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The contributions of parental lactation on offspring development: It's not udder nonsense!☆

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ABSTRACT

The Developmental Origins of Health and Disease (DOHaD) hypothesis describes how maternal stress exposures experienced during critical periods of perinatal life are linked to altered developmental trajectories in offspring. Perinatal stress also induces changes in lactogenesis, milk volume, maternal care, and the nutritive and non-nutritive components of milk, affecting short and long-term developmental outcomes in offspring. For instance, selective early life stressors shape the contents of milk, including macro/micronutrients, immune components, microbiota, enzymes, hormones, milk-derived extracellular vesicles, and milk microRNAs. In this review, we highlight the contributions of parental lactation to offspring development by examining changes in the composition of breast milk in response to three well-characterized maternal stressors: nutritive stress, immune stress, and psychological stress. We discuss recent findings in human, animal, and *in vitro* models, their clinical relevance, study limitations, and potential therapeutic significance to improving human health and infant survival. We also discuss the benefits of enrichment methods and support tools that can be used to improve milk quality and volume as well as related developmental outcomes in offspring. Lastly, we use evidence-based primary literature to convey that even though select maternal stressors may modulate lactation biology (by influencing milk composition) depending on the severity and length of exposure, exclusive and/or prolonged milk feeding may attenuate the negative *in utero* effects of early life stressors and promote healthy developmental trajectories. Overall, scientific evidence supports lactation to be protective against nutritive and immune stressors, but the benefits of lactation in response to psychological stressors need further investigation.

1. Introduction

Maternal milk is a complex, heterogenous biological fluid that shapes development and is the primary source of nutrition for most newborn mammals (Eisha et al., 2022). The World Health Organization (WHO) recommends that individuals breastfeed exclusively, if possible, for the first six months of life, and when possible, breastfeed along with food supplementation for the first two years of life or longer (WHO, 2022). In humans, milk composition is highly dynamic and changes across lactational age and circadian cycles to meet the energetic and immune demands of offspring (le Huërou-Luron et al., 2010; Paulaviciene et al., 2020). Milk is also a medium, whereby mother and offspring communicate and coregulate physiological, biochemical, and molecular

responses postpartum (Verduci et al., 2021).

Human milk is classified into three main categories based on lactational age and the gradual alteration in composition: stage 1) colostrum milk, which is produced immediately and up to 5 days postpartum, stage 2) transitional milk, which is typically produced from 6 to 15 days postpartum and stage 3) mature milk which is produced after 15 days postpartum (Aydin et al., 2006). Colostrum varies from mature milk in terms of the proportion of nutritive and bioactive components (Andreas et al., 2015). Colostrum milk has low concentrations of energy-dense lactose and fats, low potassium and calcium, and higher levels of sodium, chloride, and magnesium than later milks (Pang and Hartmann, 2007). Colostrum is also rich in non-nutritive bioactive components, including immune factors (e.g., secretory immunoglobulin, human milk

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oligosaccharides – HMOs), growth factors (e.g., epidermal growth factor – EGF), a complex microbiome with >200 different bacterial species (Fernández et al., 2013), and milk-derived extracellular vesicles (MEVs) (El-Loly, 2022; Ross et al., 2021). The primary role of colostrum milk is to protect infants as they adapt to their new non-sterile extrauterine environment (Andreas et al., 2015). Transitional milk shares characteristics of colostrum but represents a junctional period in human lactation where “ramped up” milk production takes place to support rapid infant development. The transition is characterized by tight junctional closure in the mammary gland epithelium, a decline in sodium-to-potassium ratio, and an increase in lactose levels (Ballard and Morrow, 2013). Mature milk contains higher quantities of nutritive macro- and micronutrients to keep pace with the rapid extrauterine offspring development, while the percentage of immune and growth factors are lower compared to the levels found in colostrum (Andreas et al., 2015; Godhia and Patel, 2013).

