth and nutrient accretion that would otherwise occur in utero. Although rapid catch-up growth improves anthropometric and neurodevelopmental indices, research has suggested that accelerated postnatal growth may be associated with poor long-term cardiometabolic outcomes.

Methods: We conducted a scoping review to map the evidence on human milk fortification and cardiometabolic risk factors and outcomes among low birth weight infants. We searched Ovid Medline, Ovid Embase, CINAHL, and Web of Science from inception to June 2021 and examined grey literature for relevant referenced articles. Studies were included if they were a primary study focused on fortified human milk and cardiometabolic risk factors or outcomes among low birth weight infants. A modified version of the Cochrane Collaboration Randomized Controlled Trial data collection form guided data collection. We conducted a narrative synthesis of the results structured around the Population, Concept, Context framework.

Results: We included 19 articles (14 randomized controlled trials, three quasi-randomized trials and two cohort studies) on cardiometabolic risk factors among 1,955 low birth weight infants who received fortified human milk. None of the included studies addressed long-term cardiometabolic outcomes. Body weight was the most examined risk factor in all included studies, with 13 studies observing benefit from human milk fortification. Two studies linked rapid growth with cardiometabolic risk factors.

Discussion: The focus across the 19 included studies was the anthropometric advantages of fortified HM among LBW infants. A meta-analysis was not performed for this review, but if completed may yield a different inference.

Conclusion: Limited evidence is available regarding the long-term cardiometabolic outcomes among low birth weight infants who received fortified human milk. Existing literature is focused on the short-term anthropometric benefits of fortification post-hospital discharge. Yet, some reports have linked rapid early postnatal growth with the development of cardiometabolic risk factors later in life. Future studies should explore the long-term cardiometabolic outcomes among low birth weight infants with the goal of optimizing anthropometric and brain growth while minimizing long-term cardiometabolic risk.

Keywords: fortification; human milk; pre-term infant; cardiometabolic outcomes; cardiometabolic risk factors; low birth weight infant; body weight; long term

Introduction

Background and Rationale

Human milk (HM) is the ideal source of enteral nutrition for all infants, providing critical nutrients and bioactive compounds that support healthy growth and immune development [1]. HM is particularly beneficial for preterm and low birth weight (LBW) infants (less than 2,500 grams), who have compromised immune function and are at a high risk of morbidity and mortality [2]. Due to missed nutrient accretion, growth, and development that would otherwise occur in utero, preterm and LBW infants experience numerous short- and long-term complications. These include respiratory and cardiovascular abnormalities, neurodevelopmental disabilities, and growth impairments, among others [3,4]. These complications make prematurity the leading cause of death worldwide among children under five years of age [5].

Current literature indicates that nutrition in early life is associated with long-term growth and neurodevelopment. Among preterm and LBW infants, an HM-based diet may reduce morbidity and mortality [6-9]. However, HM alone is insufficient to meet the nutritional needs of preterm and

LBW infants at regular feeding volumes [10]. Therefore, fortification of HM with protein, carbohydrates, vitamins, and minerals, is a common practice that increases nutrient uptake and supports rapid postnatal growth in this population [11]. Fortification of HM is associated with more rapid catch-up growth than unfortified feeding, allowing preterm and LBW infants to achieve age-appropriate growth and body composition [12].

Research evidence in the last decade has examined growth and neurodevelopment in the first several years of life following HM fortification. In a meta-analysis of 18 clinical trials, Brown et al. determined that multi-nutrient fortified HM compared to unfortified HM led to modest increases in weight (MD 176 g/kg/d, 95% confidence interval (CI) 1.30 to 2.22), length (MD 0.11 cm/week, 95% CI 0.08 to 0.15), and head circumference (MD 0.06 cm/week, 95% CI 0.03 to 0.08) among hospitalized preterm infants [13]. A clinical trial by Kashaki et al. showed improved neurological development in areas of auditory verbal language, cognitive domain, and social connection, among LBW infants who received HM fortified with protein supplement compared to fortified HM alone [6]. Similarly, Biasini et al. demonstrated better neurological outcomes in hospitalized LBW and Small for Gestational Age (SGA) infants who received enriched protein supplemented HM compared to fortified HM without protein supplementation [14].

Although HM-derived fortification is associated with improved short-term growth and neurodevelopmental outcomes among preterm and LBW infants, the long-term effects of HM fortification may require further investigation [15,16]. Evidence indicates that accelerated postnatal growth from HM fortification during the first two years of life may be associated with poor long-term metabolic outcomes [16,17]. Rapid weight gain during infancy, for example, is linked to a twofold to fourfold increase in childhood obesity risk, which carries significant cardiometabolic risk in later life [17]. Thus, nutritional supplements that accelerate catch-up growth may also increase the risk of childhood obesity and cardiovascular disease [15].

