Importance of human milk for infants in the clinical setting: Updates and mechanistic links

Emily Nagel, PhD, RD[1], **Kristin M. Elgersma, DM, RN**[2], **Tiffany T. Gallagher, BA, IBCLC**[2], **Kelsey E Johnson, PhD**[3], **Ellen Demerath, PhD**[1], **Cheryl A. Gale, MD**[4]

[1]School of Public Health, University of Minnesota-Twin Cities, Minnesota, USA

[2]School of Nursing, University of Minnesota-Twin Cities, Minnesota, USA

[3]Department of Genetics, Cell Biology, and Development, University of Minnesota-Twin Cities, Minnesota, USA

[4]Department of Pediatrics, University of Minnesota-Twin Cities, Minnesota, USA

Abstract

Introduction: Human milk (HM) is the optimal source of nutrition for infants and has been implicated in multiple aspects of infant health. While much of the existing literature has focused on the individual components which drive its nutritional content, examining HM as a biological system is needed for meaningful advancement of the field. Investigation of the non-nutritive bioactive components of HM and the maternal, infant, and environmental factors which affect these bioactives is important to better understand the importance of HM provision to infants. This information may inform care of clinical populations or infants who are critically ill, hospitalized, or who have chronic diseases and may benefit most from receiving HM.

Methods: In this narrative review, we reviewed literature examining maternal and infant influences on HM composition with a focus on studies published in the last 10 years that were applicable to clinical populations.

Results: We found multiple studies examining HM components implicated in infant immune and gut health and neurodevelopment. Additional work is needed to understand how donor milk and formula may be used in situations of inadequate maternal HM. Further, a better understanding of how maternal factors such as maternal genetics and metabolic health influence milk composition is needed.

Conclusion: In this review, we affirm the importance of HM for all infants, especially clinical populations. An understanding of how HM composition is modulated by maternal and environmental factors is important to progress the field forward with respect to mechanistic links between HM biology and infant health outcomes.

Keywords

human milk; infant; newborn; critical illness; hospitalization; immunity

Corresponding author: Emily Nagel, PhD, RD, 2025 East River Parkway, Minneapolis, MN 55414, nagel127@umn.edu.

Introduction

Human milk (HM) is the recommended source of nutrition for all infants and is associated with numerous health benefits, including decreased risk of mortality[1], respiratory infections[2], asthma[3], diabetes (type 1 and 2)[4,5], and gastrointestinal conditions such as severe diarrhea[2], Crohn's disease[6], and ulcerative colitis.[7] HM provision has also been linked to improved clinical outcomes for hospitalized infants, such as shorter time to full feeds[8,9], shorter time to hospital discharge[8–10], and greater than 6-fold lower in-hospital mortality compared to formula-fed infants.[11] While the health benefits for the majority of infants are well known, the importance of maternal HM specifically for infants that are hospitalized, critically ill, and/or have congenital illnesses has yet to be thoroughly described. Infants in these groups are often characterized by immature guts and fragile immune systems that may benefit from the immune-enhancing bioactives found in HM (Figure 1).[12] Due to immaturity of the gastrointestinal tract, they are also susceptible to developing necrotizing enterocolitis (NEC), an inflammatory disorder of the gastrointestinal tract that can result in ischemic necrosis of the intestinal mucosa.[13] At this time, the specific HM components responsible for its many observed benefits (e.g. immune protection, decreased risk for development of diseases such as diabetes, etc.) and their mechanisms of action remain to be fully elucidated.[14,15]

HM is a complex biofluid composed of water, macronutrients, and a vast array of non-nutritive components.[16] While early research focused on individual milk components with putative health benefits, a comprehensive approach to examining HM as a biological system is needed to successfully address knowledge gaps in HM data related to clinical practice.[17] Recent attention has been focused on factors which influence the non-nutritive components in HM, termed milk *bioactives* (e.g. hormones, proteins, cytokines, miRNA, and immunoglobulins), and there is growing evidence that these bioactives differ by maternal factors such as genetics[18], metabolic status[19], and dietary intake[20] in ways that may be important to infant health. The HM microbiome, which is an important source of microbial colonization for infants, is another area of emerging research, as alterations in the microbial equilibrium are linked to increased risk for later development of gastrointestinal disorders, asthma, and metabolic disease.[21–23]

The purpose of this narrative review is to discuss the recent HM literature (with a focus on studies published in the last 10 years; see Supplemental Materials) and its relevance to the provision of HM to vulnerable infants in the clinical setting (Figure 2). We will summarize the use of maternal HM and donor HM in the hospital setting, as well as describe the influences of maternal genetics, metabolic health, and diet on milk composition. Finally, we discuss the benefits of HM provision for infants, with a special focus on the clinical populations who may benefit most from HM. While there are known benefits of direct breastfeeding (BF), we will include studies which examine provision of HM via both direct BF and indirect HM feeding (e.g. bottle feeding). Further, while most of the existing HM research has focused on maternal HM, we will include comparisons with donor HM and/or preterm formula when available.

