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*From complex tailored nutrition to bioactive impact on child cognition and behavior*

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## Human milk: From complex tailored nutrition to bioactive impact on child cognition and behavior

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### ABSTRACT

Human milk is a highly complex liquid food tailor-made to match an infant's needs. Beyond documented positive effects of breastfeeding on infant and maternal health, there is increasing evidence that milk constituents also impact child neurodevelopment. Non-nutrient milk bioactives would contribute to the (long-term) development of child cognition and behavior, a process termed 'Lactocrine Programming'. In this review we discuss the current state of the field on human milk composition and its links with child cognitive and behavioral development. To promote state-of-the-art methodologies and designs that facilitate data pooling and meta-analytic endeavors, we present detailed recommendations and best practices for future studies. Finally, we determine important scientific gaps that need to be filled to advance the field, and discuss innovative directions for future research. Unveiling the mechanisms underlying the links between human milk and child cognition and behavior will deepen our understanding of the broad functions of this complex liquid food, as well as provide necessary information for designing future interventions.

### KEYWORDS

Lactocrine programming;  
lactational programming;  
cognition;  
behavior;  
human milk composition;  
milk bioactives

### Human milk and child development

Human milk is a complex liquid food. There is increasing evidence that the constituents in human milk impact child cognition and behavior. Nonetheless, human milk remains one of the most under-studied biological system in life sciences. This manuscript is the fruit of a close collaboration between all the participants of a 4-day hybrid workshop on lactocrine programming held in The Netherlands (November 2020). This collaborative manuscript functions as a call and

a source of inspiration for the scientific community to perform research on this extremely relevant, but unfortunately often-ignored topic.

The goal of this narrative review is to summarize and discuss the current state of the field on human milk composition in the light of its association with child behavioral and cognitive development. The sections covered include (i) introduction to human milk and child development, (ii) the different milk constituents and their associations with child

cognition and behavior, and (iii) maternal and child factors affecting milk constituents, (iv) recommendations and best practices for researchers for future research studies section presents new studies that can adopt state-of-the-art methodologies and designs that will facilitate future meta-analytic endeavors to help fill knowledge gaps, and (v) finally, the most important scientific gaps that need to be filled in order to advance the field, along with innovative directions for future research, are presented in an open questions and innovative ideas section. Appendix A contains a glossary and Appendix B a list with abbreviations used in the text.

### **Human milk from a public health and clinical perspective**

Breastfeeding, and the various nutrients and bioactive factors in human milk, are known for their undeniable long-term health benefits for both infant and mother (Fields et al. 2016; Hinde 2013; Victora et al. 2016). For infants, human milk protects against numerous severe infections including enterocolitis, diarrhea, and pneumonia, and has been shown to significantly reduce the rates of infant morbidity and mortality (Ip et al., 2007; Victora et al. 2016). In the long-term, the benefits of human milk include a reduced risk of developing later life metabolic disease, such as childhood obesity (Oddy 2012; Victora et al. 2016) and diabetes (Arshad, Karim, and Ara Hasan 2014; Desoye and Hauguel-de Mouzon 2007; Victora et al. 2016). For mothers, breastfeeding improves birth spacing, protects against breast cancer and also seems to protect against ovarian cancer and type 2 diabetes (Victora et al. 2016; Chowdhury et al. 2015). In turn, these positive effects on both mothers and infants lead to relevant societal economic impacts (e.g., Quesada, Méndez, and Martín-Gil 2020; Rollins et al. 2016; Stuebe et al. 2017).

These unique features of breastfeeding and human milk have led the World Health Organization (WHO) to endorse exclusive breastfeeding for the first six months of an infant's life, followed by breastfeeding supplemented with complementary foods until the age of two years (World Health Organization 2003). Also in the most vulnerable infants, i.e., preterm, and low birth weight infants, human milk significantly reduces the chances of severe medical complications (Quigley, Embleton, and McGuire 2019; Furman et al., 2003; Villamor-Martínez et al. 2018; Manzoni et al. 2013; Nutrition et al. 2013), and appears to predict better health and neurodevelopment later in life (Singhal, Cole, and Lucas 2001; Schneider and Garcia-Rodenas 2017; Lechner and Vohr 2017). For example, a recent study in preterm infants revealed that exclusive human milk feeding in extremely low birth weight infants, while associated with increased extrauterine growth restriction, had a protective effect on neurodevelopmental outcomes at 2 years of age as assessed through the Bayley Scales of Infant Development (Rahman et al. 2020). Hence, especially for preterm and low birth weight infants, if a mother's own milk is not available, donated human milk is currently considered the next best choice (Committee on Nutrition, Section on

Breastfeeding, and Committee on Fetus and Newborn 2017; Nutrition et al. 2013).

Although the WHO has a global recommendation for exclusive breastfeeding, many countries have not been able to achieve this goal. In practice, breastfeeding is influenced by several maternal, environmental, and societal characteristics that can hinder or facilitate breastfeeding (Standish and Parker 2021). For example, in high-income countries, mothers with higher income and education are more likely to breastfeed, while in low-income countries, those with lower socioeconomic status are more likely to breastfeed (Victora et al. 2016). Other factors such as negative social perceptions of breastfeeding in public, lack of trained health care support, and early return to work pose challenges for breastfeeding initiation and duration (Mulready-Ward and Hackett 2014; Ahluwalia, Morrow, and Hsia 2005; Thulier and Mercer 2009). These factors are often complex and interact with one another, leading mothers to feed their infants in a variety of ways in the first six months, including direct milk at the breast, pumped milk through a bottle, donor human milk, infant formula, and solids, as well as varying combinations of these feeding types. This review includes data on human milk feeding in any form, acknowledging that there are varying ways this is supplied in practice. Note that the effects of human milk on infant neurological development may be different depending on the mode of feeding (direct or pumped) and dose (amount of human milk vs infant formulas and other foods), but that these distinctions are beyond the scope of the current review.

### **Human milk and child neurodevelopment**

Next to documented positive effects on a range of physical health outcomes in both the infant and the mother, breastfeeding parameters (e.g., initiation and duration) have also been related to improved child neurodevelopment, cognition and behavior (Hou et al. 2021; Ikeda et al. 2014; Lucas 2005; Victora et al. 2016). The most active period of child brain and behavioral development occurs in the first 1000 days of life, the period beginning at conception and ending at the start of the third postnatal year (Moore 2016). For example, while at birth the brain of a child already has nearly all the neurons it will ever have, it still doubles in size during the first year of life. Synapses are overproduced and groups of neurons form pathways, which are refined through the elimination of cells and connections. This refining of neural pathways heavily depends on the child's experience and input from the environment. Cells and connections that are activated are retained and strengthened, while those not used are eliminated. This refinement is thought to be one of the primary mechanisms of brain plasticity, allowing the brain to organize itself to adapt to the environment (Prado and Dewey 2014). Nutrition would provide the fuel that drives much of this early brain growth, development, and refinement (Prado and Dewey 2014).

Meta-analyses have associated breastfeeding initiation and duration with higher performance in intelligence tests in children and adolescents. Pooled estimates of 3–5 intelligence quotient (IQ) points favoring children who have been breastfed are reported in reviews of observational studies

(Anderson, Johnstone, and Remley 1999; Drane and Logemann 2000; Jain et al. 2002; Victora et al. 2016). A large cluster-randomized trial in Belarus also provided evidence that breastfeeding has positive effects on child cognitive development (Kramer et al. 2008). Clinics were randomly assigned to a breastfeeding promotion intervention or standard healthcare. Mothers in the breastfeeding promotion group had higher rates of any and exclusive breastfeeding. At subsequent follow-up (N=13,889; child's age of 6.5 years), children in the breastfeeding promotion group had higher teacher ratings of reading and writing ability, and higher IQ scores. Promotion of breastfeeding thus not only prevents a range of physical health outcomes in infants and their mothers, but also seems to support children's cognitive and behavioral development. To what extent associations persist into later life is less clear, but some recent studies also found cognitive benefits in later childhood (e.g., Kim and Choi 2020; Lopez et al. 2021).

It is important to note that the mixture of feeding methods (i.e., direct milk at the breast, pumped milk through a bottle, donor human milk, infant formula, solids, and combinations of these methods) has complicated the comparison of outcomes between breastfeeding and non-breastfeeding infants in this research area. Also, although studies controlled for multiple confounding variables, the associations found may still be confounded by unknown factors, and studies with experimental designs are scarce. Lastly, not all available studies have found positive associations between breastfeeding parameters and child cognitive performance (e.g., Jacobson et al. 1999; Wigg et al. 1998). As such, the available scientific evidence does not unequivocally demonstrate that human milk leads to better cognitive development in the offspring.

### Human milk from an evolutionary perspective

Although not typically integrated within the public health and clinical framework, the evolutionary perspective is crucial for understanding the adaptive reaction norms that underlie how variance in milk synthesis in turn shapes and organizes infant developmental trajectories (Hinde et al. 2015; Fewtrell et al. 2020). The evolutionary success of human milk is largely dependent on its ability to alter its composition and volume to match the needs of a growing infant. Life History Theory, one of the existent evolutionary perspectives, organizes our understanding of how natural selection has (likely) shaped tradeoff allocations for maintenance, development, and reproduction across an organism's life-course (Hill 1993; Hill and Kaplan 1999). For example, time and resources allocated toward growth and development early in life delay reproductive debut, but the establishment of key somatic resources can improve reproductive performance (Pittet, Johnson, and Hinde 2017).

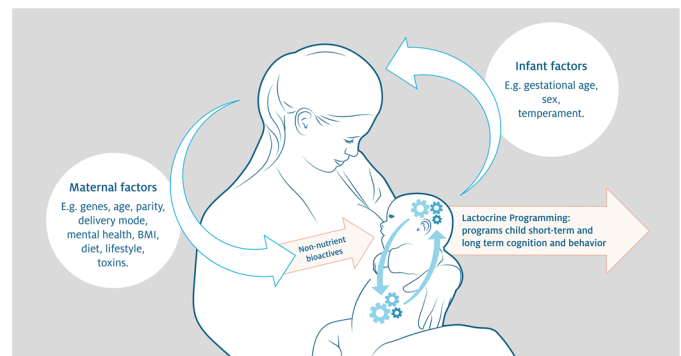
### Milk Bioactives and lactocrine programming

Environmental conditions will determine the resources available for a mother to maintain lactation and her infant. Environmental conditions may also influence the

composition of a mother's milk. As part of the lactation strategy, mothers may also transfer milk non-nutrient bioactives, also called milk-borne bioactive factors (MbFs), to the infant. These MbFs contribute to organizing infant microbial communities, behavior, cognition, and neurobiology, and as such play a role in determining the child's trajectory of development, with long-term consequences in the adult (Blum and Baumrucker 2008; Brunner et al. 2015; Donovan and Odle 1994; Hamilton et al. 2011; Nicholas et al. 2019). This process was coined 'Lactocrine Programming' (Bartol, Wiley, and Bagnell 2008; Hinde 2013) and is depicted in Figure 1. The effects of Lactocrine Programming have been documented in various mammalian species (Bartol et al. 2017; Hinde et al. 2015; H. Liu, Radlowski, et al. 2014; Neville et al. 2012; Nusser and Frawley 1997; Sharp et al. 2017). Growing evidence has suggested that milk bioactive components, such as opiates and hormones, influence feeding regulation and contribute to the organization of metabolism, growth, and energy balance (Savino and Liguori 2008; Neville, McFadden, and Forsyth 2002; Hahn-Holbrook et al. 2019). For example,  $\beta$ -casomorphin, the natural opiate found in milk (Jarmolowska et al., 2007), is speculated to influence feeding behavior by acting as a sedative, possibly affecting infant appetite.

The presence and abundance of milk bioactives could be within the suite of maternal lactation tactics to shift infant phenotypes toward maternal optima as, importantly, such physiological signals embedded within milk would be difficult for offspring to reject (Allen-Blevins, Sela, and Hinde 2015). See *Interplay of maternal-child factors* section for an evolutionary perspective-oriented discussion on how the interplay between maternal and child factors further impacts lactation.

In sum, where public health and clinical perspectives provide accumulating evidence that breastfeeding parameters



**Figure 1.** Lactocrine Programming is the process by which non-nutrient bioactives affect the developmental program of cells, tissues and organs in nursing offspring. The term 'programming' refers to the fact that while some effects on the offspring are short-term, others have lasting effects on form, function and/or health and well-being in adulthood. Mechanisms would include affecting the development of the infant's brain as well as gastro-intestinal system and gut microbiota (indicated by the clockworks in the figure). While several maternal factors may influence this process, also the infant, e.g., through crying behavior, can affect the mother and lactation. Note that the maternal and infant factors presented in the figure may not be all factors involved in Lactocrine Programming.

are linked to later child behavior and cognition, the evolutionary perspective offers an explanation for ‘why’ such mechanistic processes would operate. The combination of both perspectives leads to the hypothesis that human milk, through bioactive constituents, can influence and program child development (Hinde 2013). In the following section, we will discuss the current state of the field on milk constituents and their links with child cognitive and behavioral development.

### Human milk constituents and their associations with child cognition and behavior

The following sub-sections discuss bioactive milk components, including hormones, immune factors, maternal cells, nutrients, microbes and pollutants that are relevant for offspring cognition and behavior. Background basics on human milk can be found in [Box 1](#), details about specific milk components are summarized in [Table 1](#), and [Figure 2](#) presents a summary of milk constituents and their known associations with child cognition and behavior. At the end of this section interactions between milk constituents and links between milk energy output and child development are presented.

#### Hormones

Glucocorticoids (GCs) are among the best-characterized hormones in milk with respect to offspring development. Animal and human studies have described apparent associations of milk GCs with diverse offspring outcomes, including temperament, social behavior, and cognition (reviewed in [Hollanders et al. 2017](#)). In an experimental study, milk cortisol altered rodent offspring neurobiology and behavior ([Catalani et al. 2011](#)). In associative studies in nonhuman primates, milk cortisol concentrations were differentially related to temperament based on offspring sex: male offspring’s nervous and confident temperament ratings were predicted by changes in milk cortisol concentrations across lactation, whereas female offspring’s nervous and confident temperament ratings were predicted by cortisol concentrations in early and peak lactation, respectively ([Hinde et al. 2015](#)). Additionally, in rhesus monkeys, higher neonatal milk cortisol concentrations predicted less impulsivity on a cognitive task at 6 months of age but had no associations to effect on global social behaviors (i.e., averages of social play, grooming, etc.) ([Dettmer et al. 2018](#)). However, female infant macaques ingesting mother’s milk with higher cortisol concentrations exhibited higher frequencies of play behaviors at 4–8 months of age ([Dettmer et al. 2018](#)).