Breast milk contains essential macronutrients including lipids, carbohydrates, and proteins (Boquien, 2018; Pietrzak-Fiećko and Kamelska-Sadowska, 2020; Sharp et al., 2015). Lipids account for approximately 50% of the total energy in breast milk with a majority of lipids being triglycerides (Pietrzak-Fiećko and Kamelska-Sadowska, 2020; Yi and Kim, 2021). In addition to their importance in nutrition, lipids are also essential for inflammatory responses and neurodevelopment and function (e.g., arachidonic acid, and docosahexaenoic acid (DHA)) (Giuffrida et al., 2022). Carbohydrates also provide a significant source of energy for the offspring (approximately 40%) (Pietrzak-Fiećko and Kamelska-Sadowska, 2020). Lactose is the most abundant carbohydrate and is broken down into glucose and galactose to generate ATP through glycolysis and the tricarboxylic acid cycle (Gridneva et al., 2019; Yi and Kim, 2021). Breast milk proteins are produced by lactocytes (milk producing cells in the mammary epithelium) or are up taken from maternal circulation, and consist of caseins, whey proteins, and regulatory proteins and peptides (Andreas et al., 2015). Breast milk proteins play vital roles in offspring growth and development, including providing nutrition, aiding in the digestion and absorption of other nutrients, and providing antimicrobial protection and immune regulation (Andreas et al., 2015; Yi and Kim, 2021). Over the first four to six weeks of lactation, protein levels in breast milk decrease, while lipids and carbohydrates increase after the first two weeks, independent of milk volume (Bauer and Gerss, 2011).

Breast milk is also a great source of micronutrients (Lockyer et al., 2021). Select vitamins found in breast milk, include but are not limited to, vitamin A, which is involved in ocular function, bone development, and cell differentiation (Maia et al., 2019); thiamin (vitamin B-1), a coenzyme in carbohydrate metabolism; vitamin B-6, a cofactor for multiple enzymes involved in glycolysis and gluconeogenesis; folate, which is involved in DNA, RNA and protein biosynthesis, epigenetic regulation; and vitamin C which enhances antibody production and helps strengthen neonatal immunity (Dror and Allen, 2018; Hampel et al., 2018). Levels of thiamin, vitamin B-6 and folate are low in colostrum and increase over the first few weeks postpartum, while vitamin C is highest in colostrum and decreases over the lactational period (Dror and Allen, 2018). Select minerals found in breast milk include iron for hemoglobin synthesis; copper for cellular respiration; calcium for bone development and modulation of cell-signaling pathways (Dror and Allen, 2018; Hampel et al., 2018); and zinc for DNA and RNA metabolism, gene expression and signal transduction (Hambidge and Krebs, 2007). Levels of iron, copper and zinc are highest in colostrum and decline between the first six to twelve months of lactation (Doneray et al., 2017; Dror and Allen, 2018; Salgueiro et al., 2002). Calcium levels rapidly increase within the first five days postpartum and decline throughout the remainder of lactation (Dror and Allen, 2018).

In addition to a complex mix of nutritive components, breast milk contains non-nutritive bioactive compounds that modulate offspring development, including hormones, growth factors, a complex microbiota, immune factors, HMOs, MEVs, and small and long non-coding

RNAs (Eisha et al., 2022; Sharp et al., 2015; Vass et al., 2019). Important hormones found in breast milk include the anorexigenic hormone leptin that acts on the arcuate nucleus of the hypothalamus to decrease appetite and regulate energy expenditure, thus playing a significant role in hypothalamic pathway development in neonates (Savino et al., 2009; Vásquez-Garibay et al., 2019); the orexigenic hormone ghrelin, which acts as an antagonist to leptin, stimulates the arcuate nucleus to increase food intake and is implicated in long-term weight regulation (Vásquez-Garibay et al., 2019; Yiş et al., 2010); and adiponectin, which is involved in the metabolic regulation of fatty acids and conveys anti-inflammatory properties (Martin et al., 2006; Mohamad et al., 2018).

Major growth factors present in breast milk include neuronal growth factors (e.g., brain-derived neurotrophic factor and glial cell-line derived neurotrophic factor), which are implicated in the development of the enteral nervous system (Ballard and Morrow, 2013; Bardanzellu et al., 2020); the insulin-like growth factor (IGF) superfamily (IGF-I and IGF-II) for tissue growth, inhibition of cell death, and the stimulation of erythropoiesis (Mazzocchi et al., 2019); and epidermal growth factors (EGF) which aid with the maturation and repair of the intestinal mucosa by stimulating enterocytes in the small and large intestines to increase DNA and protein synthesis, and increase the absorbance of water and glucose in the gastrointestinal tract (Nolan et al., 2020).