Human milk in the hospital setting

Supporting direct breastfeeding is appropriate in nearly all circumstances; when direct is not possible or desired, expression of maternal HM should be facilitated in the absence of contraindications. An interdisciplinary approach that includes the guidance of clinical lactation professionals such as International Board Certified Lactation Consultants can increase the provision of maternal HM in the hospital setting, help parents sustain breastfeeding or milk expression after discharge, and manage the process of lactogenesis if milk is not being provided. To best support breastfeeding parents, including those of vulnerable infants most in need of HM, clinicians should familiarize themselves with up-to-date guidance from the Centers for Disease Control and Prevention and the American Academy of Pediatrics on contraindications for providing maternal HM [24–26], which may vary based on available resources and circumstances. For example, while maternal HIV infection has long been considered a contraindication to breastfeeding, the World Health Organization recommends antiretroviral therapy, which greatly reduces postnatal transmission of HIV through maternal HM, and supports breastfeeding as long as desired.[27] Additionally, few medications are fully incompatible with breastfeeding, and infant age and health status, lactational stage, dosage, and timing of medication may alter the risk profile for an individual infant; the InfantRisk Center at Texas Tech University Health Sciences Center (https://infantrisk.com/) provides individualized, up-to-date guidance. Provision of maternal HM to infants whose parents engage in substance use is highly variable, and we would refer providers to the Academy of Breastfeeding Medicine's protocol on managing breastfeeding in the case of substance use disorder.[28] Maternal HM composition differs between and within individuals, with variations attributed to an infant's gestational age, the frequency of milk removal, time of day, individual gene expression, and parity. The fat content and bioactives, such as melatonin, in expressed maternal HM may vary from maternal HM that is consumed directly from the breast.[29]

Although the American Academy of Pediatrics recommends pasteurized donor HM for preterm infants if maternal HM is unavailable[30], ~50% of NICUs have no access to donor HM[31,32], and only ~18% of level 1 nurseries use donor HM. Donor HM is available through either non-profit or for-profit milk banks. All HM banks in the United States are accredited by the Food and Drug Administration and local health departments as food manufacturers; additionally, non-profit milk banks in the United States and Canada are regulated by the Human Milk Banking Association of North America. Donor HM is most commonly used for medically fragile and premature infants but can also be used for healthy infants who need short-term supplementation in place of formula. The most commonly cited reason for not providing donor HM is cost; however, the direct cost savings due to prevention of NEC is substantial due to shorter lengths of stay, less surgical intervention, and lower resource use.[33] One study demonstrated a cost savings of $15,555 per infant over the course of a hospital stay, independent of the prevention of NEC, for infants fed maternal HM and donor HM.[34]

While individual-level plasticity in HM composition in response to environment circumstances is an advantage, variation in donor HM composition can pose a concern for infants who are fed primarily a diet of donor HM. The gestational age of a milk donor's

infant, and the lactational stage of the milk donor influence milk composition; for instance, mature donor HM composition differs from preterm milk, particularly in lipid metabolite concentrations.[35] This is of concern because most donor HM is mature milk. In addition, maternal genetics, dietary factors, milk collection method, and the time of collection are factors that influence milk composition. Yet, these factors are generally unknown and uncontrollable.[29] The process of pooling, analyzing, mixing, and handling donor HM may vary between facilities, and while Holder pasteurization is the most commonly used method (and used by all Human Milk Banking Association of North America -member milk banks), there can be variation in the process of pasteurization as well as nutrient loss.[29,36] Handling of donor HM within the hospital setting, including freeze-thaw cycles, also impacts composition. The process of handling, processing, and storing milk before donation and after pasteurization can lead to nutrient loss, and while this can be somewhat mitigated by pooling milk from multiple donors and using targeted pooling techniques, there may still be variation in macronutrients and the bioactive components of milk.[37] While the macronutrient composition of maternal HM has been thoroughly described[38–40], our understanding of variation in macronutrient and bioactive components of donor HM is limited. Perrin et al. (2020) included just 14 studies from 1995 to 2019 in a systematic review on donor HM composition; only 4 studies included sample sizes greater than 60 and demonstrated a two-fold or greater difference in protein, fat, and calorie composition within and between studies.[29] There is also evidence that pasteurization of donor HM may destroy critical bioactives that confer health benefits to infants, including immune components, enzymes, and microbes.[41] In contrast, human milk oligosaccharides (HMOs), which are polysaccharides that benefit infant gut health appear to be unaffected by pasteurization.[42]

Influences on maternal human milk composition

There are many factors known to influence maternal HM composition. In this review, we focus on 3 emerging factors due to their potential relevance for infant health outcomes: Maternal genetics, maternal metabolic health status, and maternal diet.

Maternal Genetics—Like all complex traits, the composition of HM is influenced by both genetic and non-genetic factors. Prior to the focal period of this review (the last 10 years), a number of candidate gene studies identified genetic variants influencing specific components of HM, including replicated associations with zinc, oligosaccharides, and fatty acids.[43–45] These and other candidate gene discoveries were the focus of a recent review.[46] In the last 15 years, the field of human genetics has shifted from candidate gene study designs, which test for associations between genetic variants in genes selected on the basis of prior knowledge, to genome-wide association studies (GWAS). GWAS take a hypothesis-free approach by testing genetic variants across the genome for association with the trait of interest. GWAS overcome many of the weaknesses of candidate gene association studies, such as high false positive rates, selection bias, and failure to discover new candidate genes.[47,48] Additionally, GWAS results can enable improved understanding of trait biology, genetic prediction for precision medicine, and genetic epidemiologic studies of the impact of an intermediate trait (e.g. milk composition) on health outcomes (e.g. infant disease risk).[49] However, the barriers to entry for a well-powered GWAS are high: this approach requires genome-wide genotype and trait data from a large number of samples. Depending

on the trait and study design, a sample size in the tens of thousands may be required to meaningfully characterize the genetic architecture of a complex trait.[49]