Milk GCs have the potential to impact many facets of offspring development; however, results thus appear to be sex-specific and are mixed. For instance, in human studies, milk cortisol concentrations have been shown to be positively associated with infant negative emotions, and specifically with fear reactivity, especially in girls ([Gray et al. 2013](#); [Nolvi et al. 2018](#)). However, separate studies did not observe an association with milk GCs and infant crying

([Hechler et al. 2018](#)) or with sleep ([Toorop et al. 2020](#)). Milk GCs are likely absorbed by the infant gut into systemic circulation ([Hinde 2013](#)), as shown in experimental studies in rodents ([Angelucci et al. 1985](#); [Yeh, Yeh, and Holt 1989](#)) and observational studies in human infants ([Benjamin Neelon et al. 2015](#); [Cao et al. 2009](#)). As GCs could impact infant brain development, this mechanism would argue for a link between milk GCs and infant behavior and cognitive development. Similarly, corticosterone levels in human milk might impact the programming of the neuroendocrine stress axis and thereby the individual’s stress sensitivity, which is a key determinant for the risk of developing psychopathologies later in life ([Lucassen et al. 2015](#)).

Other hormones present in milk may also affect offspring development. For example, one study posited that melatonin concentrations are associated with better infant sleep behavior and reduced colic ([Engler et al. 2012](#)). Additionally, early human milk metabolic hormone concentrations have been shown to be related to later infant growth and adiposity (reviewed in [Mazzocchi et al. 2019](#)). For example, leptin has been negatively associated with infant fat mass ([Sims et al. 2020](#)). However, results on other metabolic hormones including ghrelin, adiponectin, and insulin are mixed, as they have been associated with both higher and lower infant weight gain and fat mass gain (reviewed in [Mazzocchi et al. 2019](#)). Likewise, evidence related to early insulin-growth factor 1 and later adiposity is inconclusive ([Galante et al. 2020](#); [Kon et al. 2014](#)), although a recent study suggested that higher bioactive concentrations of insulin-growth factor 1 are related to lower body mass index (BMI) beyond the first year of life ([Galante et al. 2020](#)). More research, particularly experimental studies, is needed to discern the effects of these types of hormones in milk on offspring development.

Despite several studies on milk hormones, few are experimental in nature, thus limiting interpretations of causality, and few have concentrated on the direct or indirect influence of these hormones on other aspects of infant behavior, although some research points to impacts of these hormones on appetite regulation and energy homeostasis. For example, in rodent models, availability of leptin is crucial for the development of hypothalamic circuits that control eating behavior and energy homeostasis in early postnatal life ([Bouret, Draper, and Simerly 2004](#); [Yam et al. 2017](#)), and impact later risk for obesity ([Skowronski et al. 2020](#)). Although it is compelling to suggest that early postnatal leptin levels could have impact on later appetite regulation and eating behavior via the development of hypothalamic circuits ([Oddy 2012](#)), one must acknowledge that the patterns of brain development ([Cardoso-Moreira et al. 2019](#)) and systemic and milk leptin levels are different in humans as compared to nonhuman animal models ([Schubring et al. 1998](#); [Sims et al. 2020](#)).

#### Immune factors

Human milk is a rich source of immune factors that help educate the infant’s innate immune system during a critically important period of development. Emerging research

**Table 1.** Basic information on milk constituents.

Milk constituents	Subtypes	Description and basic information
<b>Hormones</b>		Human milk contains peptide and non-peptide hormones including gonadotropins (e.g., progesterone, estrogens, gonadotropin-releasing hormone), metabolic hormones (e.g., insulin, leptin, resistin, adiponectin, ghrelin, insulin-like growth factor), other hormones that support infant growth (erythropoietin, thyroid hormones), and hormones related to neuroendocrine systems or neuropeptides (glucocorticoids, melatonin, oxytocin, brain-derived neurotrophic factor, neurotrophin).
	Glucocorticoids (GCs); Cortisol Cortisone	Steroid hormones produced in the adrenal glands as the output of hypothalamic-pituitary-adrenal (HPA) axis functioning. GCs cortisol and cortisone have a multitude of functions: regulating the stress response, energy regulation and lipolysis, and anti-inflammatory and immune-suppressive effects (Fields et al. 2017; Galante et al. 2018). The primary source of breastmilk GCs is likely via the systemic circulation. Human milk GC's follow the diurnal rhythm of maternal HPA axis activity, peaking in the morning before declining throughout the day to reach the lowest point in the evening (Hollanders et al. 2019; Pundir et al. 2017; van der Voorn et al. 2016). Across non-human species, there is substantial individual variability in milk GC concentrations across lactation (Diaz et al. 2013; Hinde et al. 2015; Schwalm and Tucker 1978). In humans, milk cortisol seems to increase during the first three months postpartum (Hechler et al. 2018).
	Melatonin	Produced primarily by the pineal gland that regulates the sleep-wake cycle. Melatonin concentrations are higher in milk during night time (Engler et al. 2012; Illnerová et al. 1993).
	Leptin	Produced by adipose and mucosal cells in the small intestines; regulates energy homeostasis and inhibits hunger. Declines across lactation in sows (Estienne et al. 2000), and across first lactation days in humans (Bielicki, Huch, and von Mandach 2004).
	Ghrelin	Produced by enteroendocrine cells of the gastrointestinal tract; involved in stimulating hunger and appetite. Increases during lactation (Ilcol and Hizli 2007).
	Adiponectin	Produced primarily in adipose tissue; involved in regulating glucose levels as well as fatty acid breakdown. Declines across lactation in cows (Singh et al. 2014).
	Insulin	Produced by the pancreatic islet; regulates the metabolism by promoting the absorption of glucose. Declines across lactation in cows (Malven et al. 1987).
<b>Immune factors</b>		Many different immune factors are present in breast milk, including immunoglobulins, such as IgA, IgM and IgG, glycoproteins such as lactoferrin, as well as growth factors, cytokines, and chemokines (Ballard and Morrow 2013; Hurley and Theil 2011). The primary functions of immunoglobulins are to neutralize cell-damaging agents and limit the effects of inflammation on tissues (Jackson and Nazar 2006).
	Secretory IgA (sIgA)	The dominant immunoglobulin in milk, comprising 88–90% of the total amount of immunoglobulins (Hurley and Theil 2011). sIgA concentration is highest in colostrum, and lower in mature milk, and vary between mothers (Munblit et al. 2016; Ruiz et al. 2017). sIgA concentrations remain stable within each mother from day six postpartum to at least day 90 of lactation (Lønnerdal et al. 2017). Evidence is still inconclusive regarding circadian variation in milk sIgA (Italianer et al. 2020).
	Lactoferrin (Lf)	Most abundant protein in human milk, accounting for approximately 25% of the total protein content (Montagne et al. 2001). Lactoferrin (Lf) is a sialic acid-rich glycoprotein that carries human milk iron, and is of established importance for human health (Manzoni et al. 2018). Lf is an immune system modulator that can activate different cell functions depending on the status of the host. For example, Lf can promote the release of pro-inflammatory molecules, such as tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 8 (IL-8), to upregulate the immune system in the case of infection, and can bind to pro-inflammatory microbial products, such as lipopolysaccharides, to downregulate the recruitment of innate immune cells once infection is overcome (Legrand 2012). Lf is most concentrated in colostrum, and declines as lactation progresses (Lønnerdal et al. 2017). More research is needed to determine if milk Lf follows a circadian rhythm (Italianer et al. 2020).
<b>Maternal cells</b>	Immune cells	Leukocytes contribute to protect the infant and the mammary gland against infections by fighting pathogens through different direct and indirect mechanisms. In addition, they provide active immunity and promote the development of immunocompetence in the infant. There is a wide variety of leukocyte subsets in human milk and the major ones are myeloid precursors, neutrophils, immature granulocytes, and non-cytotoxic T cells. Their concentrations, numbers, and relative proportion depend on several factors, including stage of lactation (Trend et al. 2015). The concentrations of CD45 <sup>+</sup> leukocyte, eosinophils, myeloid, and B cell precursors, and CD16 monocytes tend to decrease across lactation, while those of neutrophils and immature granulocytes significantly increase across lactation. Maternal and infant health also seem to exert an influence on leukocytes since their concentration increases when either the mother or the infant have an infection (Hassiotou et al. 2013; Riskin et al. 2012).
	Non-immune cells	In addition to immune cells, milk also contains a myriad of cell populations including milk secretory cells (lactocytes), ducts- and alveoli-derived myoepithelial cells, and a whole hierarchy of progenitor and stem cells, from early-stage embryonic stem cells to fully differentiated mammary epithelial cells (Cregan et al. 2007; Hassiotou et al. 2012; Witkowska-Zimny and Kaminska-El-Hassan 2017). The mammary gland stem cells found in milk are involved in the formation of new mammary tissue during lactogenesis and can differentiate into alveolar, ductal, and myoepithelial cells (Hassiotou et al. 2012; Kordon and Smith 1998). Luminal and myoepithelial cells and their precursors account for most of the non-immune cells under healthy conditions. Conflicting results have been published regarding the presence of mesenchymal stem cells expressing the typical CD90, CD105 and CD73 markers in human milk (Patki et al. 2010; Kaingade et al. 2016; Kakulas, Geddes, and Hartmann 2016). In addition, human milk contains other types of stem cells that express embryonic markers, including cytokeratin, NANOG, nestin, OCT4, SOX2, SSEA4 and TRA-1 (Cregan et al. 2007; Fan et al. 2010; Hassiotou et al. 2012).
<b>Nutrients</b>		Nutrients in milk are the substance used by the offspring to survive and grow, and in addition to protein, can be divided in fats (triglycerides, LC-PUFA, sphingolipids), micronutrients (vitamins, minerals), and sugars (lactose, oligosaccharides).
<b>Fats</b>		Human milk provides about 45–55% of the total energy as fat; hence, dietary lipids are the main source of energy for infants (Ballard and Morrow 2013; Koletzko et al. 2001). In colostrum, transition, and mature milk, 98–99% of the fats is in the form of triglycerides, with the rest coming from the milk fat globule membrane as cholesterol, phospholipids, gangliosides, and sphingolipids (Demmelmaier and Koletzko 2018). The concentration of fats in milk changes significantly during the 24-hour period, increasing during the afternoon and evening, and decreasing during the night (Kent et al. 2006).

(Continued)

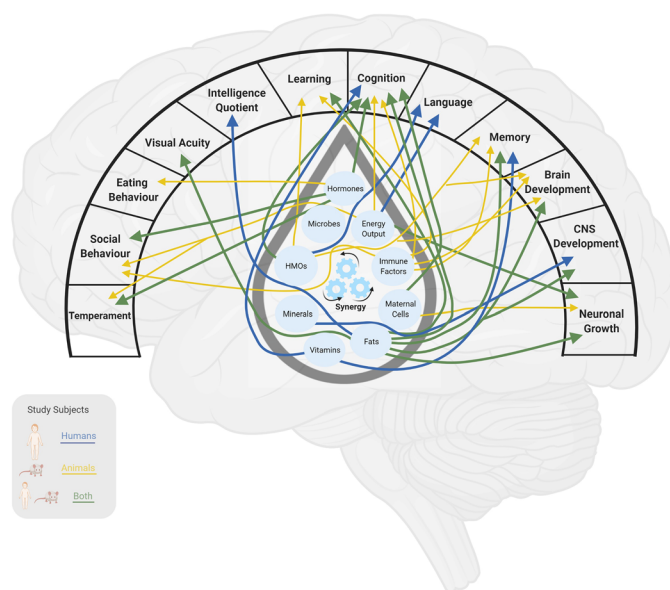
Table 1. (Continued)

Milk constituents	Subtypes	Description and basic information
	Triglycerides	Glycerol molecule with three fatty acids attached. Over 45 different fatty acids are bound in various combinations in the triglycerides in human milk. Saturated fatty acids comprise about 38%±6% of the total fatty acids with palmitic acid (16:0) comprising 20%±4% (Bourlieu and Michalski 2015). Palmitic acid is found uniquely in the middle position of the triglyceride and this position facilitates a more rapid digestibility of milk fat, preventing the formation of calcium salts which would negatively influence availability of calcium to the development of bone. Although human milk contains very small amounts of short-chain fatty acids, in Western countries there is about 12±4% of medium-chain saturated fatty acids (Bourlieu and Michalski 2015). These fatty acids are produced by the mammary gland and are rapidly hydrolyzed by gastrointestinal lipases without the need for bile salts; their products are then easily absorbed and taken directly to the liver via the portal vein.
	Long-chain polyunsaturated fatty acids (LC-PUFA)	In human milk, there are roughly 10 different long-chain polyunsaturated fatty acids (LC-PUFA), representing both the omega-3 and omega-6 series. They include the two most studied, arachidonic acid (Ara) and docosahexaenoic acid (DHA). These dietary essential LC-PUFA are required for growth, bone, and brain development. LC-PUFA are involved in the regulation of cell functions, in inter- and intracellular communication, and in the epigenetic modulation of the genome (Demmelmair and Koletzko 2018).
	Sphingolipids	Sphingolipids are a large family of polar lipids made of molecules differing in fatty acid and carbohydrates moiety and sialic acid molecule numbers. They contain a sphingosine backbone attached to varying fatty acids and a polar head. Sphingolipids are present in human milk as the main constituents of milk fat globule, globule membrane, and exosomes. Concentrations and proportions of sphingolipids vary depending on the lactation period (with ganglioside GM3 increasing and GD3 decreasing across lactation), maternal diet, geographic region, and method of milk expression (Giuffrida et al. 2016; Lee et al. 2018). Sphingolipids are classified as sphingomyelins (true phospholipids; most abundant polar lipid in milk) and glycosphingolipids (Engelking 2015). Glycosphingolipids are classified based on molecule composition and path of formation. Ceramides are the simplest sphingolipids, composed of sphingosine and a fatty acid. Cerebrosides (gluco- and galacto-cerebrosides) have a single sugar residue attached to a ceramide. Gangliosides and globosides are formed from glucocerebrosides by attaching consecutive monosaccharides and sialic acid, while sulfatides from galactocerebrosides with sulfate ester added to monosaccharide (Hoffmann et al. 2020). Glycosphingolipids are present in milk in low amounts, with cerebrosides being the most abundant, followed by ceramides, globoside, gangliosides, and sulfatides (Zheng et al. 2019). Human milk also includes enzymes -acidic sphingomyelinase and BSSL- that can initialize hydrolyzation of sphingomyelins to ceramides, then to sphingosine and free fatty acids (Nyberg et al. 1998).
Micronutrients	Vitamins	A vitamin is an organic molecule that is an essential micronutrient which an organism needs in small quantities for the proper functioning of its metabolism. Breast milk contains a wide range of vitamins. Small but significant variations have been observed in the concentrations of a wide range of vitamins according to stage of feed and time of day (Hampel et al. 2017). In a study from Bangladesh, circadian variation in concentration was observed for all vitamins, except for vitamins A and E when adjusted for milk fat (Hampel et al. 2017). In the same study, three samples collected across the same feed showed significant variations for thiamin, niacin and vitamins A and E but not for vitamins B6 or B12 (Hampel et al. 2017).
	Minerals and trace elements	A chemical element with a well-defined chemical composition and a specific crystal structure. Mineral concentrations seem to decline across lactation (Krachler et al. 1998; Li et al. 2016; Silvestre et al. 2001). Accumulating evidence also shows an impact of geographical location on the mineral profile in human milk (Li et al. 2016; Wei et al. 2020). For example, calcium concentrations were lower in countries as Nigeria and Gambia and higher in Japan and Sweden (Sánchez et al. 2020).
Sugars	Lactose	Lactose, a disaccharide sugar, is the main carbohydrate in milk, constituting around 2–8% of milk. Lactose is digested by the enzyme lactase and converted into glucose and galactose that are transported into the bloodstream through the intestinal epithelium.
	Human milk oligosaccharides (HMOs)	After lactose and lipids, human milk oligosaccharides (HMOs) are the largest solid component of human milk. All HMOs are composed of glucose, galactose, N-acetylglucosamine, fucose, and sialic acid, with lactose at their reducing end. More than 150 different HMOs have been identified so far. HMO composition varies between women, is remarkably constant throughout the day and over a week within the same woman, but changes over the longer course of lactation. Which maternal fixed and modifiable factors contribute to this interpersonal variation in HMO composition remains poorly understood. The presence of specific fucosylated HMOs is determined by the Secretor gene that codes for the enzyme $\alpha$ 1-2-fucosyltransferase (FUT2), and the Lewis gene that codes for an $\alpha$ -1,3/1,4-fucosyltransferase (FUT3).
<b>Microbes</b>		Overall, more than 200 bacterial species, belonging to approximately 50 different genera, have been isolated from human milk (Fernández et al. 2020) and culturomic approaches may increase these numbers rapidly (Schwab et al. 2019). The cultivable bacteria of human milk are usually dominated by <i>Staphylococcus</i> , <i>Streptococcus</i> , and related Gram-positive genera, although lactic acid bacteria and bifidobacteria can also be isolated.