Neonatal adaptive immunity is established through maternal-infant interactions at birth (vaginal delivery in particular) and postpartum via milk transfer (Field, 2005; Pai et al., 2018). Breast milk is a great source of anti-microbial compounds (e.g., immunoglobulins, lactoferrin, oligosaccharides), immune components (e.g., macrophages, lymphocytes, milk peptides) and anti-inflammatory compounds (e.g., cytokines, long-chain polyunsaturated fatty acids) (Field, 2005). Examples of other crucial immune factors include secretory immunoglobulin A (SIgA), the predominant antibody in breast milk which binds to pathogens (e.g., *Escherichia coli*, rotavirus) to prevent them from adhering to the infant's intestinal mucosa (Kosaka et al., 2010); lactoferrin, an antimicrobial glycoprotein with a high affinity to iron that exerts both bacteriostatic and bactericidal effects on pathogens (Yang et al., 2018); cytokines such as tumor necrosis factor α (TNF α), interleukin-1 β (IL-1 β), and interferon- γ (IFN- γ) which can have immunomodulatory roles, recruit neutrophils, decrease infection rates, and increase intestinal development (Ballard and Morrow, 2013; Nolan et al., 2020; Yi and Kim, 2021). Other important immunomodulatory factors found in breast milk include leukocytes, lymphocytes, T cells, and stem cells (Nolan et al., 2020).

Human milk oligosaccharides (HMOs) are the third most abundant macromolecule in breast milk (5–15 g/L in mature milk), after lactose and fat (Bode, 2012). HMOs are structurally composed of five monosaccharides: glucose, galactose, fucose, *N*-acetylglucosamine, and sialic acid, usually *N*-acetylneuraminic acid (Bode, 2012; Ray et al., 2019). HMOs are not digested by infants for nutritive purposes but serve a variety of critical biological functions and influence developmental trajectories (Thongaram et al., 2017). HMOs modulate infant immune system, aid neurodevelopment, act as signaling molecules to improve gut immunity, act as anti-inflammatory and pro-survival factors, provide defense against pathogens and infections, and act as prebiotics to stimulate the colonization of beneficial microorganisms in the gastrointestinal (GI) tract (Bode, 2012; Boquien, 2018; Lagström et al., 2020; Ray et al., 2019). Given their importance in GI tract establishment and developmental modulation, two HMOs, 2'-fucosyllactose (2'FL) and lato-*N*-neotetraose (LNnT) are now being supplemented to select infant formula (Lagström et al., 2020). Biological functions of HMOs are thoroughly discussed elsewhere (see Bode, 2012, 2019).

Neonatal microbiomes are developed during the birthing process, via milk transfer, as well as from environmental and maternal exposures post-parturition (Duale et al., 2022; Yao et al., 2021). The offspring microbiome is sensitive to early life factors such as maternal diet, delivery method (i.e., vaginal birth or caesarian section), breastfeeding methods (exclusive or supplemented breastfeeding, direct feeding, or bottle feeding), and the household environment (Pannaraj et al., 2017).

Some common microorganisms that colonize the GI tract of breastfed neonates include *Bifidobacterium* spp. and *Lactobacillus* spp., which are in high proportion during early postnatal life, and *Bacteroides* spp. and *Firmicutes* spp., which begin increasing as the infant matures (Fallani et al., 2010; Yao et al., 2021).

Breast milk is also rich in milk-derived extracellular vesicles (MEVs) (Chen et al., 2016). MEVs are small, lipid-coated nanovesicles that range from 30 to 150 nm in diameter (Reif et al., 2019). A majority of MEVs are secreted by mammary gland epithelial cells and carry biologically functional cargo including small non-coding RNA, mRNA, DNA, lipids, peptides, and hormones (Chen et al., 2016; Manca et al., 2018; Reif et al., 2019). Small, noncoding milk-derived microRNA (miRNA) in particular can influence gene expression, cell proliferation, cell differentiation, cell-signaling, regulation of cell death, metabolism, neural circuits, and immune regulation in infants (Chen et al., 2017a, 2017b; Feng et al., 2021; García-Martínez et al., 2022; Hock et al., 2017; Jiang et al., 2021). An *in vitro* study comparing the biological effects of MEV miRNA supplementation in control colon epithelial cells (CCD 841) compared to colon tumor cells (LS123) found that MEV miR-148a promotes cellular proliferation in CCD 841 cells, whereas in tumor LS123 cells miR-148a inhibits proliferation (Reif et al., 2019). Furthermore, a study by Guo et al. (2022) compared the effects of MEV and MEV miRNA supplementation in intestinal epithelial cells and in a necrotizing enterocolitis mouse model. They reported that independent supplementation of MEVs and MEV miR-148a-3p protected both systems against chronic inflammatory damage and NEC progression (Guo et al., 2022). Thus, MEV miRNAs are shown to be important for modulating epigenetic and developmental cascades (Abuaish et al., 2020b; Guo et al., 2022; Hock et al., 2017; Izumi et al., 2014; Reif et al., 2019).