Nevertheless, 2 recent studies have applied the GWAS approach to HM composition. First, a genome-wide association study of the abundance of 26 fatty acids in HM made use of 3 cohorts from Bangladesh with HM fatty acid profiles and infant genotypes in a total of 1,142 mother-infant pairs.[50] The authors identified 4 regions of the genomes significantly associated with milk fatty acids. These associated regions included the previously known fatty acid desaturase gene cluster, which was associated with arachidonic acid abundance in HM. Additional significant loci included an intronic variant in *SNX29* associated with the polyunsaturated fatty acid (PUFA) 6/PUFA 3 ratio, an intergenic genetic variant associated with eicosenoic acid, and an intronic genetic variant in *COG3* associated with capric acid. Notably, the authors performed their GWAS by imputing maternal genotypes from infant genotypes. The authors' discovery of several new significant loci despite the loss of information inherent in this approach, and their relatively modest sample size for a GWAS, suggests there are many genetic associations with milk fatty acid composition yet to be discovered. Second, a recent study combined genetic and HM oligosaccharides (HMO) composition data to perform a GWAS in 395 women from 11 cohorts.[51] This work replicated the previously known association between *FUT2* genotype and multiple HMOs, as well as identifying associations at 4 additional loci. This study again highlights the possibility for discovery of new genetic associations with milk composition as sample sizes and the number of traits measured in milk expand.

In parallel to the rise of GWAS, functional genomic approaches have improved our understanding of the molecular processes connecting genetic variation to traits. One powerful approach is expression quantitative trait locus (eQTL) mapping, which tests for genetic variants associated with gene expression in a specific tissue or cell type.[52] Our group's recent preprint applied this approach to HM, identifying genetic variants associated with the expression of 2,690 genes in milk.[53] Most gene expression in milk is derived from the milk-producing mammary epithelial cells.[54] Thus, these eQTLs represent critical data for interpreting existing and future HM GWAS, as they may enable identification of the causal genes underlying genetic associations with milk composition. Future studies that expand the sample sizes of HM composition GWAS and integrate genetic associations with functional genomics data will yield critical insights into the biology of HM production and its impact on maternal and infant health.

Maternal metabolic health—Because obesity and gestational diabetes affect a large and increasing proportion of pregnancies in the United States and are also associated with increased relative risk of important perinatal outcomes including preterm birth[55,56] and congenital structural anomalies[57,58], maternal metabolic status is an important consideration for the role of maternal HM in the clinical setting. A 2020 systematic review and meta-analysis (31 studies in qualitative synthesis and 9 studies in quantitative synthesis) found that maternal BMI (body mass index) and adiposity were associated with higher maternal HM fat and lactose concentrations, but protein content did not differ by weight status.[59] Recent work has focused on concentrations of milk bioactives, many of which are correlated with and derive from maternal circulation. Maternal obesity is associated with

higher concentrations of leptin and insulin and decreased concentrations of adiponectin and ghrelin.[19,60,61] Leptin is an appetite-regulating hormone that increases energy expenditure, and milk concentrations are reflective of maternal serum concentrations.[62–64] Insulin has been noted to play a key role in milk synthesis and secretion, and high concentrations in HM have been associated with both higher pre-pregnancy BMI and pregnancy hyperglycemia and insulin resistance.[61] Adiponectin, one of the most abundant milk hormones, is secreted by adipose tissue, modulates glucose and lipid metabolism, and is inversely associated with adiposity.[19,65] Ghrelin stimulates appetite, inducing adiposity and may be synthesized and secreted by the breast.[66,67] Of these associations, the evidence appears strongest for leptin. A systematic review of 26 studies revealed that despite differences in methodology, maternal BMI was consistently positively associated with concentrations of milk leptin. [68]

Due to co-existing low-grade inflammation, mothers with altered metabolic status also have increased milk concentrations of pro-inflammatory cytokines, such as TNF-α, IL-6, and CRP. In a cohort of exclusively breastfeeding participants (n=134), pre-pregnancy BMI (β: 0.49, p<0.001 and excessive gestational weight gain (β: 0.51, p=.011), were positively associated with maternal HM CRP but not IL-6.[69] Exposure to higher CRP via maternal HM could have health consequences for infants as these cytokines may remain active in infant circulation, and higher levels of proinflammatory cytokines such as CRP are associated with cardiovascular disease and adverse metabolic health.[70,71] Maternal inflammation, as reflected in elevations in milk CRP and TNF-α, has recently been found to be associated with low milk supply and disruption of fatty acid transfer from maternal circulation to the milk in lactating women.[72] Chronic low-grade inflammation is emerging as a central concept in both breastfeeding challenges and milk composition.

Maternal weight status may also be associated with HM oligosaccharide (HMO) concentrations. HMOs are complex polysaccharides abundant in HM that are not digestible by the infant.[73] HMOs play a role in modulating the immune system both by supporting a healthy gut microbiome and by influencing healthy immune development.[73,74] These bioactive components are not digested by the infant gut[75] but are fermented by beneficial gut bacteria, leading to production of metabolites such as short chain fatty acids, which may assist in maturation of the intestinal epithelial cells.[76–78] A recent scoping review found moderately compelling evidence that maternal body composition and HMO profiles are associated.[79] While the largest multi-site international study (n=410 participants in 11 international cohorts)[80] included in the review found a link between maternal weight status/BMI and specific HMOs during lactation, HMO profiles also varied by geographic region, even among healthy women. The authors concluded that the variable results from the studies that have been conducted thus far and the inconsistencies in methodology hampered the ability to make conclusive statements about the relationship between maternal BMI and overall HMO composition.