is showing a link between immune factors and neurodevelopment (Mudd et al. 2016; Taki et al. 2020). It is hypothesized that milk immunoglobulins may be linked to neurodevelopment through the gut-immune-brain axis (Azhari, Azizan, and Esposito 2019). Milk IgA contributes to the innate immunity of the infant gut and modulates how microbes interact with host cells (Ramanan et al. 2020). Cross-fostering studies in mice have shown that milk secretory IgA influences the composition and activity of

commensal gut bacteria (Rogier et al. 2014), and emerging research links infant gut microbes to cognitive development and behavioral disorders such as autism spectrum disorder (Carlson et al. 2018; Laue et al. 2020). However, the underlying mechanisms and the specific bacterial taxa involved remain to be determined (Nitschke, Deonandan, and Konkle 2020).

Lactoferrin (Lf), also considered a component of the immune system, is one of the most abundant proteins in



**Figure 2.** Summary of milk constituents and their known associations with child cognition and behavior. The color of the arrows represents the nature of the scientific evidence (i.e., animal, human or both). Microbes have no arrows because there is not yet evidence linking microbes to markers of neurodevelopment. CNS, central nervous system; HMOs, human milk oligosaccharides. Created with BioRender.com.

human milk. Supplementation of Lf was shown to promote some measures of neurodevelopment and cognition in piglets and rats compared to a standard formula with low Lf (Chen et al. 2015; Mudd et al. 2016; Shumake et al. 2014). Rats tended to show less risk-taking behavior and faster escape responses compared to non-supplemented controls (Shumake et al. 2014); however, there was no effect on spatial memory. Of interest, sex differences were observed, with stronger effects for males compared to females (Shumake et al. 2014). Piglets supplemented with bovine Lf showed enhanced cognitive functioning and learning as assessed by the eight-arm radial maze test (Chen et al. 2015). Further, a cocktail of prebiotics, lactoferrin and milk fat globule membrane administered to piglets resulted in decreased gray brain matter (indicating earlier synapse development and pruning), but no improvement in the spatial T-maze behavioral assessment, compared to controls (Mudd et al. 2016). A mechanistic study to explore the function of Lf showed that Lf appears to upregulate the brain-derived neurotrophic factor signaling pathway which is important in memory development, synaptic plasticity, and learning (Chen et al. 2015). The authors suggested that the sialic acid moieties of Lf are cleaved from the protein and absorbed to be used for hippocampal and prefrontal cortex development (Chen et al. 2015). These same sialic acid moieties and other nitrogen-containing glycans could also promote growth of probiotic gut bacteria and be metabolized to compounds related to neurodevelopment through the gut-brain axis (Cerdó et al. 2016; Vega-Bautista et al. 2019).

Recent literature has linked other milk immune factors, including specific cytokines and chemokines, to decreased social dominance behavior and improved hippocampal development and memory in rodents (B. Liu, Radlowski, et al.

2014; Taki et al. 2020). However, how this translates to human biology remains to be determined. More clinical and experimental research is needed to elucidate these complex pathways linking human milk immunoglobulins, lactoferrin, and other milk immune factors to cognitive development and behavior in offspring through the gut-immune-brain pathway.

## Maternal cells

### Immune cells

Immunologically active cells, including neutrophils, lymphocytes, macrophages, and epithelial cells, are normal constituents of human colostrum and milk. Milk leukocytes can translocate from the gastrointestinal tract to the blood and distant sites, including the lymph nodes, spleen, liver, and mucosa-associated lymphoid tissues (Cabinian et al. 2016). In this way, lactocrine-mediated maternal microchimerism may also affect postnatal developmental trajectories (Bartol et al. 2017).

Maternal immune cells have been found to play relevant roles for infant behavior and cognitive development (Bilbo and Schwarz 2012). Human milk contains a relatively high concentration of macrophages and a plethora of immune factors (cytokines, chemokines, and their receptors) with the potential to interact with microglia (the primary phagocytic cells of the central nervous system) and other brain immunocompetent cells, including astrocytes (Bilbo and Schwarz 2009; Salvador, de Lima, and Kipnis 2021). There are direct physical interactions between immune cells (dendritic cells) and the nervous system (vagus nerve) during lactation and, in fact, it has been suggested that dendritic cells may act as modulators of neuroinflammation in mood disorders (Leite Dantas et al. 2021).

Although there appears to be crosstalk between immune cells and factors present in human milk and in the central nervous system of the infant, the mechanisms and implications for brain development remain essentially unknown. In contrast with adulthood, microglia are activated in early life and are sensitive to immune signals (Bilbo 2010). These cells have been considered as potential markers for long-term changes within the brain and may have an early role in later life cognitive decline (Hoeijmakers et al. 2016, 2017). Microglia appear to play direct roles in cognition (Tremblay et al. 2011), as these cells harbor receptors for several neurotransmitters and neuromodulators (Pocock and Kettenmann 2007), many of which are present in human milk. Alterations in glial priming or cytokine production during this period may have lifelong consequences on behavior and cognitive functions (Williamson et al. 2011). The functionality of the blood-brain barrier (formed by endothelial cells, astrocytes, and microglia) is pivotal in the interactions between the immune components of human milk and the central nervous system and, as a consequence, in the pathophysiology of many neuropsychiatric disorders that may have a developmental origin (Yarlagadda, Alfson, and Clayton 2009). It must be reminded that permeability of the blood-brain barrier is



higher during early life (Saunders, Knott, and Dziegielewska 2000). Further studies are required to elucidate mechanisms underlying these complex interactions, as well as their clinical significance.

### **Non-immune cells**

Studies carried out during the last decade have shown that human milk cells are more heterogeneous than previously thought. For example, human milk contains mammary gland stem cells and other types of stem cells that can differentiate in vitro into a variety of cell types, including neurons (Hassiotou et al. 2012; Hosseini et al. 2014). The properties of human milk stem cells make them suitable candidates for microchimerism in the infant tissue (Ninkina et al. 2019). Indeed, some studies suggest that human milk stem cells may differentiate and become integrated into different infant tissues (Twigger et al. 2013; Hosseini et al. 2014), and it has been found that human milk stem cells reach the brain of mouse pups, settling there and differentiating into both neuronal and glial cell types (Aydın et al. 2018). Thus, these cells could have an association with child behavior and cognitive development, although this is currently only a hypothesis (Molès et al. 2017). The implications of breastfeeding-induced microchimerism remain poorly understood but this phenomenon might be involved in proliferation, development, or epigenetic regulation of tissues in the infant (Molès et al. 2018). Future studies are required to explore their properties and benefits for mothers and infants as well as their potential roles in therapy and regenerative medicine.

### **Nutrients**

#### **Fats**

Human milk fats are the major energy source for infant growth. Human milk contains a considerable amount of long-chain polyunsaturated fatty acids (LC-PUFA), docosahexanoic acid (DHA) and arachidonic acid (Ara) and it has been suggested that this is one of the key advantages of breastfeeding over formula feeding with respect to brain development (Basak, Vilasagaram, and Duttaroy 2020; Steiner 2019). However, this has not yet been proven in humans and the data is somewhat conflicted, as two recent meta-analyses could not draw a conclusion regarding the importance of these nutrients for child cognitive development (Verfuerden et al. 2020; Lehner et al. 2021). This may not be surprising, as the studies were done in formula-fed infants and many of the important controlling/influencing variables were not, or could not, be collected. In a study by Colombo et al. (2019), higher maternal blood DHA concentrations in pregnancy were related to higher IQs but the effect was confounded by social economic status, a factor that is associated with the choice and ability to breastfeed. Recent advances in high-resolution mass spectrometry methods have enabled a more detailed lipidomic profiling of human milk. Using this method, marked differences in the lipidomic profiles between exclusively breastfed and formulafed infants have been reported (Prentice et al. 2015). These methods have

identified other lipid components that may contribute to the cognitive development of the infant. Perhaps the most studied is the human milk fat globule membrane, which in addition to containing important proteins, also contains several bioactive lipids that can potentially change brain structure and function (Brink and Lönnerdal 2020). The polar lipids (phospholipids) are major structural and functional components of the brain and are involved in brain function (Zheng et al. 2019). An exploratory observational study in children found preliminary evidence that sphingomyelin, one of the phospholipids, was associated with brain development and better verbal development (Schneider et al. 2019). Human milk fat has a distinctive distribution pattern of palmitic acid (C16:0) with approximately 85% distributed at the sn-1 and sn-2 position of triacylglycerol which in addition to improving absorption, may also influence brain development (Viriato et al. 2020). Finally, there are several sialylated oligosaccharides and glycoconjugates that are also present in human milk which have been demonstrated in animal models to influence brain structure and development (Lis-Kuberka and Orczyk-Pawilowicz 2019).

**Sphingolipids.** Rapid neurodevelopment and growth of the brain during the first two years of life coincide with a peak rate in the accretion of brain complex polar lipids, including sphingolipids (Schnaar, Gerardy-Schahn, and Hildebrandt 2014). Sphingolipids are classified as sphingomyelins and glycosphingolipids. Sphingomyelins are particularly rich in the myelin sheath of the central nervous system and play an essential role in axonal maturation and myelin integrity (Bienias et al. 2016; Narayan and Thomas 2011). This suggests a critical role for these lipids in brain development and function, including neuronal growth, migration, maturation, and myelination (Olsen and Færgeman 2017; Zheng et al. 2019; B. Wang, Xu, et al. 2021).

The majority of brain sphingolipids originate from endogenous synthesis; however, dietary supplementation enhances sphingolipid composition (Ortega-Anaya and Jiménez-Flores 2019). Studies conducted in young animals and human infants demonstrated a critical role of sphingolipids and sphingomyelins for cognitive development. Young rats and piglets supplemented with complex milk lipids, rich in gangliosides, sphingomyelins, and phospholipids, displayed improved learning and memory (H. Liu, Radlowski, et al. 2014; Vickers et al. 2009). Complex milk lipids and milk fat globule membranes (MFGM) supplementation in human infants showed a similar effect. In RCTs, supplemented or breastfed infants achieved higher scores for hand and eye coordination, performance, and general IQ at 6 months (Gurnida et al. 2012), enhanced cognitive scores at 12 months of age (Timby et al. 2014), accelerated neurodevelopmental profile at 12 months and improved language development at 18 months (Li et al. 2019). The administration of sphingomyelin-fortified formula to very low birth weight infants improved latency of visual evoked potentials, sustained attention, intelligence, and behavior rating (Tanaka

et al. 2013). These few studies demonstrate enhanced cognitive skills in breastfed, as well as complex milk lipid and MFGM supplemented infants at an early developmental stage. It must be acknowledged that both complex milk lipids and MFGM supplementation delivers a mixture of complex lipids. Thus, the enhanced neurodevelopment observed in supplemented pups and infants might not only be confined to the effect of sphingolipids. Therefore, further studies should focus on more precise definitions of exposures and explore if early cognitive advantages associated with sphingolipids prolong later in life.

### **Proteins and amino acids**

Proteome and peptidome analyses show that human milk contains proteins and also free amino acids, and that these change in composition especially in the first few weeks following birth (Dingess et al. 2017; Zhang et al. 2016). Furthermore, the concentration of the major milk proteins in human milk decrease over the first 6 months postpartum (Zhang et al. 2021). Cohort studies in compromised pediatric populations, such as preterm infants, suggest a positive association between protein intake and IQ (van Goudoever et al. 2018; Rozé et al. 2021). However, the RCTs performed to date, especially in preterm formula-fed infants, do not provide an optimal range of protein intake for studying cognitive outcomes (Hortensius et al. 2021; Roelants et al. 2018; Ruys et al. 2019). High early amino acid intake in preterm infants was associated with higher survival rates in boys, but with a lower mental developmental index among a subgroup of girls who survived without disability (Uthaya et al. 2016; van den Akker et al. 2014). Finally, a systematic review on the administration of the amino acid glutamine in preterm infants concluded that no significant effect was observed in the three RCTs that examined neurocognitive development in children aged 18 to 24 months and beyond (Moe-Byrne, Brown, and McGuire 2016). In sum, the evidence on effects of protein and amino acid on cognition and behavior comes from RCTs in infants with compromised health and results are mixed. To our knowledge, there is a lack of (observational) studies on associations between protein and amino acid content of human milk and cognitive and behavioral development of fullterm infants.

### **Micronutrients and related compounds**

Adequate maternal intakes of minerals and trace elements, including iron, calcium, copper, iodine, selenium, and zinc during pregnancy and lactation are critical for a healthy pregnancy and for fetal growth and infant development (González and Visentin 2016; Wu et al. 2004). Human milk provides minerals and trace elements for the developing infant (Allen and Hampel 2020) with implication for adequate brain development and cognition (Deoni et al. 2018; Pang et al. 2020). Minerals are known to have a range of effects on the processes of neurodevelopment. For example, calcium and iron are known to have effects of myelination, dopamine receptors, and neurotransmission (Deoni et al.