Objective

A scoping review is a type of evidence synthesis that incorporates a range of study designs to answer research questions that go beyond assessing intervention effectiveness. Thus, scoping reviews can be used to examine the research activity on a topic, identify gaps in the available evidence, and determine the value of conducting a systematic review, among others [20]. The objective of this scoping review is to map the evidence on HM fortification and cardiometabolic risk factors and outcomes among LBW infants (Table 1).

Population: Low birth weight infants born at less than 2,500 grams.
Concept: Relationship of human milk fortification and cardiometabolic risk factors and outcomes.
Cardiometabolic risk factors include hemoglobin A1c (HbA1c), fasting plasma glucose, fasting insulin, blood lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, triglycerides, and apolipoprotein B (apo B), weight, body mass index (BMI), waist circumference and systolic and diastolic blood pressure [18].
Cardiometabolic outcomes include total cardiovascular mortality, coronary heart disease (CHD) mortality, stroke mortality, myocardial infarction mortality, cardiovascular disease (CVD) incidence, coronary heart disease (CHD) incidence, stroke incidence, myocardial infarction incidence, and diabetes incidence [18].
Context: Any time post-discharge from the Neonatal Intensive Care Unit.

Table 1. Population, Concept, Context Framework.

Methods

Arksey and O'Malley's methodological framework for scoping reviews with refinements by Levac et al. [19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [20] guided the conduct and reporting of this review, respectively.

Protocol and Registration

We did not publish a protocol for this review.

Identifying Relevant Studies

We searched the electronic databases Ovid Medline, Ovid Embase, CINAHL, and Web of Science from inception to June 2021. The search strategies were developed in consultation with a professional librarian and employed a combination of the following terms, modified as appropriate for each database: "very low birth weight," "preterm," and "human milk fortification." Additionally, grey literature publications were searched. This was completed through a hand search of relevant sources of the New York Academy of Medicine's Grey Literature Publisher's List, including the Association of Maternal and Child Health Programs, All Kids Count, World Health Organization: Department of Child and Adolescent Health and Development, and Canadian Institute for Health Information. The reference list of relevant articles and those pulled for full text were also reviewed (Table 2).

1. Exp Infant, low birth weight/ or exp Infant, premature/ or exp Infant, extremely premature/
2. Exp Intensive care units, neonatal/
3. Exp Neonatology/
4. Exp Infant, small for gestational age/
5. OR/1-4
6. Exp Milk, human/
7. Multi-nutrient fortification.mp
8. Breast milk fortification.mp
9. Donor milk fortification.mp
10. Exp Milk banks/
11. Human milk fortification.mp
12. Targeted fortification.mp
13. Standard fortification.mp
14. Adjustable fortification.mp
15. Individualized fortification.mp
16. Multi nutrient fortifier.mp
17. Human milk-derived fortifier.mp
18. Mothers' milk.mp
19. OR/6-18
20. 5 AND 19

Table 2. Ovid Medline Search Strategy**.**

Study Selection and Eligibility Criteria

We exported all citations to Covidence for deduplication and screening by two independent reviewers (SP, LC, or SM). Inclusion criteria at the title and abstract stage included any peer-reviewed article written in English, that described research of any design on LBW infants and human milk fortification. For this review, LBW refers to an infant weighing less than 2,500 grams at birth, while fortification was defined as the addition of any protein, carbohydrate, vitamin, and/or mineral to breast milk to support postnatal growth. At this stage, non-English language articles were excluded due to the authors' abilities. Following title and abstract screening, eligible articles were reviewed at the full-text level. The inclusion criteria at this stage included studies of any design focused on the use of fortified HM in LBW infants and reported at least one of the cardiometabolic risk factors and outcomes listed in Table 1. At this stage, any articles for which an associated full-text was unable to be retrieved was excluded. Case reports, commentaries, editorials, essays, historical articles, letters to the editor, narratives, opinion pieces, study protocols, and systematic reviews were also excluded at this stage. However, the reference lists of all eligible articles were reviewed for further relevant studies. Any disagreements during the study selection process were resolved through discussion with a third reviewer (SP, LC, or SM).