While evidence is still emerging, maternal pre-pregnancy BMI has been linked to differences in the HM microbiome. A prospective cohort study of Canadian women (n=113) found an association between maternal-pre-pregnancy BMI and microbiota beta-diversity in milk samples collected at 3 months postpartum (Bray-Curtis $R^2 = 0.037$).[81] Women with a BMI classified as obese had a greater incidence of milk *Bacteroidetes* (IRR: 3.70; 95% CI: 1.61–

8.48) and reduced incidence of *Proteobacteria* (IRR: 0.62; 95% CI: 0.43–0.90) compared to women with overweight BMI. Additionally, mothers with gestational diabetes and pre-pregnancy BMI classified as overweight had an increased incidence of *Gemella* (IRR: 5.96; 95% CI: 1.85–19.21) compared to women with BMI within the normal range. Functional analysis revealed that milk of participants with pre-pregnancy obesity was associated with enrichment of the biosynthesis of secondary metabolites pathway (coefficient = 0.0024, $P_{FDR} < 0.1$), which could indicate an upregulated response to maternal metabolic status.

Maternal Diet—Maternal diet is known to impact several HM micronutrients (e.g. vitamin A, vitamin B-6, vitamin B-12, folate, iodine, and selenium), as well as fatty acids, while the relationship between diet and other macronutrients in HM is less clear.[38,82,83] A 2016 systematic review found that 17 of 36 included publications focused on the fatty acid composition of maternal HM.[84] However, only 3 studies included the same exposure and outcome variables (milk DHA and maternal fish consumption), and the results were variable. The authors acknowledged a paucity of research on the amount of variability in HM composition attributable to maternal diet and noted the diversity in research methods and results. Some of the diversity in study results may be related to various milk collection procedures[85] and statistical methods used, as well as the examination of maternal diet based upon individual components versus dietary patterns. Multiple studies have found associations between various maternal dietary patterns and maternal HM composition.[86,87] A 2023 systematic review and meta-analysis categorized 27 cross-sectional studies by dietary pattern (rational protein + rational fat, rational fat + high protein, high fat + high protein, high fat + rational protein) and overall macronutrient intake. [88] Dietary intake of fat was positively associated with increased maternal HM fat composition, while maternal intake of protein and lactose were not associated with maternal HM concentrations. However, dietary patterns were also associated with maternal HM composition. For example, the high fat + rational protein dietary pattern was associated with the highest maternal HM protein concentration, while the rational fat + high protein dietary pattern was associated with the highest concentration of maternal HM lactose. The MEDIDIET study also examined maternal dietary patterns and maternal HM composition. [87] In a sample of healthy Italian mothers (n=300), maternal dietary patterns such as "fatty acids with fins" (diet with greatest loading on eicosapentaenoic acid, docosahexaenoic acid, vitamin D, and docosapentaenoic acid) and "vitamins, minerals, and fiber" were correlated with maternal HM fatty acids (particularly n-3 fatty acids) using principal component analysis. While the authors examined the associations between other macronutrients and dietary patterns, no strong correlations were observed.

There is also preliminary evidence that maternal diet may affect maternal HM microbiota composition and diversity.[89] In a sample of healthy women (n=21), longitudinal samples of maternal HM and 24-hour dietary recalls were obtained at 9 postpartum time points through 6 months postpartum.[90] While the milk microbiome was relatively stable over time, maternal diet was linked with relative abundances of several bacterial taxa. Protein intake was positively correlated with the relative abundance of *Gemella* ($r_s = 0.46$; p = 0.037), saturated fatty acids ($r_s = -0.59$; p = 0.005) and monounsaturated fatty acids ($r_s = -0.46$; p = 0.036) were inversely associated with the relative abundance of *Corynebacterium*, and

total carbohydrates ($r_s = -0.54$; p = 0.011), disaccharides ($r_s = -0.47$; p = 0.031), and lactose ($r_s = -0.51$; p = 0.018) were negatively associated with Firmicutes.[90] A larger cross-sectional study of a sample of healthy mothers in the MAMI (MAternal MIcrobes) cohort (n=120) examined associations between two maternal dietary patterns or clusters (cluster I: high intake of plant protein, fiber and carbohydrates; cluster II: high intake of animal protein and lipids). maternal HM microbiota was different by dietary cluster; compared to participants in cluster II, maternal HM from participants in cluster I showed higher relative abundance of *Bacteriodetes* (p<.001) and *Actinobacteria* (p=.014) at the phylum level and higher relative abundance of *Staphylococcus* (p=.036), *Lactobacillus* (p=.022), and *Bifidobacterium* (p=.026) at the genus level.[91] maternal HM from participants in cluster I also revealed higher bacterial richness and diversity compared to that from participants in cluster II. When examining specific macronutrients, there was also evidence of associations between macronutrients and microbial genera (e.g. *Staphylococcus* was associated with higher carbohydrates and lower protein intake and *Bifidobacterium* was associated with higher carbohydrates and polyphenols, which have been proposed to have prebiotic and antimicrobial properties.[92]

Maternal diet may also alter the HMO composition of maternal HM, which may then modify the maternal HM microbiome and thus the composition of bacteria delivered to the developing infant gut. In a single-blinded crossover study of women (n=14),[93] the specific type of maternal dietary carbohydrate and energy source intake were associated with variations in HMO concentrations in maternal HM and HM microbiome composition. For example, women ingesting a diet enriched with galactose as an energy source had higher concentrations of HMO-bound fucose in their milk, and this was associated with an increased abundance of fucosidase-producing bacteria in milk.