2013). Selenium is essential for the newborn (Dórea 2002) and has a range of functions depending on the form; for example, the recently discovered Selenoprotein P has important neurological functions (Arias-Borrego et al. 2019; Pitts et al. 2014). Iodine is necessary for the biosynthesis of thyroid hormones and the function of the central nervous system (Zimmermann 2011). Deficiency or excess of those minerals would affect the human milk mineral and trace elements profile with potential influence in the infant neurocognitive and behavioral development.

Choline, a nutrient with an amino acid-like metabolism, has been associated to recognition memory abilities (Cheatham and Sheppard 2015). Higher concentrations of long-chain PUFAs, choline, folic acid, sphingolipids and phosphatides, have been associated with higher myelin levels and cognitive scores (Deoni et al. 2018).

There is pre-clinical evidence that early life adversity leads to a deficit in micronutrient composition in the plasma and the brain, possibly contributing to later life cognitive impairment. Supplementation of micronutrients (including Vit B6, B12, folate and additional minerals and amino acids, including zinc, choline and methionine) to lactating dams during stress exposure, restored the micronutrient deficit observed in their early life adversity exposed pups, reaching control levels, as well as partly protected against the early life adversity-induced cognitive decline (Naninck et al. 2017).

Vitamins known to have specific effects on early brain development and subsequent function include vitamin B12, folate and choline (Georgieff et al. 2018). It has been reported that term milk contains lower concentrations of vitamins (group B) and higher concentrations of vitamins A, E, as well as of carotenes (photosynthetic pigments  $\beta$ -carotene,  $\beta$ -cryptoxanthin, lutein, zeaxanthin and lycopene) than those observed in preterm milk, with potential effects on development (Redeuil et al. 2021). Carotenes would exert pivotal effects on brain and ocular development (Giampietri et al. 2016) but, in general, there is as yet limited data linking vitamins and carotenes to optimal infant neurocognitive development.

### **Human milk oligosaccharides (HMOs)**

After lactose and lipids, human milk oligosaccharides (HMOs) are the largest solid component of human milk (Bode 2012; Kunz et al. 2000). HMOs are a group of unconjugated glucans (complex carbohydrates/sugars) composed of glucose, galactose, N-acetylglucosamine, fucose, and sialic acid, with lactose at their reducing end. More than 150 different HMOs have been identified so far. HMO amount and composition vary between women, are remarkably constant throughout the day and over a week within the same woman but change over the longer course of lactation. How the intake of different HMOs affects immediate and long-term infant health and development, including cognition and behavior, is an active area of research (Docq et al. 2020). HMOs may directly interact with infant cells and tissues or/and act indirectly by shaping infant intestinal microbiota (Underwood et al. 2015; Totten et al. 2012). In many cases, the structure of the HMO

determines the function of the HMO (Bode and Jantscher-Krenn 2012).

There have been several studies on the impact of HMOs on cognition in both animals and humans. Two rodent studies showed a positive impact of the HMO 2'-fucosyl-lactose (2'-FL) on memory and learning. In one study, newborn rat pups were gavaged with either 1 g 2'-FL/kg body weight or water during the suckling period (Oliveros et al. 2016). Rats were then evaluated at 4–6 weeks and 1 year of age using methods to assess cognition. Just after weaning, both groups performed similarly on the Novel Object Recognition test, but at 1 year, rats receiving 2'-FL as pups performed significantly better on this test as well as the Y maze test compared to controls (Oliveros et al. 2016). In a separate study, adult rodents were fed 350 mg of 2'-FL/kg body weight for either 5 weeks in rats or 12 weeks in mice (Vázquez et al. 2015). Both rats and mice fed 2'-FL performed better on cognitive challenges than the controls in each study. Moreover, there was evidence to show increased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and striatum, increased cytoplasmic phosphorylated calcium/calmodulin-dependent kinase II in the hippocampus, and post-synaptic density protein 95 in the hippocampus and frontal cortex (Vázquez et al. 2015). More recently, a mouse model was developed where one of the genes responsible for synthesis of 6'SL was knocked out (Hauser et al. 2021). Compared to control mice, wild-type mice fostered on dams unable to produce 6'SL during lactation exhibited alterations in cognition.

Several studies on piglets confirm the importance of supplementation of sialic acid and/or 2'-FL on cognition. In one study, 3-day old male piglets were provided milk containing up to 830 mg/L of sialic acid (Wang et al. 2007). Piglets receiving the sialic acid supplement performed better on learning and memory tests than those not receiving the supplement, and also showed higher mRNA expression of *ST8SIA4*, a sialyltransferase enzyme, in the frontal cortex and hippocampus, and *GNE*, an enzyme that regulates biosynthesis of N-acetylneuraminic acid, in the hippocampus and liver (Wang et al. 2007). Preterm piglets supplemented with a formula containing 433 mg/L sialyllactose performed better than preterm piglets, not fed sialyllactose, in a spatial T-maze task, and additionally had upregulated genes related to myelination and ganglioside biosynthesis in the hippocampus including glial fibrillary acidic protein (*GFAP*), myelin-associated glycoprotein (*MAG*), myelin basic protein (*MBP*), neuraminidase 1 (*NEU1*), sialin (*SLC17A5*), and b-1,3-galactosyltransferase 4 (*B3GALT4*) (Obelitz-Ryom et al. 2019). However, in term piglets, provision of 380 mg/L of sialyllactose from post-natal day (PND) 2 to 22 did not alter recognition memory at PND17 (Fleming et al. 2018). In a separate study, piglets provided a combination of 1 g/L 2'-FL + 0.5 g/L LNnT in addition to 12.4 g/L of bovine milk derived oligosaccharides (containing galactooligosaccharides as well as 3'-SL and 6'-SL) had larger volumes of the cortices and corpus callosum, and they exhibited increased recognition memory, and increased time investigating objects compared to control piglets (Fleming et al. 2020a). In a separate study by the same group, provision of oligofructose

with 2'-FL also resulted in increased recognition memory after a 48 h delay (Fleming et al. 2020b). Mediation analysis on several of the piglet studies done by this group revealed an association between bacterial genera selected for by oligosaccharides and short-term as well as long-term memory through GABAergic and glutamatergic genes, as well as myelination transcription factors, brain volume and exploratory behavior (Fleming et al. 2021).

Whether HMO effects on cognition translate from animal models to humans is currently under investigation. Several recent human studies revealed correlations between HMOs and infant cognition. In one study on 50 mother-infant dyads of Hispanic origin living in the Los Angeles area, a higher level of 2'-FL in milk at 1 month was correlated with higher cognitive scores of infants on the Bayley-III test at 24 months (Berger et al. 2020). Similarly, in the PREOBE study, human milk 2'Fl concentrations were associated with infant composite motor scores at 6 months and 6'SL concentrations were associated with composite cognitive scores at 18 months (Oliveros et al. 2021). In a separate study of 659 Malawian mother-infant dyads, it was determined that there was a positive association between the relative abundance of fucosylated and sialylated HMOs in milk and language at 18 months (Jorgensen et al. 2020). Finally, a study on 99 mother-child dyads revealed that maternal blood type may have an important role to play in the relationship between HMOs and cognition (Cho et al. 2021). For women having blood type A and able to synthesize the HMO alpha-tetrasaccharide, significant associations between 3'-SL and the Mullen Scales of Early Learning (MSEL), particularly receptive and expressive language, was observed. Analysis of the entire dataset did not reveal any associations between HMOs and cognition (Cho et al. 2021). Ultimately, human intervention studies with structurally defined HMOs and long-term infant follow-up are required to fully define the potential benefits of HMOs on human cognitive and behavioral development.

### Microorganisms

Several studies have revealed the existence of a site-specific microbiota and bacteriome in the pre-colostrum, colostrum, and mature milk of healthy women (Cabrera-Rubio et al. 2012; Fernández et al. 2020; Hunt et al. 2011; Jiménez et al. 2015; Jost et al. 2014; Ruiz et al. 2019; Ward et al. 2013) (Table 2). In addition to bacteria, human milk harbor viruses, phages, archaea, fungi, and protozoa (Boix-Amorós et al. 2019; Jiménez et al. 2015; Pannaraj et al. 2018), although our knowledge about the presence of these microbes in this biological fluid is very limited.

Human milk is an important source of microorganisms that may play a key role in shaping the infant oral and gut microbiome (Biagi et al. 2017; Dzidic et al. 2018; Le Doare et al. 2018; Martín et al. 2003; Martín et al. 2012; Milani et al. 2017; Solís et al. 2010). In fact, the infant fecal microbiome seems to be dominated by human milk bacteria for as long as infants are breastfed, independently of the introduction or not of other foods (Bäckhed et al. 2015). As a

**Table 2.** Summary of the bacterial genera identified with different methodologies in human breast milk samples.

	Bacterial genus	Cultivation	Molecular biology (PCR-methods)	16s sequencing	Metagenomics	
<b>Firmicutes</b>	<i>Streptococcus</i>	X	X	X	X	
	<i>Staphylococcus</i>	X	X	X	X	
	<i>Lactobacillus</i> *	X	X	X	X	
	<i>Enterococcus</i>	X	X	X		
	<i>Leuconostoc</i> *	X	X	X		
	<i>Veillonella</i>	X	X	X		
	<i>Lactococcus</i>	X	X			
	<i>Pediococcus</i>	X				
	<i>Weisella</i>	X		X		
	<i>Faecalibacterium</i>			X		
	<i>Blautia</i>			X		
	<i>Clostridium spp</i>			X		
	<i>Gemella</i>			X		
	<i>Bacteroides</i>			X		
<b>Bacteroidetes</b>	<i>Bifidobacterium</i>	X	X	X		
	<i>Cutinobacterium</i>	X	X	X	X	
<b>Actinobacteria</b>	<i>Rothia</i>	X		X	X	
	<i>Coriobacterium</i>			X		
	<i>Eggerella</i>			X		
	<i>Corynebacterium</i>			X	X	
	<b>Proteobacteria</b>	<i>Acinetobacter</i>			X	
		<i>Enterobacter</i>	X		X	
		<i>Pseudomonas</i>			X	X
		<i>Klebsiella</i>	X		X	
		<i>Escherichia-Shigella</i>	X		X	X
		<i>Ralstonia</i>			X	
<i>Peptoniphilus</i>				X		
<i>Fingoldia</i>				X		
<i>Halomonas</i>				X		
<i>Serratia</i>				X		
<b>Verrucomicrobia</b>	<i>Akkermansia</i>		X	X	X	

Note: Publications available in PubMed from 2000 to 2020 have been revised. There are other bacterial genera identified in the literature, but here the most frequent ones have been included. \*The taxonomy of the new family of *Lactobacillaceae* included all genera that were previously included in families *Lactobacillaceae* and *Leuconostocaceae*. Furthermore, the genus *Lactobacillus* has been reclassified into 25 genera including the emended genus *Lactobacillus* and 23 novel genera (Zheng et al., 2020).

consequence, such early and persistent colonizers may play a role in priming the development and function of many infant systems (Ojo-Okunola, Nicol, and du Toit 2018), including the postnatal development of the infant brain through the establishment of the microbiota-gut-brain axis (de Weerth 2017; Ratsika et al. 2021). And indeed, infant gut microbiota community composition, including milk-oriented microbes, is associated with cognitive and behavioral development (Aatsinki et al. 2019; Carlson et al. 2018; Carlson et al. 2021; de Weerth, Fuentes, and de Vos 2013a, de Weerth et al. 2013b; Loughman et al. 2020).

There are many pathways to communicate between the gut microbiota and the brain, including (a) direct or metabolite-mediated interactions with the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamic-pituitary-adrenal axis (HPA); (b), interactions with the innate and the adaptive immune system; (c) entero-endocrine signaling; and (d) participation in the biosynthesis and response to several key neurochemicals (e.g., tryptophan precursors and their metabolites, serotonin,  $\gamma$ -amino butyric acid [GABA], catecholamines, etc.), bile metabolites, peptidoglycan, branched chain amino acids, short-chain fatty acids and other compounds that are involved in host cognition, behavior and mood (Allen-Blevins, Sela, and Hinde 2015; Carlson et al. 2021; Cryan et al. 2019; Fox et al. 2021; Rhee, Pothoulakis, and Mayer 2009).

Adequate gut microbial colonization has been associated with enhanced neurodevelopment (Allen-Blevins, Sela, and

Hinde 2015; Oliphant et al. 2021; Tamana et al. 2021). Some strains belonging to lactobacilli and bifidobacteria species, which are frequently detected in human milk, can exert an influence in neurogenesis, neurotransmission, expression of neuropeptides, neuroinflammation and behavior (Cryan et al. 2019; Janik et al. 2016; Perez-Burgos et al. 2013; Sherwin et al. 2016). More specifically, they seem to contribute to the establishment of brain neural circuits (Luck et al. 2020), in hypothalamic posterior pituitary activity (Erdman and Poutahidis 2014), and in the restoration of social behavior after its alteration (Buffington et al. 2016). It must be highlighted that the beneficial effects of some of these bacterial species on social behavior using a genetic mouse model of autism were not detected in vagotomized animals (Sgritta et al. 2019). In addition, DNA of some strict anaerobes (e.g., *Faecalibacterium prausnitzii*, *Akkermansia muciniphila* or *Bacteroides* spp.), has been detected in human milk and infant feces (Benítez-Páez et al. 2020; Collado et al. 2012; Jeurink et al. 2013; Jiménez et al. 2015; Ward et al. 2013). These organisms can potentially exert strong influences on infant neurodevelopment (Hao et al. 2019; Song et al. 2019; Tamana et al. 2021; Yaghoufar et al. 2020; Yaghoufar et al. 2021; J. Wang, Xu, et al. 2021).

Finally, human milk bacteria are one of the drivers of the differences existing between the gut microbiota of breastfed infants and that of formula-fed infants, mainly due to the presence of *Bifidobacterium* strains. Some

Bifidobacterium strains are able to modulate the tryptophan metabolism (Tian et al. 2022), or to produce neurotransmitters, such as Gamma aminobutyric acid GABA (Duranti et al. 2020; Yunes et al. 2016), and Indole-3-lactic acid (a metabolite of tryptophan, Meng et al. 2020). Interestingly, formula diet alters the colon microbiota of piglets and appears to shift tryptophan metabolism from serotonin to tryptamine (Saraf et al. 2017). Altogether, studies performed so far suggest that milk bacteria play relevant roles for infant cognitive and behavioral development, but their actual relevance and impact are far from elucidated yet.