Charting the Data

A modified version of the Cochrane Collaboration Randomized Controlled Trial data collection form [21] guided data collection. As the original version was designed for RCTs, modifications to the form only consisted of excluding queries that were not applicable or relevant to a scoping review. For example, the risk of bias assessment was not completed. The collection form was first piloted among all reviewers to determine usability and efficacy. Data extraction was performed by one reviewer (SP, LC, or SM) and independently verified by a second reviewer (SP, LC, or SM). Guided by the modified document, we extracted information about the study author, funding source, study year and design as well as information on the population demographic, such as gestational age, birth weight, and details regarding HM fortification. Data extraction was also completed regarding cardiometabolic risk factors and outcomes.

Critical Appraisal of Individual Sources of Evidence

We did not perform a risk of bias assessment as this was not a necessary step for this review, given that our objective was to map the literature, rather than to determine effectiveness.

Collating, Summarizing and Reporting the Results

We conducted a narrative synthesis of the study results structured around the Population, Concept, Context (PCC) framework. We described the population (gestational age, birth weight, postnatal age), concept (fortification details, cardiometabolic risk factors and outcomes examined), and context (setting post-discharge from the neonatal intensive care unit).

Results

Study Selection

As a result of the database and grey literature searches, 17,839 articles were obtained. 4,382 articles were removed following deduplication and 13,457 articles were screened at the title and abstract level. 39 articles were screened at the full-text level and 19 studies were included in our final review [12,22-39] (Figure 1).