INFANT HEALTH BENEFITS OF HUMAN MILK PROVISION

Immune and gastrointestinal health

Infant gut and immune health are closely linked, with the intestinal tract comprising the largest immune organ in the human body.[94] The infant gut microbiome promotes immune health by maintaining integrity of the intestinal barrier and preventing inflammatory pathogenic bacteria from colonizing the infant gut.[95] Over the past decade, advances in analysis of HM composition and the human microbiome (i.e. 'omics-based analyses) have uncovered mechanisms by which HM/breastfeeding could shape the developing immune system, promote immunoregulatory processes, and aid in prevention of disease. Arguably, the infants who may benefit most from the provision of HM are critically ill infants, such as preterm infants or infants diagnosed with life-threatening congenital illnesses. Preterm infants are born with nutritional deficits[96], immature brain development[97,98], and impaired immune systems[99,100] that place them at risk for medical complications and neurodevelopmental disabilities.[101] The incidence of NEC ranges from 2–13% in preterm infants and ~7% for very low birth weight infants (<1500 g).[102] Infants in a post-operative state or with other conditions resulting in hypoperfusion to the gastrointestinal tract, such as congenital heart disease (up to 9% prevalence of NEC for single ventricle physiology), are also at risk for NEC as blood is shunted away from the intestines and toward critical

organs for survival, potentially leading to hypoxic ischemic injury. Reperfusion may trigger the inflammatory cascade, damaging the mucosal barrier and allowing for invasion of pathogenic bacteria that contribute to the development of NEC.[103–105] Preterm infants fed formula have 6–10 times the risk of NEC compared to infants fed exclusive maternal HM.[106] Similarly, a large, retrospective cohort study (n=546) found that infants with congenital heart disease receiving exclusive, unfortified HM before neonatal cardiac surgery were significantly less likely to develop NEC (OR=0.17, 95% CI=0.04–0.84) than those receiving formula, fortified feeds, or no preoperative feeds.[107]

Maternal HM/breastfeeding may also be protective against allergic diseases such as asthma, atopic dermatitis, and food allergy. Protection against these diseases may be particularly important for hospitalized populations, as there is strong evidence that preterm and very low birth weight infants are at increased risk for asthma[108], and emerging evidence that infants with congenital surgical anomalies may also have higher rates of asthma and other allergic diseases.[109–111] Most studies suggest that increased HM/breastfeeding dose and duration is protective against asthma/wheeze [112–114], but the relationship between HM/breastfeeding and other allergic diseases is less clear.[115] Rosas-Salazar et al.'s large, population-based prospective cohort study (n= 1495) used robust statistical methods to support causal inference and investigated associations between dose and duration of breastfeeding, infant illness and allergy, upper respiratory tract cytokines, and both upper respiratory tract and gut microbiome.[116] The authors found dose-dependent differences in the upper respiratory tract and gut microbiome related to breastfeeding; lower alpha-diversity in both microbiome sites, lower abundance of respiratory *Acinetobacter* (an emerging respiratory pathogen),[117] and higher abundance of gut *Bifidobacterium* (a bacteria positively associated with health) were observed in exclusively breastfeeding infants. This study also reported significant reductions in infant lower respiratory tract infections, allergic rhinitis (ever) at age 4 years, and asthma at age 4 years related to dose and duration of exclusive breastfeeding. Each 4 weeks of exclusive breastfeeding was associated with ~5% lower odds of these health outcomes in both traditional adjusted regression and in propensity score matched cohorts. Interestingly, exploratory analysis revealed that neither cytokine levels (i.e., IFN-α, IFN-γ, and IL-17) nor the upper respiratory tract microbiome mediated the relationship between breastfeeding practices and infection/allergy but that beta-diversity of the gut microbiome was a significant mediator of the association between exclusive breastfeeding and asthma. Cytokine and microbiome measures occurred only at initial study enrollment, however, and may not have been fully reflective of physiology throughout infancy.

Several milk bioactives are implicated in the beneficial effects of maternal HM on infant gut and immune health. HMOs exhibit both antiviral and antimicrobial activity[118] and have been observed to interact with dendritic cell receptors, resulting in promotion of regulatory T cells (Tregs), which aid in maintenance of immune response balance, upregulation of anti-inflammatory cytokines (i.e., IL-10, IL-27), and suppression of inflammation induced by lipopolysaccharide.[119] Interestingly, HMOs may synergistically improve the performance of the pharmaceutical antibiotics vancomycin and ciprofloxacin against group B *Streptococcus* (GBS), likely by increasing bacterial cell permeability[120], with potential implications for drug-resistant infection.[121] Antibacterial and/or antibiofilm properties of HMOs against GBS, methicillin-resistant *Staphylococcus aureus*, and *Acinetobacter baumannii* have been

further demonstrated in multiple studies.[122–124] Mechanisms underlying these effects are under investigation and may include decreased bacterial production of biofilm components[124], interruption of capsule biosynthesis[125], and/or alteration of cellular metabolism.[125]