### **Pollutants**

Human milk does not only contain naturally occurring constituents. Environmental pollution leads to the introduction of novel and often toxic substances to milk. In many cases, these milk components are poorly metabolized and hardly excreted. The accumulation of milk pollutants in an infant's bones, kidneys, liver, and fat tissue is associated with long-term and negative consequences for health and development (Al-Saleh 2021; Rebelo and Caldas 2016). Persistent organic pollutants (POPs) and heavy metals are the most extensively studied air and food pollutants found in human milk sampled from different regions worldwide (reviewed in Pajewska-Szmyt, Sinkiewicz-Darol, and Gadzała-Kopciuch 2019). POPs and heavy metals present strong geno-, immuno-, and cytotoxic properties and have been shown to be associated with a range of adverse health outcomes, including neurological and behavioral disorders regardless of the period of exposure (Bauer et al. 2020; Nelson et al. 2019; Vrijheid et al. 2016). Concentrations of various POP groups in maternal milk have been estimated to be up to six times higher than in maternal serum (Thundiyil, Solomon, and Miller 2007). Compared to maternal serum, elevated levels in milk have also been demonstrated for some heavy metals (Sharma et al. 2019; Dórea 2021).

Although maternal exposure to both POPs and heavy metals during pregnancy has been shown to cause child neurodevelopmental delay (Benjamin et al. 2017; Castriotta et al. 2020; Nishijo et al. 2014; Yamazaki et al. 2018), epidemiological studies on postnatal exposure via breastfeeding are inconclusive, demonstrating from none to significant effects (Gascon et al. 2013; Pajewska-Szmyt, Sinkiewicz-Darol, and Gadzała-Kopciuch 2019). A recent study conducted in Taiwanese mother–breastfed infant pairs (Kao et al. 2019) demonstrated that higher milk concentrations of 4,4'-dichlorodiphenyltrichloroethane were related to lower infant cognitive and language performance, while higher milk trans-chlordane concentrations were related to lower social and emotional performance, between 8 and 12 months of age. Similar negative associations were found for concentrations of milk dioxins and cognitive and motor skills in 4-month-old Vietnamese infants (Tai et al. 2013).

Drinking water and soil are important sources of exposure for heavy metals (cadmium, chromium, mercury, manganese, and lead) in breastfed infants (Cardoso et al. 2014).

Concentrations of metals in breast milk vary significantly between countries and studies (Dórea 2019). These concentrations reflect prenatal exposure when most neurodevelopmental effects are already programmed (Dórea 2021). Long half-life metals (lead, cadmium) accumulating in various maternal organs pose a risk for breastfed infants even before conception. In mothers with a high body accumulation of pollutants, breast milk is an important determinant of infant health risks (Ettinger et al. 2014). For example, the physiological mechanisms that are in place to supply calcium to the fetus and infant, lead to the mobilization of maternal bone lead, an important lead source in breast milk. Ronchetti et al. (2006) hypothesized that maternal bone lead storage is the most important factor predicting its neurotoxicity associated with child IQ. However, in addition to milk concentrations, neurodevelopmental outcomes will also depend on current maternal diet, child nutritional status, and genetic makeup, and the nature of exposure to metals (acute vs. chronic). Although many studies have investigated the concentrations of heavy metals in breast milk, only a few specifically assessed the effect of the exposure to heavy metals from breast milk on neurodevelopmental outcomes. An epidemiological study in Brazil demonstrated that higher milk concentrations of lead and mercury correlated negatively with mental and psychomotor development, as well as the age of walking and talking, in infants and toddlers living in the vicinity of tin ore kilns and smelters (Marques et al. 2014). Increased concentrations of mercury in breast milk were also associated with lower parental evaluations of neurodevelopmental status (Al-Saleh et al. 2016). In the same population, increased multichemical exposure, including manganese and selenium in breastmilk, was related to a higher risk of lower parental evaluations of neurodevelopmental status (Al-Saleh et al. 2019). Contrarily, no consistent association between breast milk mercury levels and infant cognitive outcomes was found in Mediterranean countries (Greece, Croatia, Slovenia, Italy); however, higher milk mercury concentrations were related to suboptimal infant fine motor performance (Barbone et al. 2019).

### **Interactions among milk constituents**

The majority of research on the composition of human milk evaluates the effects of individual milk components. This is a result of mostly siloed research areas, lack of statistical methods to integrate different types of data, and lack of advanced laboratory analysis techniques to measure multiple milk components concurrently. Nonetheless, interactions and synergistic relations between human milk components are now an area of much interest due to the rise of interdisciplinary and collaborative team science, the development of multi-omic techniques that can simultaneously examine multiple components from the same milk sample, and the emergence of machine learning based methods for integrating and analyzing diverse datasets. Human milk scientists are calling for new approaches and proposing advanced computational methods to study milk as a “system within a system” (Christian et al. 2021; Shenhav

and Azad 2022) – that is, milk itself is a biological system comprising many components, which collectively serve as a fundamental component of the mother-milk-infant “triad” that directs early development (Bode et al. 2020).

Recent studies show correlations between different human milk components, including amino acids, sugars, lipids, proteins, hormones, HMOs, and milk microbiota (Gómez-Gallego et al. 2018; Linderborg et al. 2020; Moossavi et al. 2019a; Williams et al. 2017; Pace et al. 2021). Gómez-Gallego et al. (2018), showed that lactate, creatine, proline, lacto-N-fucopentaose 1, 2'-fucosyllactose and very low-density lipoprotein particles were positively correlated with gammaproteobacteria and negatively correlated with alphaproteobacteria, betaproteobacteria and bacilli. In addition, Moossavi et al. (2019a), showed that certain HMOs are positively correlated with bifidobacteria in milk, and certain fatty acids are correlated with milk microbiota richness and diversity. Williams et al. (2017), showed correlations between complex bacterial communities in milk and HMOs, maternal cells, and other nutrients. The same group further showed that variations in these milk components were collectively associated with differences in the microbial community structures of infant feces and the abundance of specific taxa (Pace et al. 2021). Finally, Linderborg et al. (2020), showed that higher milk cortisol concentrations are related to a greater abundance of lauric and myristic fatty acids. These correlational studies suggest that individual milk components are inter-related and potentially influence one another. Next steps involve moving beyond correlational analyses to understand how different milk components may be modifying the biological effects of other components through synergistic interactions that can up or down regulate their individual functions and impact on neurodevelopment. This type of systems biology approach has been used successfully in other areas of research, such as multi-omic characterization of maternal serum in the context of preterm birth (Jehan et al. 2020).

Two observational studies have examined the synergistic effects of milk components on human brain and cognitive development (Cheatham and Sheppard 2015; Wang et al. 2003). Cheatham and Sheppard (2015), showed that higher choline combined with higher lutein, and increased DHA combined with higher choline in milk samples were related to better recognition memory in infants at 6 months. Wang et al. (2003) found significant correlations between brain sialic acid and brain LC-PUFA concentrations among breast-fed infants, which may also indicate that these individual components work together to improve infant brain development. Overall, more research is needed to characterize the interactions and synergies between milk components and to evaluate milk “as a whole” – both in general, and in the context of infant neurodevelopment.

### **Milk energy output**

Adequate energy intake is essential for brain development, especially during sensitive periods (Uberos et al. 2021,

Bautista et al. 2019). Additionally, energy deprivation in preterm neonates is associated with poorer indicators of brain development, such as language development (Lithoxopoulou et al. 2019). Animal studies have shown considerable evidence that milk energy output is particularly important for offspring growth and development, including biobehavioral development (Hinde 2007, 2009). Moreover, higher milk energy may facilitate offspring engagement in energy-requiring behavior and social interactions and potentially program behavioral development. Hinde and Capitanio (2010) presented the first evidence for the association between the natural variation in Available Milk Energy (AME) and infant behavior and temperament in rhesus macaques: heavier mothers with multiple previous pregnancies produced greater AME in the early postnatal period and their infants showed higher activity levels and greater confidence in a stressful setting (Hinde and Capitanio 2010). The availability of milk energy might reflect the maternal environment and constitute a signal that helps the infant to adapt appropriately. Likewise, Dettmer and colleagues (Dettmer et al. 2018) showed that rhesus macaques' milk yield, which affects AME, was associated with social behavior in female offspring and cognition in both sexes. Female infants who received more milk during early postnatal life showed more mounting behavior. Higher early postnatal milk yield also accounted for better cognitive inhibitory control at later developmental stages (Dettmer et al. 2018).

Interestingly, infant formula may have higher energy content than human milk (Hester et al. 2012), and formula feeding has been associated with adverse developmental outcomes compared to human milk feeding (Pang et al. 2020), although multiple mechanisms and human milk components may underlie this association. A double-blinded, randomized controlled trial (RCT) showed that infants fed with reduced-energy MFGM supplemented formula had better cognitive scores at the age of one year compared to infants fed with standard formula (Timby et al. 2014), although the differences in neurocognitive performance were attenuated by the age of 6 years (Timby et al. 2021). This suggests that at least in WEIRD (Western, Educated, Industrialized, Rich, and Democratic) populations, reducing the energy content of formula in early life does not have significant impact on later neurocognitive outcomes, and subsequently, that other components of milk may be more relevant for neurocognitive development.

## **Factors affecting milk constituents**

### **Maternal factors**

There is considerable variation in milk composition between mothers. Numerous maternal factors, such as age, parity, smoking, delivery mode, and environmental pollution, have been suggested to contribute to this inter-individual variation in milk composition (Azad et al. 2018; Bachour et al. 2012; Bahreynian, Feizi, and Kelishadi 2020; Bernstein and Hinde 2016; Burianova et al. 2019; Dritsakou et al. 2017; Hahn et al. 2018; Fernández et al. 2020; Moossavi et al.

2019b; Pittet, Johnson, and Hinde 2017; Pundir et al. 2019; Samuel et al. 2020; Whitfield et al. 2020). For example, a recent study found an association between lipid and energy contents in breast milk and maternal pregestational nutritional status, gestational weight gain, smoking and hypertension (Amaral et al. 2021). However, maternal factors affecting milk composition, overall, show inconsistent findings or may have been understudied (Samuel et al. 2020). Also, the evidence comes mainly from high-income rather than low-middle income populations, while the variability of some human milk components could be influenced by geographical locations and sociodemographic factors (Samuel et al. 2020). Modifiable maternal factors may also interrelate with fixed factors such as maternal traits, characteristics, or genetics, and might be important targets for interventions to optimize the lactation process (see also Figure 1). Nevertheless, there is a large body of literature on maternal diet and mental health in relation to human milk composition and below we will describe the current state of research of those two factors.

### Maternal diet

There is a general acceptance of the importance of maternal diet in determining breast milk composition. This mostly accounts for human milk's fatty acids composition, such as PUFA's, which have been studied extensively and appear to be influenced by maternal diet (Bravi et al. 2016; Jonsson et al. 2016; Keikha et al. 2017; Perrin et al. 2019). In addition to the intake of individual nutrients or foods that have been related to human milk's fatty acid composition, Bravi and colleagues (Bravi et al. 2021) recently also found an association between maternal dietary patterns and the fatty acid composition in human milk. Traditionally, other milk macronutrients such as carbohydrates and protein were considered less sensitive to maternal dietary intake (Bravi et al. 2021; Dror and Allen 2018; Keikha et al. 2017), leading to the hypothesis that gross human milk composition is buffered for variations in maternal dietary intake (Mitoulas et al. 2002). However, this idea has been challenged by recent findings (Samuel et al. 2020). For example, Ward and colleagues (Ward et al. 2021) showed that high-fat and high-sugar meals result in acute changes (i.e., within 24 hours) in fat, lactose and protein levels in breast milk. Regarding human milk's micronutrients, there is probable evidence for an influence of maternal diet, although this differs for specific constituents (for a review, see Samuel et al. 2020). For instance, adherence to a Mediterranean diet was found to influence the concentration of iodine and selenium in human milk (Sánchez et al. 2020; Valent et al. 2011). Contrarily, Butts and colleagues (Butts et al. 2018) found that maternal variations in calcium intake, were not reflected in their milk. This may be explained by physiological changes in calcium metabolism during lactation (Olausson et al. 2012). The levels of certain vitamins in human breast milk are associated with maternal dietary intake (Keikha et al. 2017). Specifically, the intake of fat-soluble vitamins such as vitamin B1, B2, and C is related to their concentrations in

human milk (Keikha et al. 2021). There is some first evidence suggesting that certain bioactive factors, such as human milk microbiota, are sensitive to maternal diet (Moubareck 2021; Williams et al. 2017). For example, Kumar and colleagues (Kumar et al. 2016) reported on multiple associations between the intake of fatty acids and milk microbiota, for example monounsaturated fatty acids of milk were negatively associated with proteobacteria, but positively associated with the *Lactobacillus* genus.

There are more indications from both human and animal studies for potential programming effects of maternal diet on offspring's behavioral and cognitive development, mediated by human milk composition. Specifically, maternal consumption of fatty acids would be of great importance for infant brain development, as previously described in the *Fats* section. De Melo and colleagues (de Melo et al. 2019) supplemented female rats with avocado oil and pulp resulting in improved memory in adolescent and adult offspring. Similarly, memory performance and cognitive functioning of offspring improved when the lactating dam's diet was supplemented with cashew nuts (de Melo et al. 2017), fish oil (Rachetti et al. 2013), olive oil (Pase et al. 2015), and linseed oil (Fernandes et al. 2011). On the contrary, maternal intake of *unhealthy* fats such as trans fatty acids (Islam et al. 2019), resulted in adverse effects on offspring's cognitive development. For example, Pase and colleagues (Pase et al. 2017) found that memory functioning was impaired in adult offspring of the rats that received a diet rich in trans fatty acids during lactation, compared to receiving a diet with an optimal ratio of n-6/n-3. There are a few longitudinal human studies investigating maternal fatty acid intake, specifically DHA supplementation during lactation, and offspring behavioral and/or cognitive development. Positive relationships have been found between maternal DHA supplementation, DHA levels in human milk and infant and child's cognition and behavior, such as improved mental development (Jensen et al., 2005), sustained attention (Jensen et al., 2010), a sex-specific association on problem-solving and language development (Lauritzen et al. 2005), boy's prosocial behavior (Cheatham et al. 2011) and mental test scores (Helland et al., 2003). However, an association of DHA supplementation and most of the (other) studied behavioral and cognitive outcomes is lacking or only present at a certain age. Since evidence is still limited on potential programming effects, caution is warranted in interpreting these results and more investigation is needed.

Finally, certain food flavors of the mother's diet transfer from mother to child through the amniotic fluid and breast milk and shape the child's later food preferences and acceptance (Cooke and Fildes 2011; Ventura 2017). Consistent with this, a recent systematic review shows moderate evidence that maternal diet during lactation can influence the flavors profile of human milk within hours or months of recurrent food intake (Spahn et al. 2019). Next to flavor, human milk odor has been shown to promote more (non-)nutritive sucking in a feeding context compared to infant formula odor or water (Loos, Reger, and Schaal 2019).