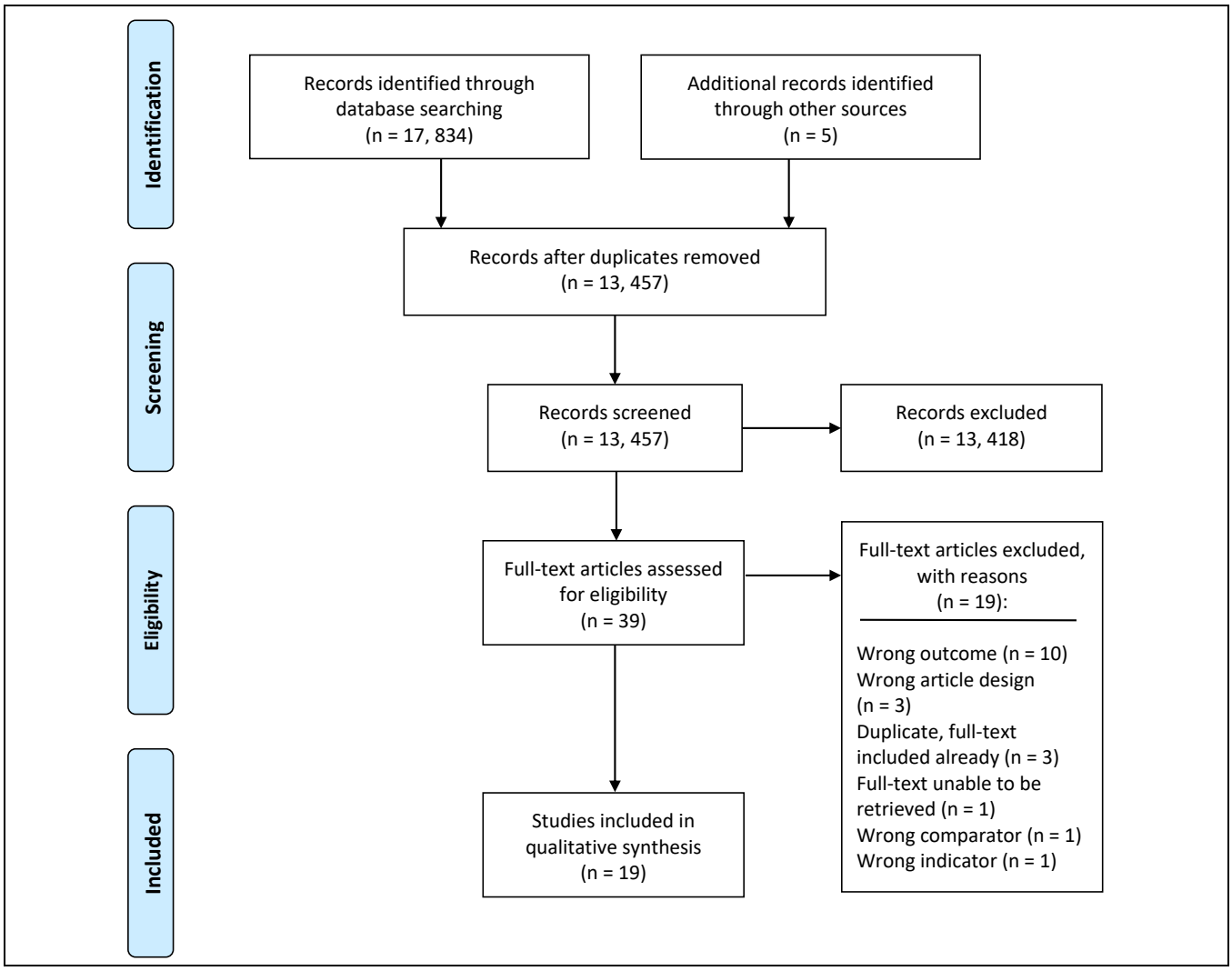

Figure 1. Flow Diagram for the Study Selection Process. This figure was created with Microsoft Word.

Study Characteristics

Study Design Characteristics

Of the 19 included studies, 14 (74%) were randomized controlled trials [12,22-25,27,28,32,33,35-39], 3 (16%) were quasi-randomized controlled trials [26,29,30], and 2 were cohort studies (one prospective and one retrospective, 10%) [31,34].

PCC

Population

The pooled sample size across the included studies was 1,955 LBW infants. In studies that provided data on the mean (SD) gestational age and weight at birth, infants ranged from 26.4 (2.1) to 30.8 (0.3) weeks and 773.9 (143.7) to 1,407 (58) grams (Appendix Table 1).

Concept

Twelve cardiometabolic risk factors were examined across 19 studies. Bodyweight was the most frequently studied risk factor in all 19 studies. None of the studies investigated any cardiometabolic outcomes.

Context

Postnatal age in studies that provided this data ranged from 37.8 (3.3) weeks corrected gestational age to 11 years. In all articles that included this information, study conduct was primarily in the context of an outpatient follow-up (eight of nine studies, 89%) [22,23,25,28,29,34,35,38]. One study took place in the context of a post-discharge home visiting program [27].

HM-Fortification Details

The methods of HM-fortification used across the 19 included studies varied. Six studies (32%) detailed the use of fortified or unfortified donor milk [26,34,35,37,38,39]. Eighty-four percent (16 of 19) of studies examined the use of standard fortification [12,22-25,27-34,36,37,39], while the remaining three examined protein fortification that was

adjusted based on blood urea nitrogen levels [26,35,38]. Of the 12 studies that detailed the macro and micronutrients that were added to HM, nine (75%) specified the addition of protein [12,23,25-27,35-38], four (33%) specified the addition of carbohydrates [12,25,27,36], four (33%) specified the addition of micronutrients, including calcium, phosphorus, and zinc [23,24,30,32], and one (8%) specified the addition of medium-chain triglyceride oil and docosahexaenoic and arachidonic acid [37]. Four studies (21%) described supplementation of HM with a type of formula [31-33,39].

Summary of Results

Evidence on HM-Fortification and Cardiometabolic Risk Factors

All included studies addressed cardiometabolic risk factors among LBW infants who received fortified human milk. The most frequent risk factor examined was weight in all included studies, followed by BMI in three studies [36,37,39], blood pressure [36,39], and cholesterol and HbA1c [36,37] in two studies. The other cardiometabolic risk factors included waist circumference, plasma glucose, insulin, and triglycerides, addressed in two studies [36, 39]. Thirteen of 19 studies (68%) that examined weight gain observed benefit from HM fortification, finding either growth that was on target compared to growth charts or growth that exceeded that of control infants or infants unexposed to fortification [12,22,23,26,27,28,30,31,32,33, 34,38,39].

Toftlund et al. conducted a randomized controlled trial of 239 very preterm infants to determine the association between three types of early nutrition strategies (unfortified HM, fortified HM, or preterm formula) and early growth and their influence on metabolic outcomes at six years of age [36]. BMI, blood pressure, plasma glucose, HbA1c, insulin, and cholesterol were not significantly different between the three nutritional groups. Blood lipids were higher in formula-fed compared to HM-fed infants, which included infants fed fortified HM Early rapid growth was observed in 53% of infants between 34 weeks to two months and was also more frequent among preterm formula-fed than HM-fed infants, although not significantly (80% vs. 53%, $p = 0.20$). Early rapid growth correlated with fat mass, fat mass index, fat-free mass, lean mass, and abdominal fat mass. The authors concluded that early rapid growth could influence metabolic syndrome in later childhood and adulthood. Thus, nutritional strategies for preterm infants must be carefully considered, particularly among formula-fed infants [36].