Fatty acids found in maternal HM may also play a role in immune health. Higher levels of certain long-chain polyunsaturated fatty acids (LC PUFAs) in HM (e.g., arachidonic acid, gamma-linolenic acid) have been associated with lower production of pro-inflammatory cytokines associated with asthma and allergy, including IL-17 and IL-5.[126] However, study results have not been consistent, with smaller studies finding no significant associations between maternal HM fatty acid profiles and allergic diseases, such as asthma/wheeze[127] and atopic dermatitis.[128] Recent work has demonstrated the potential of the metabolite butyrate, a short chain fatty acid, to mediate immune development and protect against food allergy in children.[129] A study of healthy mother-infant dyads (n=135) found that HM from mothers of infants without food allergies had significantly higher levels of butyrate-producing bacteria than in a group with food allergy.[130] Taken as a whole, the nature of the relationship between fatty acids in HM and allergic disease is not clear, although it seems plausible that HM fatty acids contribute to the complex development of immunity.

Neurodevelopmental Health

Preterm infants (especially early preterm infants) and infants with congenital illnesses are at increased risk for neurodevelopmental impairments.[131–135] Multiple studies have reported associations between maternal HM intake and improved neurodevelopmental outcomes for both term and preterm infants.[136–139]

A recent longitudinal study of preterm infants (n=180) in the Victorian Infant Brain Studies cohort examined the proportion of maternal HM received for the first 28 days of life and found increases in deep nuclear gray matter at term-equivalent age and higher Full Scale IQ scores at 7 years of age for each day of maternal HM intake > 50% total intake (0.5 points/day; 95% CI: 0.2–0.8). This study also found a positive association between average daily maternal HM intake and hippocampal volume at term age (0.15 cc/day; 95% CI: 0.05, 0.25).[140] Another observational study of VLBW infants (n=430) found that each 10 mL/kg/day increase in the provision of maternal HM during NICU hospitalization was associated with a 0.35 point increase in cognitive index score (95% CI: 0.03–0.66, p = 0.03) on the Bayley III Index Scores at 20 months' corrected age.[138] In a third cohort of VLBW infants (n=316) from Italy, maternal HM intake at NICU discharge was associated with 3.8 points higher General Quotient score at 24 months' corrected age using the Griffiths Mental Development Scale (β = 0.109, p = 0.050).[141] In this study, infant nutritional intake was categorized as maternal HM, mixed maternal HM and formula feeding (maternal HM > 50% daily intake), or exclusive formula. Project Viva, a large US-based cohort study of term infants (n=1037) found that breastfeeding duration was associated with language assessed using the Peabody Picture Vocabulary Test (0.21 points; 95% CI: 0.03–0.38 points per month breastfed) at 3 years of age and verbal and non-verbal intelligence at 7 years of age using the Kaufman Brief Intelligence Test (0.35 points; 95% CI:0.16–0.53 verbal points per month breastfed; and 0.29 points; 95% CI :0.05–0.54 nonverbal points per month

breastfed).[142] However, in the same cohort, breastfeeding was not associated with improved executive function, behavior, or social-emotional development in mid-childhood, indicating that breastfeeding may benefit specific aspects of neurodevelopment.[143]

In contrast to the aforementioned studies showing associations between maternal HM and neurodevelopment, an observational study of a sample of preterm infants (n=611) enrolled 33 weeks gestation in the DHA for Improvement of Neurodevelopmental Outcomes Study (Australia) found that neither the volume nor duration of maternal HM intake were associated with Bayley Scales of Infant Development II, Mental and Psychomotor development Indexes at 18 month corrected age.[144] Infants in this sample were receiving only maternal HM, both maternal HM and preterm formula, or preterm formula only; donor HM was not included. maternal HM was fortified per NICU standard practice per the clinical team. The authors hypothesized that while maternal HM is typically sufficient to meet the needs of term infants, preterm infants have specialized nutritional needs that may not be met by maternal HM composition alone (thus, why fortification of maternal HM is standard practice in neonatal intensive care units) and that the timing of exposure to HM is different than infants born at term. However, they also acknowledged that 18 months corrected age may be too early to identify neurodevelopmental deficits, which were observed in later childhood in other studies.

Previous studies establishing a link between HM and improved neurodevelopment were conducted in infants receiving only maternal HM and not donor HM, but the growing availability of donor HM has led to additional studies examining the use of maternal HM in preterm infants with comparisons against donor HM and preterm formula.[145] Clinical trials examining maternal HM vs donor HM vs preterm formula are often unfeasible due to ethical concerns with randomization to donor HM or preterm formula alone when the benefits of maternal HM have been well established. A Canadian clinical trial of very low birth weight preterm infants (n=363) found no difference in neurodevelopmental assessment scores (Bayley Scales of Infant Development III) at 18 months for infants randomized to supplemental donor HM vs preterm formula.[146] In this study, infants were given either donor HM or preterm formula to supplement maternal HM for 90 days or to discharge home, whichever came first. Another observational cohort study of preterm infants predominantly (>50%) supplemented with donor HM (n=27) versus mostly maternal HM (n=29) or preterm formula (n=25) found that the donor HM group scored significantly lower than non-donor HM-fed infants in cognition and language at 1 year in simple analyses and significantly lower than preterm formula-fed infants in adjusted analyses (e.g. mean [standard deviation, SD] scores cognition: maternal HM: 93.0 [9.6]; preterm formula, 97.1 [11.8]; donor HM, 83.1 [11.6]; [donor HM vs preterm formula, $p = 0.002$; using Bayley Scales of Infant Development III) compared to infants fed non-donor HM. However, the adjusted models accounted for very few covariates (bronchopulmonary dysplasia, multiple births, and social work involvement) that may have confounded the associations.[147] Inconclusive study findings may be related to inconsistency in HM intake quantification (total volume vs percent intake vs other categorical feeding classification) and timing of quantification (e.g. entire hospitalization vs first 30 days of life) among studies, and variability among comparator feeding regimens (donor HM vs various preterm formulas).