### Maternal mental health

Another important factor influencing milk composition and volume is the mother's mental health and psychological state. Several studies indicate that maternal psychological distress may influence the immune properties of human milk, but the results are conflicting. For example, postpartum-specific stress and negative states (e.g., anxiety and hostility) were inversely associated with the milk concentration of secretory IgA (Hart et al., 2004; Kawano and Emori 2015; Moirasgenti et al. 2019) and lactoferrin (Ziomkiewicz et al. 2021b). In contrast, a positive correlation was found between maternal distress and milk secretory IgA (Groër et al., 1994; Hart et al., 2004; O'Connor et al. 1998). Finally, a recent study reported no association between maternal psychosocial distress and 22 immunological factors in milk (Aparicio et al. 2020). With respect to positive mental health factors, maternal social support was recently found to be correlated with milk IgG (Ziomkiewicz et al. 2021a). Therefore, larger studies with long-term follow-up are suggested to further investigate the potential influence of maternal mental health factors on breast milk immunoglobulins. Findings also suggest a potential association between maternal psychosocial distress and milk microbiota, with the bacterial diversity in milk at 3 months post-delivery being lower in women experiencing high maternal psychosocial distress (Browne et al. 2019).

Regarding milk hormones, a positive association was found between maternal psychosocial distress in the early postnatal period and milk cortisol concentrations (Aparicio et al. 2020). Another study found a relation between maternal hostility and milk cortisol concentrations (Hart et al., 2004). However, a recent study found no significant difference in breast milk glucocorticoid circadian rhythm between mothers seeking consultation for psychiatric complaints and a control group with no mental health issues (Romijn et al. 2021). Interestingly, an RCT demonstrated that relaxation therapy reduced maternal stress and hindmilk cortisol concentrations in the early postnatal period (2 weeks), but no effect on milk cortisol was found later on. Moreover, relaxation group infants were also reported to sleep longer, have higher milk intake, and demonstrate greater weight gain (Mohd Shukri et al. 2019). Other experimental studies using relaxation therapies, such as meditation and music therapy, showed beneficial effects of the intervention on milk volume or expression, energy and milk fat (Ak et al. 2015; Dabas et al. 2019; Feher et al., 1989; Keith, Weaver, and Vogel 2012; Kittithanesuan et al. 2017; Varişoğlu and Güngör Satılmış 2020). Furthermore, milk energy density, fat, and medium-chain and long-chain saturated fatty acids were also found to be associated with long-term stress during the postpartum period (Ziomkiewicz et al. 2021b).

### Child factors

Some fetal and child factors, such as biological sex and gestational age at birth, are associated with milk constituents that are related to offspring cognition and behavior, as

demonstrated by human and nonhuman animal studies (reviewed in Galante et al. 2018). One of the best studied factors is offspring sex. Accumulating evidence suggests that the concentration of milk bioactives as well as the sensitivity and time windows for their effects vary between male and female offspring (Dettmer et al. 2018; Galante et al. 2018; Hinde et al. 2013, 2014; Hinde 2009; Petrullo, Hinde, and Lu 2019). At present, sex effects are difficult to test experimentally.

Milk constituents have been found to differ as a consequence of offspring sex in several mammal species. In rhesus monkeys, mothers produce different milk for males than for females: during peak lactation at 3–4 months of age, male infants receive milk higher in energy density whereas female infants receive higher milk yield (Hinde 2009); these differences relate to sex-specific differences in infant mass and growth (Hinde 2009; Hinde et al. 2015). Rhesus monkey female offspring also receive mothers' milk with greater calcium concentrations (Hinde et al. 2013), which is likely related to earlier skeletal ossification in female primates (Cheverud 1981). However, mothers of male and female offspring exhibit no differences in the amount of milk cortisol in early (1 month) or peak (3–4 months) lactation (Hinde et al. 2015), or in phosphorous at peak lactation (Hinde et al. 2013). In dairy cows, Holsteins produce more milk for female than male offspring, and gestating a female (heifer) first results in greater milk yield for the second offspring (Hess et al., 2016; Hinde et al. 2014). One study also found higher fat content in the colostrum of cows that birthed heifers (Angulo et al. 2015), and another found reduced saturated fatty acid content in milk produced by mothers of heifers (Gillespie et al., 2017). Additionally, in marsupials (e.g., kangaroos and wallabies), mothers produced milk with higher protein content for male offspring (though there were no sex differences in energy content or milk volume; Robert and Braun 2012). In humans, differences relating infant sex to mother's milk composition are much less clear and likely due to the paucity of studies on the topic, other differences in global regions studied, as well as sampling and analytical techniques used (reviewed in Galante et al. 2018). For example, one study of Filipino mothers that did not include foremilk samples found no relations of sex with milk composition, whereas other studies in Iraq, the United States, South Korea, Kenya, and Australia found associations of infant sex with calcium, phosphorous, insulin, and leptin concentrations and the macronutrient and energy content, depending on the study (see Galante et al. 2018).

Another factor influencing milk composition is gestational age at birth, a factor that has only been studied in humans thus far, and consequently has not been studied experimentally (although one can envision experimental studies in nonhuman animals). An early study found that, across the first 12 weeks postpartum, mothers of preterm infants had higher protein nitrogen and lower calcium and phosphorous concentrations than those of full-term infants (with no differences in non-protein nitrogen, energy, fat, sodium, magnesium, or zinc; Butte et al. 1984). More recent studies have confirmed differences in calcium and phosphate in preterm



milk (Underwood 2013), and reported less zinc, copper, and selenium than observed in milk from term deliveries (Sabatier et al. 2019). Likewise, the milk of mothers who delivered prenatally had higher fat and energy content (Fischer Fumeaux et al., 2019), higher concentration of 3FL and lower concentration of other HMO's (Austin et al. 2019). A review of studies comparing fatty acid composition in the milk of mothers of preterm compared to full-term infants found that DHA values were higher in preterm milk, with no differences in the concentration of saturated and monounsaturated fatty acids (Bokor, Koletzko, and Decsi 2007), while a more recent study suggested a lower concentration of medium- and short-chain fatty acids in the milk of mothers of preterm infants (Dai et al. 2020). Human milk microbiota also appears to be different according to gestational age at birth (Khodayar-Pardo et al. 2014), but gestational age was not associated with the microbiota composition at 3–4 months postpartum (Moossavi et al. 2019b). However, the microbial communities in the human milk microbiota of mothers delivering prematurely are highly individualized in the first two months postpartum, and are affected by maternal factors (Asbury et al. 2020).

Finally, certain hormones are present in higher concentrations in milk of mothers delivering preterm compared to term. The list includes neurotrophic factors (Collado et al. 2015) and glucocorticoids (Pundir et al. 2019), but not gonadotrophins, thyroid hormones (Vass et al. 2020) or leptin (Resto et al. 2001). Infant factors that may be expected to influence maternal milk composition but that have not been extensively studied to date include infant birth order, oral microbiota, behavior, and illness. For example, illness in the infant has been associated with changes in immune factors in the mother's milk (Breakey et al. 2015; Bryan et al. 2007; Riskin et al. 2012).

### **Interplay of maternal-child factors**

#### **Tradeoff allocations**

As stated previously (*Human milk and child development section*), evolutionary theory helps inform lactation and human milk composition in the light of natural selection. Life History Theory organizes our understanding of how natural selection has (likely) shaped lifespan investments and tradeoff allocations for maintenance, development, and reproduction across an organism's life-course (Hill 1993; Hill and Kaplan 1999). Due to the high resource demands of female reproduction, investment strategies critical to reproductive success have been strongly shaped by natural selection (Jasienska, 2009). Lactation often exceeds the costs of gestation due to increased energy demands of larger, more active *ex utero* offspring and due to lower efficiency of energy transfer via milk compared to nutrient transport via the placenta (Jasienska, 2009; Tully and Ball 2013; Hinde and Milligan 2011). At any given time, tradeoff allocations can therefore be between maternal condition and reproduction, maternal survival and reproduction, the quantity and condition of offspring, and for young mothers, their own growth/development and reproduction (Clutton-Brock 1991;

Stearns 1992). Additionally, a female's reproductive success is determined by her production of surviving, reproductive offspring across a reproductive career; hence, there can be tradeoffs for the mother between allocation of resources toward current offspring and transitions to allocation for future reproduction (Tully and Ball 2013; Clutton-Brock 1991; Wells 2003). All these tradeoffs have the potential to impact milk composition.

#### **Parent-offspring conflict**

At the same time, within a life history framework, we must simultaneously consider the developmental priorities and tradeoffs of the offspring (Trivers 1974). Due to divergent relatedness between self and siblings, an individual offspring's tradeoff priorities are expected to often diverge from the mother's tradeoff priorities. This is the core tenet of parent-offspring conflict (Trivers 1974) and an essential evolutionary theory construct for investigating mother's milk and infant development (Allen-Blevins, Sela, and Hinde 2015).

During lactation, maternal-offspring conflict may occur across all dimensions of the lactation strategy including the frequency of nursing bouts, the duration of lactation until completion of weaning, and the composition and yield of mother's milk (Hinde and Milligan 2011). Communication and signaling between mother and infant are the interface in which mother and offspring negotiate nursing behavior and milk production and transfer (Allen-Blevins, Sela, and Hinde 2015). Infants can signal with behaviors such as high vocalization and/or frequent non-nutritive suckling, whereas the mother could respond through restricting nipple access, affecting the amount and composition of milk produced (Wells 2003; Fewtrell et al. 2020).

Maternal and offspring lactation tradeoffs are even starker for malnourished, ill, stressed, or adolescent mothers and their offspring with greater mortality risk (Pittet, Johnson, and Hinde 2017). Under such marginal conditions, transferring milk components to regulate infant feeding behavior may be more about coordination than conflictual, so that the infant might prioritize honest signals when truly hungry rather than wasting energy to demand for feed (Wells 2003; Allen-Blevins, Sela, and Hinde 2015).

RCTs can help uncover how clinical interventions may reduce the tension of parent-offspring conflict through mother-infant signaling. For example, mothers who received relaxation therapy during breastfeeding (reducing maternal stress, hence preventing waste of energy) showed altered milk composition and increased infant milk intake, which subsequently increased infant sleeping duration and promoted growth (Mohd Shukri et al. 2019). Although the overall evidence on the relation between milk components and infant behavioral outcomes are often equivocal and remain poorly understood, these new studies are demonstrating important opportunities to understanding underappreciated lactation adaptations with the potential for improving clinical support of lactation and mother-infant dyads (Fewtrell et al. 2020; Pittet, Johnson, and Hinde 2017; Neville et al. 2012).

## Recommendations and best practices for future research studies

### Study set-up

Following best practices in milk research requires careful study design that accounts for many variables, including an in-depth understanding of breastfeeding practices of the population studied for human studies, choosing appropriate animal models for specific research questions, and the logistics of milk collection, storage, and analysis. To ensure best practices are being followed, a large amount of work needs to be done prior to starting a human milk study. Table 3 presents a comprehensive set of questions that researchers can use to guide their study design. The questions are divided into more general study design issues and more specific methodological issues. This guide is not necessarily exhaustive, but by using it, researchers can avoid inadvertently overlooking important criteria when setting up new studies. Figure 3 is a detailed graphical representation of the necessary steps to take and decisions to make when setting up a human milk study. Further resources that may be useful for setting up a human milk study are the articles by Miller et al. (2013) on field and laboratory methods and Neville et al. (2012) on defining and refining critical questions, and the books by McGuire and O'Connor (2020) on sampling and measuring constituents, and by Akers (2002) on lactation and the mammary gland.

The majority of milk research has been conducted in WEIRD populations, and extending this research beyond these populations is critical to our advancement of knowledge in this field. However, researchers may have to account for unique challenges in research design and limits to data collection when doing so. For example, when possible, it is ideal to collect and report information from study participants about gestational age and infant

maturity at birth, but this information may be lacking or inaccurate in populations with limited access to prenatal care. Similarly, it is ideal to collect data about potential interactions with the milk components being investigated, such as medications and vitamins the participant is taking, but this information may be difficult to obtain in some populations, such as populations with high rates of illiteracy. Thus, gold standard collection, storage, and analysis protocols may need to be modified for some studies. Taking on these challenges means planning for the realities of fieldwork in these settings and acknowledging how adjustments made to accommodate logistic compromises may bias the sample integrity.

### Assessment of child cognitive and behavioral development

A cognitive assessment for (young) children usually includes an assessment of a) comprehensive background information through interviews with the child (if old enough), parents and, in some cases also school teachers, and b) the administration of standardized tests by trained professionals. Example standardized tests that are often used include the Wechsler Preschool and Primary Scale of Intelligence (WPPSI; ages 2.5–7 years) and the Wechsler Intelligence Scales for Children (WISC; ages 6–17 years) (Wechsler 1967; Wechsler 2014). These tests are continuously updated, making it important to use the most current one. It is also possible to use tests for more specific cognitive functions, such as the STROOP task to measure the ability to inhibit cognitive interference (Stroop 1935) and the Rey–Osterrieth Complex Figure Task to measure visuospatial constructional ability and memory (Davies et al. 2011). Also, parental report to measure child executive functions, like the Behavior Rating Inventory of Executive Function (BRIEF), are often

**Table 3.** Guide for setting up a research study with human milk.

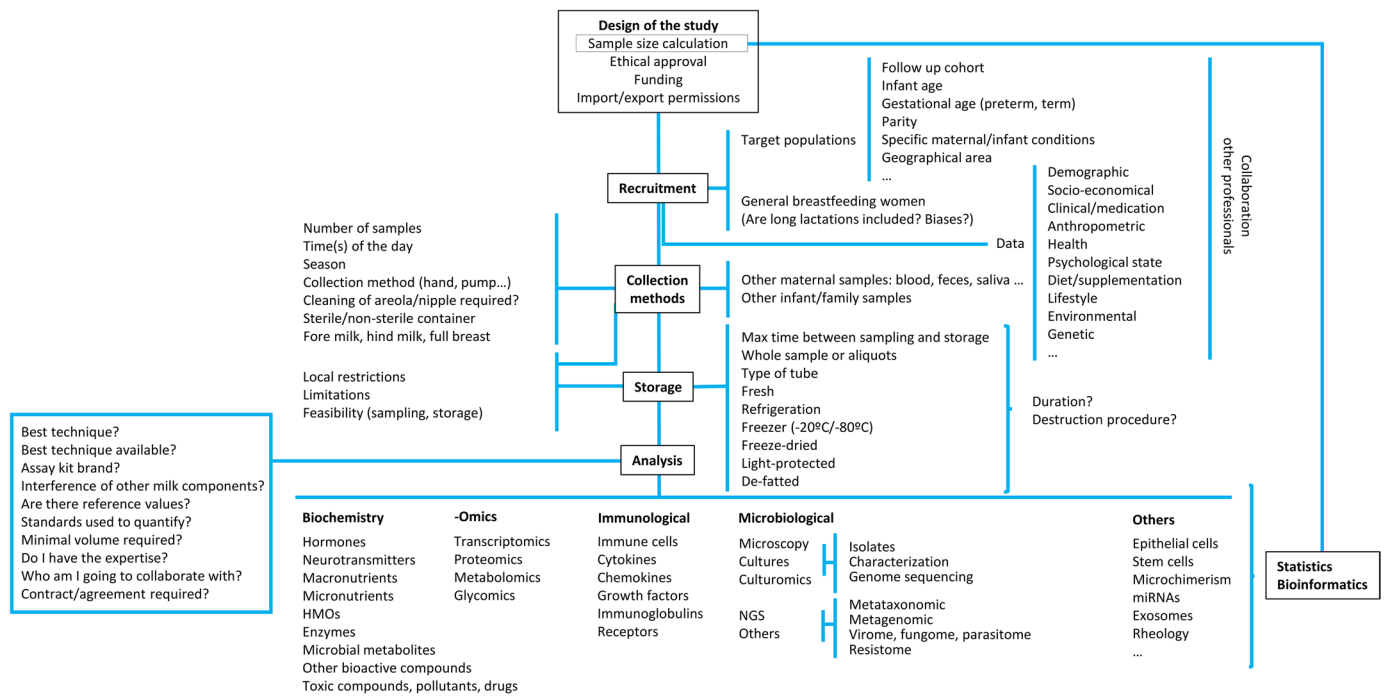
Questions to ask when setting up a research study with human milk