The Developmental Origins of Health and Disease (DOHaD) hypothesis describes how maternal exposures and stress experienced during critical periods of perinatal life by the offspring (collectively defined as the prenatal and postnatal periods) are linked to altered developmental trajectories with later life implications (Heindel and Vandenberg, 2015; Makris et al., 2022; Malik and Spencer, 2019; Mandy and

Nyirenda, 2018). Examples of potent perinatal insults that can mediate developmental trajectories include maternal over- or undernutrition (Makris et al., 2022; Mandy and Nyirenda, 2018), immune activation (Mandy and Nyirenda, 2018), and maternal psychosocial stress (Makris et al., 2022). These maternal stressors not only affect the health of the mother, they also increase offspring's risk of developing congenital defects: spina bifida, heart disease (Leddy et al., 2008); metabolic diseases: obesity, type II diabetes, cardiovascular disease, chronic kidney disease (Glastras et al., 2018); neurodevelopmental disorders: attention-deficit/hyperactivity disorder, autism spectrum disorders, developmental delays, intellectual disability (Davis and Mire, 2021); neuropsychiatric disorders: depression, schizophrenia (Davis and Mire, 2021); and chronic inflammation (Glastras et al., 2018). Perinatal stress also induces changes in maternal milk with short and long-term developmental outcomes in offspring (Bozack et al., 2021; Shah et al., 2021).

In this review, we highlight the contributions of parental lactation to offspring development during key periods of early postnatal life by examining changes occurring in the composition of milk in response to three well characterized maternal stressors: 1) nutritive stress, 2) immune stress, and 3) psychological stress (Fig. 1). We discuss recent findings in human, animal and *in vitro* models, their clinical relevance, study limitations, and potential therapeutic significance to improving human health and infant survival. We also discuss the benefits of enrichment methods and support tools that can be used to improve the quality and volume of breast milk as well as related developmental outcomes in offspring. Lastly, we hope to convey that while exposure to perinatal stress may result in adverse developmental outcomes in neonates, as communicated in part through changes in milk composition, the overall pro-survival effects conferred by milk feeding during critical periods of development likely compensate for the maternal stress-specific changes to select milk components. As such, the type of maternal stress, potency, time of exposure, and duration should be taken into consideration when assessing developmental impacts of maternal stress and milk transfer.