Beyond the support provided by adequate nutrition (e.g. calories, macronutrients, and micronutrients), several HM components may be implicated in the link between maternal HM and improved neurodevelopmental outcomes.[148] Some of the essential brain developmental processes which occur in infancy and early childhood include structural changes in gray and white matter, connectivity, myelination, and synaptic pruning.[149] Components which may aid in brain myelination or the formation of lipid-containing myelin around the neural axons include LC PUFAs and phospholipids, among others.[150,151] The 2 primary LC PUFAs found in the human brain are docosahexaenoic (DHA; 22:6n-3) and arachidonic acid (20:4n-6).[152,153] Alpha-linolenic acid, an essential fatty acid that must be derived from the maternal diet, is the precursor for DHA, which plays a role in phospholipid structure.[153] Arachidonic acid is synthesized from linoleic acid, is found in larger concentrations than DHA in HM, and is thought to be unrelated to maternal dietary intake. [152,153] While LC PUFAs positively impact infant brain development, randomized controlled trials of infant formula supplementation with LC PUFAs have yielded variable results, which may be partially due to the differences in neurodevelopmental assessment measures used and the covariates included in analyses.[154–156]

Sphingomyelin is a type of lipid found in cell membranes and is the major phospholipid in HM.[157] In addition to regulating inflammation and other cellular processes, sphingomyelin plays an important role in myelin integrity and function and axonal maturation and may be implicated in infant brain development.[157,158] In an observational study of a subset of participants (healthy term infants when enrolled) in the ongoing Brown University Assessment of Myelination and Behavior Across Maturation (BAMBAM) cohort (n=88), exposure to higher levels of dietary sphingomyelin in the first 3 months of life was associated with higher rates of change in verbal development in the first 3 years of life via the Mullen Scales of Early Learning (r = 0.65, p<.001).[157] Higher dietary sphingomyelin was also associated with higher levels of brain myelin content at 12–24 months and differing rates of myelination in other areas of the brain. In this unique study, researchers also used an *in vitro* model to complement their clinical results and found that sphingomyelin treatment was related to increased proliferation, maturation, and differentiation of oligodendrocyte precursor cells and increased axon myelination. The results of this study aligned with a previous randomized controlled trial of a sample of very-low-birth-weight infants (n=24), which found that infants randomized to sphingomyelin-fortified milk had better neurodevelopment scores at 18 months (via Bayley Scales of Infant Development II, Fagan test scores, latency of visual evoked potentials, and sustained attention scores).[159]

Milk bioactives involved in supporting the infant immune system may indirectly benefit neurodevelopment through interactions of the gut-brain axis. In additional to their role in the infant immune system and gut microbiome, HMOs in HM have also been associated with infant neurodevelopment.[160] A recent study of Hispanic mother-infant dyads (n=50) found that early exposure to the most abundant HMO in HM 2'-fucosyllactose (2'FL) at 1 month of age was associated with better cognitive development at 24 months of age (β = 0.59; p .01) using the Bayley Scales of Infant Development III. [161] Additionally, exposure to 2'FL mediated the association between the frequency of maternal HM feedings at 1 month and improved cognitive development. These results strengthen those of similar studies, which found exposure to 2'FL was associated with improved early learning composite

scores, language scores, and other neurodevelopmental outcomes (e.g. motor skills, communication, etc.).[162,163] While the mechanisms by which HMOs may promote optimal neurodevelopment are still unclear and are informed mostly by preclinical models[164], one possible explanation is that HMOs interact with the gut microbiota to influence the gut-brain axis.[165] Finally, HMOs may promote neurodevelopment by upregulating expression of compounds involved in neural plasticity, thereby promoting infant cognition and memory.[164]

Discussion

This review of recent HM literature supports the continued provision of HM for all infants, with high importance for hospitalized and critically ill infants due to the many potential benefits of HM, including support for a vulnerable immune system and the complex interaction between infant gut and immune health. Future research will benefit from the assessment of HM as a biological system rather than examination of individual components.[17] Further, the use of standardized procedures in milk collection, storage, and processing, and analysis in HM research will allow for direct comparison between HM studies and assist in more clearly elucidating the associations between HM components and these factors.[166] Attention to donor HM processing and handling, including innovations and strategies to prevent or mitigate alterations of bioactive components of maternal HM is needed. While the current research does not appear to support donor HM as an equivalent to maternal HM relevant to neurodevelopmental benefits[138,146], evidence strongly supports the use of donor HM for the prevention of NEC.[167] Additional research from a systems standpoint will help elucidate whether supplementation can provide similar benefits to those conferred by maternal HM. For example, adding fresh and frozen maternal HM to inoculate donor HM with beneficial bacteria to overcome destruction of bioactives during the pasteurization process represents another area for continued exploration.[168] Also of note, synthetic HMOs have been recently added to term infant formulas in the US and Europe, but are not currently found in preterm formulas. Whether synthetic HMOs confer similar health benefits to those provided by maternal HM requires further investigation.[169]