#### General study design

- Do you have the right team with the appropriate expertise to answer your questions? Have you effectively partnered with members of the study community to serve their needs?
- Are human models, animal models, or a combination, the best way to address the research question(s)?
- If your research design includes animals, which animal model is the most appropriate model to the research question based on the biological systems being investigated and corresponding periods of plasticity?
- If your research design includes human participants, what portion of the population does your approach include and whom does it exclude?
- What is your target population? What measurement tools are appropriate for your population? What limitations do you expect?
- Have you calculated the appropriate sample size for your study using a power analysis based on the primary outcomes?
- How can you ensure that your research sampling minimizes disruption to mother and infant?
- What data are needed on mother and infant (diet, age, parity, infant sex, pre- & postnatal health, medications, etc.)?
- What nutritive and non-nutritive milk components have known interactions with the components you are investigating that may need to be analyzed and controlled for in the analysis?
- What is the most reliable, well-suited and fine-grained measurement to measure my child outcome of interest?

#### Specific methodological issues (consult the current best practices)

- What volume of sample do you need? Can you obtain the amount needed given your study population?
- How many samples will you need per participant and across what duration?
- What does the milk sample represent? Consider day of lactation, hour of day, within feeds.
- What is the timing of sampling, and what components and populations is this important for?
- What is the sample collection method (e.g., hand expression, sterile versus non-sterile, pump)?
- What are the necessary storage conditions for the component you want to analyze? (e.g., frozen, freeze-dried, type of tube, light versus dark)
- What is the treatment of samples (e.g., maximum time allowed between collection and freezing, number of freeze/thaw cycles)?
- Type of analysis and optimal method to use?
- Determine what the least common denominators are (common sampling & assay techniques, etc.)
- For studies in non-WEIRD populations: how can samples be collected, stored, and imported/exported in different regions of the world? How will you ship and store this amount of milk given how many samples you plan to collect?



**Figure 3.** Detailed visual representation of the steps that need to be considered and the decisions that need to be taken when setting up a human milk study, from study design to laboratory analyses and bioinformatics.

used, preferably in combination with cognitive tasks (Wallisch et al. 2018).

To test the development of even younger children and infants, the Bayley Scales of Infant and Toddler Development are often used (ages 1–42 months) (Bayley 1969). This measure consists of a series of developmental play tasks and derives a developmental quotient (DQ) rather than an intelligence quotient (IQ). A comparable instrument of widespread use is the Mullen Scales of Early Learning (MSEL; Mullen 1995) that measures cognitive and motor development in children ages 0–68 months. Also in this younger age group, parental report is often used to measure toddler executive functioning (e.g., the BRIEF for Preschoolers, the BRIEF-P; Wallisch et al. 2018; Sherman and Brooks 2010).

As many standardized tests are often tailored to Western populations and costly, they are not available nor adequate for non-Western children. Recently, an open-source WHO-supported instrument has been developed to increase accessibility and promote universal use, the Infant and Young Child Development (IYCD) Indicators. This simple-to-use caregiver report tool is for children ages 0–3 years, contains 100 items, performs well for cognitive testing, and has been shown to be a reliable across countries (Gladstone et al., 2021; Lancaster et al. 2018).

The cognitive tests described above have the advantage of being often used. However, they render measures of cognition that may be too crude to accurately measure the specific cognitive processes that are (slightly) quantitatively impacted by early nourishment. Tests that make use of advanced methodologies that deliver fine-grained measurements are also showing to be promising instruments for predicting cognition. For example, the use of eye-tracking technology has delivered research results

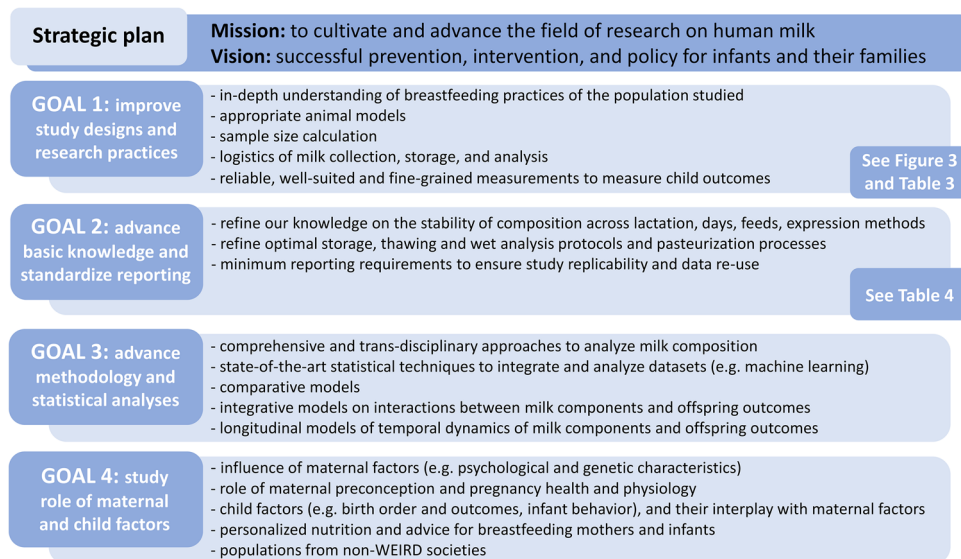
relating pupil size (only in adults to date; Tsukahara and Engle 2021) and infant habituation performance to cognitive abilities. Infant habituation performance (i.e., looking behavior) has considerable predictive power from early infancy to school age, adolescence, and even adulthood intelligence (Bornstein and Sigman 1986; Fagan et al., 2007; Kavšek 2004), and explains as much as 40% of the variance in cognitive performance (Fagan & McGrath, 1981).

Behavior assessments are different from cognitive assessments, as they have no right or wrong answers. Instead, behavior assessments investigate how children interact with the people and world around them. Many behavior assessments can identify behavior patterns as well as reasons for the behavior. Often parents, teachers and/or others are asked to observe the child in daily life and answer questions. Also, children can be asked to fill out a questionnaire about their own behavior, thoughts and emotions, but, pending on the length and difficulty of the questionnaire, this often proves difficult before the age of 10. Some commonly used behavior assessments include the Behavior Assessment System for Children (BASC; Reynolds and Kamphaus 2004), Achenbach Child Behavior Checklist (Achenbach 1991), and the Strengths and Difficulties Questionnaire (Goodman, 1997). As these behavior assessments are mostly developed for use in Western populations, the cross-cultural suitability should be checked before use. Next to reports and questionnaires, child behavior can also be observed. For example, standardized instruments designed to assess behavioral dimensions through a series of episodes that mimic everyday situations can be used. Examples are the Laboratory Temperament Assessment Battery (Lab-TAB; infancy to middle childhood; Gagne et al. 2011) and the Neonatal Behavioral Assessment Scale (Brazelton and Nugent 2011).

**Table 4.** Minimum reporting requirements for human milk studies.

Study Aspect	Details
Collection methods	Date and time of sample collection Expression method (hand expression, type of pump, sterility) Volume of milk collected in sample Fore or hind milk, mid-feed or full mammary evacuation
Storage conditions	Temperature Duration Number of freeze-thaw cycles
Laboratory analysis methodology	Sample preparation Materials and equipment information, such as assay kit brand, etc. Standards used to quantify
Key participant metadata	Parity Infant age in days/weeks Infant sex Gestational age of infant at birth Maternal medication and supplement use
Data Analysis	Mean or median, standard deviation, and range of milk components analyzed Number of samples replicated per plate and across plates Number of milk samples analyzed per participant and duration between sample collection Variation based on sample collection (ex. Time of day of collection, infant age) Between and within individual variation in component measured Method for accounting for variation between samples (ex. across wells within plates and between plates), along with the calculated variation and percent of samples outside of the acceptable range of variation and excluded from analysis
Child outcome	Reference of the behavioral and/or cognitive assessment Assesment procedure, including number of items/questions/tasks Information on training and reliability of tester

Note: All variables should include average, SD, and/or SEM for interpretation and meta-analysis purposes.



**Figure 4.** Strategic plan to advance the field of research on human milk. Pursuing these goals and sub-goals will help fill important gaps in knowledge and, in the future, provide a solid theoretical and methodological basis for streamlined and cost-efficient research.

### Minimum reporting requirements

Table 4 presents a list of study characteristics that ideally should be included in all studies of human milk. These recommendations for researchers on minimal reporting issues for human milk studies and analyses are meant to ensure that the quality of reporting is high, the research is replicable, and that the data can eventually be re-used, e.g., integrated to that of other studies for meta-analytic purposes. It may not always be possible to follow gold standard practices in every research setting, but detailed high-quality reporting of processes is fundamental for understanding study results.

### Open questions and innovative ideas

Our understanding of human milk research has come a long way in the past 20 years; however, there is still much that we do not know. Also, despite having a growing number of studies with persuasive results, we cannot yet state that there is compelling scientific evidence that unequivocally demonstrates that breast milk affects offspring behavior and builds better cognition. As discussed in the *Assessment of child cognitive and behavioral development* section, many of the tools used to date may be too coarse to detect subtle effects on developmental outcomes that are quantitatively impacted by early nourishment. Additionally, despite much having been established regarding analysis (McGuire and

O'Connor 2020), methodological studies are still needed to refine our knowledge on the stability of milk components across lactation, days and feeds, optimal storage and thawing protocols, and methods to analyze the different components. Finally, it is important to keep in mind that a large amount of the current knowledge on human milk comes from WEIRD societies. In fact, while we do not know how this impacts human milk composition studies, there is evidence across other fields that samples derived from WEIRD societies might not be adequate for generalizations across all populations (Henrich et al. 2010). To develop a richer literature on the science of human milk, including other populations in this field of research is necessary. However, research designs will need to be adapted to suit different populations.

In [Figure 4](#) we present a strategic plan to cultivate and advance the field of research on human milk. This plan will aid in filling relevant gaps in knowledge, hence providing the necessary solid basis, both theoretical as well as methodological, for internationally streamlined and cost-efficient future research. In time, results will contribute to designing prevention, intervention, and policy for infants and their families. In the following sections, several relevant and innovative sub-goals of this strategic plan are discussed in more detail.

### **Pumping**

An important question to investigate in this context is whether pumping milk impacts its composition. There are many reasons why mothers pump their milk, including breastfeeding issues, trying to increase milk supply, and because of returning to work. Previous studies have shown that women's pumping and milk storage practices vary greatly (Felice et al. 2017a, 2017b; O'Sullivan, Geraghty, and Rasmussen 2017). Therefore, pumping can be hypothesized to alter milk composition. Indeed, an in-home, randomized, crossover trial of two collection methods indicated that milk collected with mothers' own supplies yielded more Proteobacteria, including higher relative abundances of *Acinetobacter* and *Stenotrophomonas*, compared to milk collected with (sterile) hospital supplies (Reyes et al. 2021). Moreover, in-depth, semi-structured interviews to investigate maternal attitudes and perceptions toward pumping indicate that, although pumping fills important roles and enables continued breastfeeding success, many mothers reported it to be time-consuming, costly, and unpleasant, compared to the infant feeding at the breast (Felice et al. 2017a). Whether and how these negative attitudes and perceptions toward pumping affect milk composition remains a question for future research.

### **Donated milk and pasteurization**

The process of pasteurization is also in need of more research. As mentioned before, in clinical settings, donated human milk is often used to replace the mother's milk when it is unavailable. In order to provide a safe product, most

centers require that donated milk is pasteurized before administration. However, while the most commonly used heat treatment, Holder Pasteurization (i.e., milk heated to 62.5°C for 30 minutes), has a minimal effect on the macronutrient content, it can impact several functional aspects of human milk by deactivating enzymes and destroying immune cells and other factors (Ewaschuk et al. 2011; Peila et al. 2016). Promising alternatives to Holder Pasteurization are being tested in lab settings (see Pitino et al. 2019; Wesolowska et al. 2018; Wesolowska et al. 2019). Given the large impact of pasteurization on minor but likely important bioactive milk constituents, future efforts should focus on improving the pasteurization process or alternatively, the donor screening process, to enable better preservation of the biological functional aspects of donor human milk while ensuring safety.

### **Data modeling and study designs**

A large portion of the work to date has been done on isolated or small groups of milk constituents. New methodologies in systems biology will assist in integrating multiple components in human milk with other biological, social and psychological inputs. We recommend taking a comprehensive and trans-disciplinary approach to analyze human milk composition (i.e., targeted and exploratory approaches to assess nutritive and non-nutritive components) and to apply statistical techniques, such as cluster analyses and machine learning, to integrate and analyze these datasets (Munblit et al. 2017; Shenhav and Azad 2022). Additionally, to be able to develop first comprehensive models unveiling causality and mechanisms, there is a dire need for deeply phenotyped longitudinal studies with a large number of repeated assessments. These studies will also help shed light on the critical windows for lactocrine programming of child cognitive and behavioral outcomes.