Henriksen et al. conducted a randomized controlled trial of 98 very LBW infants to determine the association between supplementation with docosahexaenoic acid and arachidonic acid and placebo on growth and metabolic markers at six years of age [37]. There were no significant differences in weight or BMI between the intervention and control groups. However, rapid growth after one year of age was associated with high BMI and unfavourable metabolic markers. The authors hypothesized that rapid growth and poor metabolic markers could be due to weaning from breast milk, which may be metabolically protective [37].

Evidence on HM-Fortification and Cardiometabolic Outcomes

None of the included studies addressed long-term cardiometabolic outcomes among LBW infants who received fortified human milk.

Discussion

Summary of Evidence

This scoping review mapped the available evidence on HM fortification and cardiometabolic risk factors among LBW infants. The predominant focus across the 19 included studies was the anthropometric advantages of fortified HM among LBW infants. The existing evidence demonstrates similar findings. A Cochrane review by Brown et al. observed that multi-nutrient fortification of HM, compared to unfortified HM, resulted in improved in-hospital weight gain [40]. However, data was non-existent regarding the long-term advantages of fortification on growth and development beyond infancy. Kunz et al. also demonstrated that fortification of HM promotes rapid weight gain, beneficial for neurodevelopmental outcomes. However, it may be associated with small increases in cardiometabolic risk factors [41]. Two studies in our review also linked rapid growth with cardiometabolic risk factors [36,37].

None of the included studies addressed cardiometabolic outcomes. However, this could be because only five studies investigated cardiometabolic risk factors beyond toddlerhood, between five and 11 years of age. Typically, cardiometabolic outcomes, such as hypertension and diabetes, appear in later childhood or adulthood.

Toftlund et al. noted that six years of age was still too early to see fully evolved metabolic syndrome [36]. They recommended investigating the incidence of cardiometabolic outcomes at later childhood and even into early adulthood [36]. Future studies should measure long-term cardiometabolic outcomes. Finally, socioeconomic status is significantly associated with a predisposition to metabolic conditions, such as obesity. Thus, future research should consider the effect of socioeconomic factors when investigating the development of cardiometabolic risk factors and outcomes among LBW infants.

Limitations

We attempted to collect all available literature on HM fortification and cardiometabolic risk factors and outcomes among LBW infants. However, the existing evidence mainly consisted of studies that were focused on short-term anthropometric benefits and no long-term cardiometabolic outcomes were addressed. One possible reason for this is that our search strategy could have been improved. We

developed our search terms in consultation with a professional librarian and searched four large databases and grey literature publications. However, our database search could have been more comprehensive. For example, more databases, such as Scopus, could have also been searched. We also excluded non-English language studies due to the abilities of the authors, which may have limited our results further.

Conclusions

This scoping review revealed that there is limited evidence regarding the long-term cardiometabolic risk factors and seemingly none regarding cardiometabolic outcomes among LBW infants who received fortified HM. The included studies primarily focused on the short-term anthropometric benefits of fortification post-discharge from the NICU. However, experts remain concerned regarding the possibility of long-term programmed metabolic consequences due to accelerated early extrauterine growth in this population [16,17]. Future efforts should explore the long-term cardiometabolic outcomes among LBW infants through feasible methods. Studies that leverage large existing databases or use retrospective methods, such as historic cohorts or ecologic studies, may provide a start to optimizing anthropometric and brain growth in the critical phase of early extrauterine life while minimizing long-term cardiometabolic risk factors and outcomes for LBW infants.

List of Abbreviations Used

HM: human milk
LBW: low birth weight
SGA: small for gestational age
HBA1C: hemoglobin A1c
LDL: low-density lipoprotein
HDL: high-density lipoprotein
apo B: apolipoprotein B
BMI: body mass index
CHD: coronary heart disease
CVD: cardiovascular disease
CHD: coronary heart disease
PRISMA-ScR: preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
PCC: population, concept, context
SD: standard deviation
RCT: randomized controlled trial
N/R: not reported
CGA: corrected gestational age
BP: blood pressure
BUN: blood urea nitrogen
WHO: World Health Organization
NICU: neonatal intensive care unit

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This study did not require ethics approval or participant consent as all participant data was anonymous and acquired from existing literature.

Authors' Contributions

SM: contributed to the design of the study, collected and analysed data, drafted the manuscript, revised the manuscript critically, and gave final approval of the version to be published.
SP: contributed to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
LC: contributed to the design of the study, collected and analysed data, drafted the manuscript, revised the manuscript critically, and gave final approval of the version to be published.

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