Regarding maternal metabolic status, the relationship between maternal adiposity and bioactive concentrations should be further explored to understand mechanisms as they relate to infant outcomes. As validated body composition tools are readily available, examination of BMI as a proxy for adiposity should be replaced with more sophisticated methods of determining adiposity for assessment of these outcomes. Maternal stress, anxiety, and depression have been associated with increased inflammatory factors, such as CRP and TNA-α[170], which are also elevated in women with obesity. How discrimination, weight stigma, and other factors may affect the relationship between maternal metabolic status and overall maternal HM composition is an avenue for future exploration. Regardless of maternal metabolic or weight status, maternal HM feeding should continue to be the primary goal as breastfeeding likely has bidirectional health benefits for lactating people, including long term improvements in metabolic health.[171,172]

Studies examining HM bioactives are important and continuing to examine these non-nutritive components in the context of maternal, infant, and environmental factors is essential to better understanding their potential roles in infant health. Additional work is

needed to understand the mechanisms by which bioactive components may interact to confer immune protection and neurodevelopmental benefits to clinically vulnerable infants. For example, while a large body of research has focused on preterm infants, there is no evidence regarding the relationship between HM and neurodevelopment for infants with CHD, who are at risk for suboptimal neurodevelopment.[133] Key to all future examinations is clear identification of neurodevelopmental targets (e.g. cognitive vs. emotional) with longitudinal assessments spanning from infancy into childhood. Similarly, continued work on the interplay between infant gut and immune health is needed, with a focus on mechanisms by which HM components may confer protection against allergy and disease and on how these components may also affect the infant gut microbiome.

Finally, while the promotion of breastfeeding and provision of HM are important to infant health, we recognize that many barriers to sustained lactation exist, and that most people in the US do not meet their own breastfeeding goals[173] or sustain exclusive breastfeeding through 6 months as recommended.[24,174] Given the greater morbidity and mortality rates of birthing people of color and their infants in the United States [175,176], examination of medical racism and the social determinants of health[177], in addition to the biological and physiological processes governing lactation, are extremely important in understanding and eliminating breastfeeding disparities, especially for critically ill and hospitalized infants for whom maternal HM is most crucial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources:

Abbreviations

BMI	body mass index
eQTLs	expression quantitative trait locus
GWAS	genome-wide association studies
HM	human milk
HMOs	human milk oligosaccharides
NICU	neonatal intensive care unit

LC PUFA   long chain polyunsaturated fatty acids

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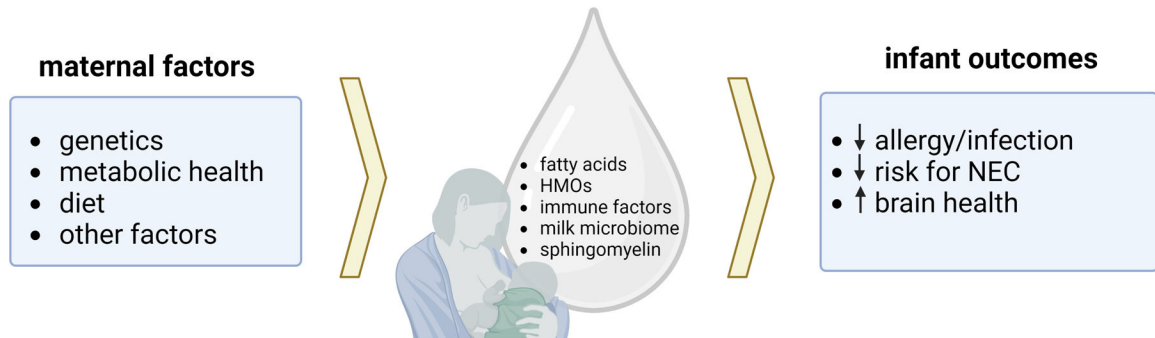
Figure 1.

Clinical populations (including hospitalized infants) may be at risk for health issues such as immune system dysregulation, increased risk of infection, necrotizing enterocolitis, and suboptimal neurodevelopment. In this review, we discuss maternal factors which may influence human milk composition (e.g. genetics, metabolic health, and diet) and review selected milk components and their potential impact on infant health.

Human milk in the hospital setting

- Human milk is the recommended source of nutrition for all infants
- Human milk is associated with improved clinical outcomes for hospitalized infants (e.g. time to full feeds, shorter length of stay, lower in-hospital mortality)
- Donor human milk can be used in the clinical setting, but processing and/or person-specific characteristics can affect its composition

Influences on human milk composition

- Non-nutritive components in human milk have been linked to improved infant health outcomes
- Maternal genetics, metabolic status, and diet influence human milk composition
- Specific components of interest include fatty acids, immune factors, human milk oligosaccharides, and the human milk microbiome.

Infant benefits of human milk provision

- Human milk is of particular benefit to infants who are hospitalized, critically ill, and/or have congenital illnesses
- Human milk provides protection against infection and promotes infant gut health
- Maternal human milk has been implicated in improved neurodevelopment for infants

Future Directions

- Using standardized research procedures for collection, storage, processing, and analysis of human milk is recommended
- Elucidating mechanisms by which milk bioactives confer benefits is needed
- Examining medical racism and the social determinants of health are essential to understanding and eliminating breastfeeding disparities.

Figure 2.
Key takeaways from this narrative review of human milk for clinical populations.