### **Comparative models**

Comparative models can also shed light on causality and mechanisms underlying lactational programming. Specific constituents of milk, including proteins, carbohydrates, and lipids, are common to the primary mammalian lineages (Langer 2009; Oftedal 2012). Genomic studies indicate that there are several conserved milk proteins and other elements of the lactome in monotreme, marsupial and eutherian mammals (Lefèvre, Sharp, and Nicholas 2010). To further understand the complex interactions between milk components and their implications for offspring cognition and behavior, we recommend identifying and using carefully selected experimental animal models to manipulate milk components and test the impact on offspring behavior and neurodevelopment. In biology, the comparative method facilitates organization of information and recognition of unique and conserved patterns in nature (Martinez 2018). Milk composition varies significantly among mammalian species, and studies designed to compare milk composition are complicated by the fact that milk composition differentially

changes throughout lactation (Langer 2009; Oftedal 2012; Park 2009; Park and Haenlein 2006; Sharp et al. 2017).

Sharp and colleagues (2014) observed that efforts to define the functions of milk bioactives, and to identify functional components of milk that affect lactocrine programming of organ development, can benefit from the use of comparative mammalian models that display extreme adaptations to lactation. In this regard, marsupials may be especially valuable. In contrast to the situation in eutherian mammals (including humans), the majority of development in marsupial young occurs postnatally and is supported exclusively by milk bioactives (Nicholas et al. 2019; Sharp et al. 2014; Sharp et al. 2017). Further, in contrast to eutherian milk, which remains relatively unchanged in composition throughout lactation (Langer 2009), milk composition in both marsupial and monotreme mammals changes systematically throughout lactation. This provides a natural model system for identification of unique and conserved roles of milk bioactives in lactocrine programming of organ development, including the central nervous system. In marsupial pouch young both the brain and spinal cord develop rapidly in offspring during the first 100 days of milk consumption (Harrison and Porter 1992; Saunders et al. 1989; Sharp et al. 2014). Insights into the role of lactocrine-active milk bioactives in regulation of central nervous system development will benefit markedly by studies designed to exploit comparative methodologies.

### **Maternal and child factors**

The influence of maternal factors, especially psychological and genetic characteristics, on milk composition is still a field with limited research. Additionally, we know little on how maternal pregnancy health and physiology impact the mammary gland (e.g., placenta-to-mammary pathway) and milk composition. Moreover, investigations have shifted to an even earlier period, the pre-conception period, to better understand the role of this formative period on human health and disease (Keenan et al. 2018). Prior to conception, the health status of the mother, including aspects related to her diet and well-being, is an important determinant of pregnancy outcomes, maternal perinatal health, and child development. Questions on how maternal pre-conception factors are associated with breastfeeding and milk composition remain to be answered in future studies. Moreover, relatively little work has been done on human milk to understand how child factors (e.g., birth order, birth outcomes, infant temperament and behavior) contribute to variation in milk composition.

### **Formula and applied research**

One example of an area of application is infant formula production and regulation. Infants might be fed formula for various reasons, including medical indications and adoption. Human milk research will lead to advancements in formula manufacturing, including the ability to optimize formula composition based on infant age, sex, or specific health

needs. Outcomes for formula-fed infants can be better served with evidence-based formula design (Kent 2014). Another area for future applied research is that of personalized nutrition for breastfeeding mothers. As discussed before (*Maternal diet* section), what a mother eats will importantly impact her milk composition, and in turn, most probably her infant's physical, cognitive, and behavioral development. Depending on maternal factors (e.g., mental and physical health and age), as well as on infant factors (e.g., age, sex, and physical health), personalized nutrition advice as well as personalized food supplements may be developed to optimize maternal well-being and lactation, and infant physical and mental development. Finally, an innovative area of application using the knowledge gleaned from how milk components stimulate healthy brain development in infants, is to develop future food supplements designed to prevent or treat cognitive decline in the elderly.

### **General conclusion**

This narrative review presents a complex picture of the current state of knowledge on human milk, as well as its relevance in scientific studies. It constitutes a tantalizing window into the role of human milk and its components in the development of neurological processes and cognitive performance in infants. Several conclusions can be drawn. First, human milk is a tailored nutrition that varies over time, between persons, and with maternal and child factors. Second, there is highly compelling emerging evidence that breast milk is central in nourishing, protecting, and guiding neurological development in human infants. Third, potential effects and mechanisms of lactocrine programming on child cognition and behavior are starting to be uncovered.

The review also offers both practical and theoretical recommendations to advance this emerging area of research. Cultivating the body of research on human milk is important in the face of development of future interventions and policy for (breastfed) infants and their families. Research aimed at highlighting the cost of stressors and lack of support for human milk production and composition has the power to inspire social and political support for improvements in breastfeeding opportunities and enhancement of families' social, physical, psychological, and environmental context.

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Writing - Original Draft, HL: Writing - Original Draft, NHMS: Writing - Original Draft, SEM: Writing - Original Draft, SP: Writing - Original Draft, JMR: Writing - Original Draft, Visualization, CMS: Writing - Original Draft, ST: Writing - Original Draft, Visualization, JBVg: Writing - Original Draft, AZ: Writing - Original Draft, RB: Writing - Review & Editing, Visualization, Supervision, Funding acquisition.

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## Appendix A. Glossary.

**16S Sequencing** amplification of specific bacteria gene, 16S rRNA, by use of sequencing methodologies (Sanger, next generation sequencing) that allow the adequate bacterial phylogeny and taxonomy assignment. The 16S rRNA gene is commonly used for phylogenetic studies as it is highly conserved between different bacterial species.

**Available milk energy (AME)** determined by the milk's energy density (the kilocalories derived from protein, carbohydrate, and fat concentrations) and the amount of milk that mothers produce.

**Colostrum** is the first form of milk produced by the mammary glands immediately following delivery of the newborn. Colostrum has especially high amounts of bioactive compounds compared to mature milk. Specifically, colostrum contains antibodies to protect the newborn against disease and infection, and immune and growth factors, and other bioactives that help activate the newborn's immune system, jumpstart the gut function, and seed a healthy gut microbiome in the first few days of life.

**Culturomic approach** is a high-throughput approach based on the isolation and grow of different microorganisms with different culture media and conditions.

**Donor milk** is defined as human milk expressed by a mother that is processed by a donor milk bank for use by a recipient that is not the mother's own infant.

**Eutherian mammals** 'Placental mammals' (including humans) - represent the largest of three branches or clades of mammals. The others include Metatheria (Marsupials) and Prototheria (Monotremata). All eutherian mammals have a chorioallantoic placenta. In eutherian mammals, maternal energy invested in developing young prenatally (through the course of gestation via the placenta) and postnatally (via lactation and milk) is roughly equal. By contrast, marsupial gestation is brief and lactation is extended (Abbot and Capra 2017).

**Fear reactivity** Depicts propensity to express distress in response to sudden changes in stimulation or novel social or nonsocial stimuli.

**Fore milk** Milk produced toward the beginning of feeding.

**Heavy metals** Metals with relatively high densities, atomic weights, or atomic numbers. Within this large group, chromium, arsenic, cadmium, mercury, and lead have the greatest potential to pose a health threat on account of their extensive use and widespread distribution in the environment.

**Hind milk** Milk produced toward the end of feeding.

**Human milk oligosaccharides (HMOs)** a group of complex carbohydrates (sugars) that after lactose and lipids represent the third most abundant components of human milk and are thought to impact infant health and development through microbiome-dependent and -independent mechanisms.

**Lactational Programming** Aspects of the biobehavioral exchange between mother and baby, including nursing patterns and the communication of both nutrient and signaling molecules in milk, through which offspring development is orchestrated.

**Lactocrine** A mechanism through which milk-borne bioactive factors are delivered from mother to offspring by consequence of nursing.

**Lactocrine Programming** Effects of lactocrine-active factors (e.g., milk-borne bioactive factors) on the developmental program of cells, tissues and organs in nursing offspring that have lasting effects on form, function and/or health and well-being in adulthood.

**Lactome** The entire set of genes that contribute to production of milk.

**Life-history theory** Life-history theory describes the basic principle for a living organism in maximizing its fitness and reproduction throughout life in diverse environmental conditions, by making decision for energy or resources allocation used for one over the another life functions (growth, reproduction, storage and maintenance (including repair)).

**Marsupial mammals** Marsupialia - are a distinct class of mammals endemic to Australasia and the Americas. Included in this group are kangaroos, wallabies, koalas and opossums. Relative to eutherian mammals, marsupial mammals display short gestational periods and comparatively longer lactational periods during which a great deal of

offspring development occurs supported by lactation and milk (Abbot and Capra 2017).

**Mastitis** is inflammation of the breast or udder, usually associated with breastfeeding. Symptoms typically include fever, local pain and redness. Onset is typically fairly rapid and usually occurs within the first few months of delivery.

**Mature milk** Milk produced around the later stages of lactation (around 3–4th week of postpartum), once lactation has become fully established.

**Metagenomics** is the analysis of the total DNA recovered from a milk sample by use of next generation sequencing

**Microchimerism** The presence of somatic cells within one individual that originate from another, genetically distinct individual. Maternal microchimerism can occur through lactocrine transmission of maternal somatic cells to nursing offspring.

**Milk bioactives (milk-borne bioactive factors)** Non-nutrient components in human milk that comprised immune components, hormones, naturally occurring opiates, enzymes and many other active molecules.

**Moiety** A functional subgroup of a molecule.

**Monotreme mammals** Monotremata - 'egg-laying mammals' - include the echidna and duck-billed platypus (Abbot and Capra 2017).

**Multi-lineage potential** The property of (embryonic and/or adult) stem cells to develop into different types of cells depending upon micro-environmental conditions as defined in vitro or in vivo.

**Negative emotionality** One of the three main dimensions of temperament, which describes individual differences in predisposition to experience negative emotions (such as sadness, frustration and fearfulness), and includes the threshold, intensity, and duration of emotions (Rothbart 2007).

**Next generation sequencing** is the technology that allow a massively parallel sequencing of DNA and RNA from different samples.

**Parent-offspring conflict** The conflict arising between parents and offspring regarding investment of resources (including time and effort) given divergent investment optima for maximizing fitness (Trivers 1974).

**Pasteurization** is a process in which milk is usually treated with mild heat to eliminate pathogens and extend shelf life.

**Persistent organic pollutants (POPs)** Chemical compounds resistant to environmental degradation through chemical, biological, and photolytic processes, and frequently used as pesticides, solvents, pharmaceuticals, and industrial chemicals.

**Polymerase Chain Reaction (PCR)** is a technique used to "amplify" specific segments of DNA such as 16S rRNA regions or whole gene.

**Prebiotic** Non-digestible compounds in food (usually consisting of sugars, fibers, and carbohydrates) that induce the growth or activity of microorganisms such as bacteria and fungi.

**Probiotic** Live microorganisms that, when consumed in adequate amounts, confer a health benefit on the host organism.

**Transitional milk** produced after colostrum, starting about 2–5 days post-delivery, and present mature milk is produced.

**WEIRD populations** Populations that come from Western, Educated, Industrialized, Rich, and Democratic societies.

## Appendix B. Abbreviations in the text

- Ara (arachidonic acid)
- AME (available milk energy)
- BMI (body mass index)
- DHA (docosahexaenoic acid)
- DNA (Deoxyribonucleic acid)
- GCs (glucocorticoids)
- HMOs (human milk oligosaccharides)
- HPA axis (hypothalamic-pituitary-adrenal axis)
- Ig (immunoglobulin)
- IQ (intelligence quotient)
- LC-PUFA (long-chain polyunsaturated fatty acids)
- Lf (lactoferrin)

- MbFs (milk-borne bioactive factors)
- MFGM (milk fat globule membranes)
- RCT (randomized controlled trial)
- PCR (polymerase chain reaction)
- POPs (persistent organic pollutants)

### Box 1. Human milk composition: the basics

#### Human milk composition: the basics

Given the importance of human milk for infants and its long-term health benefits, significant research has been performed to understand the complexities of human milk and the factors modulating its composition (e.g., stage of lactation). Depending on the stage of lactation, human milk is most often differentiated into three categories: colostrum, transitional milk, and mature milk. Colostrum is the first fluid produced by mammary glands immediately after birth, and it provides high concentrations of essential nutrients (i.e., proteins, lipids, carbohydrates and micronutrients). Colostrum also contains many other components including immunologic factors, growth factors, and signaling peptides. Colostrum is known to carry different commensal bacteria (including species from the *Lactobacillus* and *Bifidobacterium* genera), that have been recognized for helping to establish and shape the infant's immune system and to develop a healthy microbiome (Fernández et al. 2020; Neville 2001). As breastfeeding continues, the immunoglobulins and protein/nitrogen concentrations decrease, changing colostrum into transitional milk, present from day 7 to 14. At around 2 weeks postpartum human milk changes from transitional to mature milk (Ballard and Morrow 2013; Ruiz et al. 2019).

In contrast to colostrum and transitional milk, mature milk exhibits less compositional variability. However, it is thought that more subtle, but possibly biologically relevant, changes occur over the remainder of lactation (Ballard and Morrow 2013). Mature milk composition varies over the course of the day. For example, the concentration of fats and hormones (e.g., cortisol, melatonin) changes

significantly during the 24-hour period (see Table 1). Also, the composition of mature milk varies within a feed. As such, mature milk is categorized into fore milk - produced toward the beginning of a feeding- and hind milk -- produced toward the end of a feeding, and containing possibly 2–3 times higher fat than fore milk (Bishara et al. 2009). Note that maternal and child factors, as well as the interplay between both, play an important role in dictating the composition of milk (see *Maternal factors*, *Child factors*, and *Interplay of maternal-child factors* sub-sections), and that variations over the course of lactation, the course of the day, and/or across feeds have not yet been studied for all milk components.

A way of characterizing overall human milk composition is by the Available Milk Energy, or AME, that refers to the energy output of human milk. On average, human milk contains 0.62 kcal/ g (2.6 kJ/g) energy (Reilly, Ashworth, and Wells 2005). The main source of energy in human milk is fat (see Table 1). Mature milk contains more energy than colostrum (Gidrewicz and Fenton 2014). It was believed at one point that milk energy content was relatively stable during the first year of lactation (Nommsen et al. 1991; Saarela, Kokkonen, and Koivisto 2005). However, there is preliminary evidence that mothers who breastfeed for over one year produce milk with higher fat and energy content (Mandel et al. 2005). Due to the changes in fat content discussed above, day and evening samples are more energy dense than night or morning samples (Moran-Lev et al. 2015; Paulaviciene et al. 2020). Moreover, energy content changes during the feed as hind milk contains more energy than fore milk (Saarela, Kokkonen, and Koivisto 2005).

Human milk energy content is affected by pregnancy duration (Mills et al. 2019), and by child characteristics as well as maternal factors (see *Factors affecting milk constituents* section). In comparison to a non-pregnant woman, a breastfeeding woman requires approximately 500 more kcal/day. The total volume of milk produced by a mother is nearly 780 mL/day (range 450–1200 mL/day), and the energy content of the milk ranges between 60 and 70 kcal/100 mL. Therefore, a breastfeeding mother who uses her nutrient stores will lose 0.5–1.0 kg/month after the first postpartum month (Kominiarek and Rajan 2016).