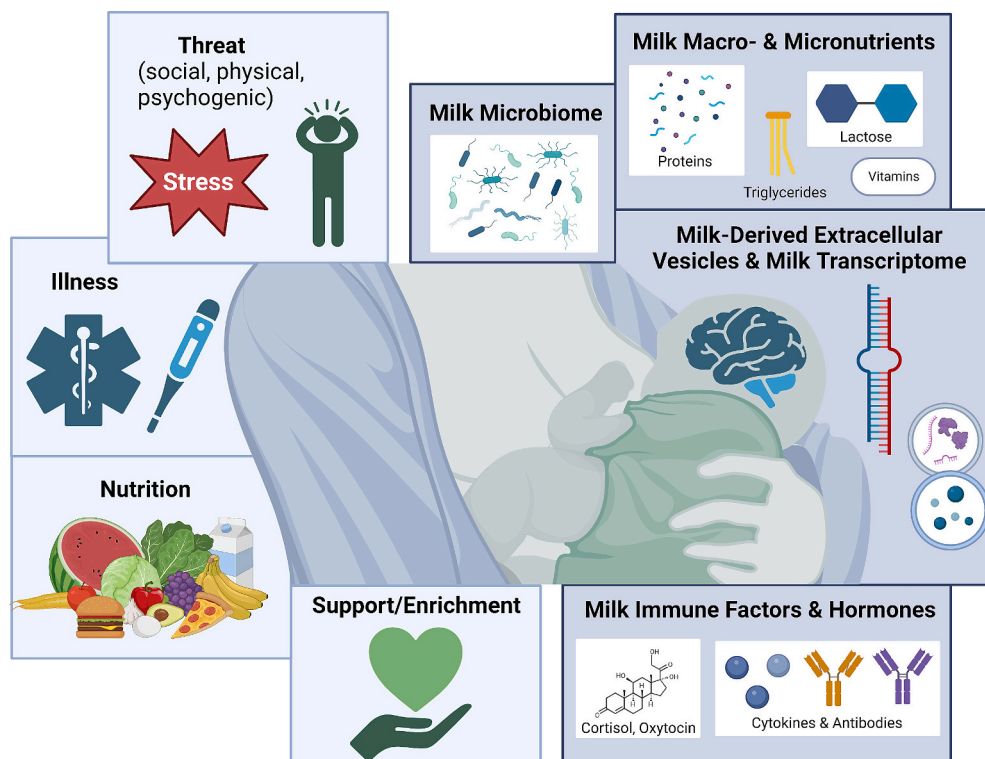


Fig. 1. Illustrative depiction of selective stressors and support systems on breast milk composition. Changes occur in the composition of milk through the milk microbiome, milk micro- and macronutrients, milk-derived extracellular vesicles and transcription factors, and milk immune factors and hormones.

2. Impact of maternal diet on milk composition & offspring development

Maternal obesity and maternal diet, in particular the increased consumption of saturated fats during the perinatal period can alter the nutritional and non-nutritional composition of milk. In rodents, the milk of obese dams has increased fat and insulin concentration, when compared to lean rat dams (Ahuja et al., 2011). In humans, breast milk of mothers with obesity and/or overweight status, categorized by the body mass index (BMI) > 25, contain higher total fat, glucose, insulin, adipokine hormones, leptin, and adiponectin (Aydin et al., 2008; Barbosa et al., 1997; Newburg et al., 2010; Savino and Liguori, 2008). Maternal milk also conveys developmental programming effects. Developmental programming is the process by which an event occurring during a critical period of development results in long-term or permanent effects on the structure and function of an organism (Lucas, 1998). In mammals, developmental programming begins during gametogenesis and continues through fertilization, gestation, and lactation (Edwards et al., 2021). Cross fostering rodent studies show that with lactation-only exposure to a maternal high fat diet (mHFD), neonates born to control, metabolically healthy dams, exhibit increased body weight and a non-alcoholic fatty liver by 3 months of age and develop metabolic syndromes as adults (Howie et al., 2009). When neonates of obesity-resistant dams were cross fostered soon after birth to dams with diet-induced obesity, the offspring exhibited increased adiposity and reduced insulin sensitivity as adults and were prone to developing type II diabetes (Gorski et al., 2006). Studies have also shown that the breast milk of mothers with obesity has elevated levels of pro-inflammatory cytokines (Panagos et al., 2016), low levels of neuroprotective carotenoids (Hahn-Holbrook et al., 2019), and altered immunological profiles (Erliana and Fly, 2019). Immunological components of milk and maternal immune activation are discussed in Section 3. Likewise, maternal nutrient stress during lactation lead to irregular metabolic imprinting, a higher tendency to gain bodyweight, increased visceral fat deposition, and the development of metabolic, inflammatory, and neurodevelopmental disorders in offspring (Bautista et al., 2016; Buonfiglio et al., 2016; Dietz, 1997; Gillman, 2008). Further, exposure to mHFD during gestation and lactation, leads to sex-specific physiological, epigenetic, endocrine, and immune programming in offspring that continues to adulthood, long after the initial exposure (Bilbo and Tsang, 2010; Sasaki et al., 2013, 2014). In particular, Wijenayake and colleagues reported that mHFD male offspring exhibit enhanced pro-inflammation, and mHFD female littermates exhibit enhanced anti-inflammation in key regions of the HPA axis that modulates stress in response to an acute immune challenge (lipopolysaccharide-induced) and physiological (corticosterone-induced) stress in adulthood (Wijenayake et al., 2020). Interestingly, neonatal studies have shown that female rat offspring are generally more sensitive to perinatal mHFD exposure at postnatal day 7, immediately following the stress-hyporesponsive period (Abuaish et al., 2018; Abuaish et al., 2020a; Abuaish et al., 2020b). The stress-hyporesponsive period is a developmental stage during which neonatal rodents exhibit a reduced response to maternal stress and is marked by a significant reduction of adrenocorticotropin and corticosterone levels (Walker and Vrana, 1993). Together, these studies demonstrate that maternal diet may influence milk composition, which in turn may shape the developmental trajectories and life-long health outcomes in offspring.

2.1. The effects of maternal diet on proteins

Human milk proteins are unlikely to be influenced by amino acid intake through diet (Ding et al., 2010). However, a recent prospective longitudinal study of human milk macronutrients reported that gestational age at birth and duration of lactation between very preterm (<32 gestational weeks), preterm (32–37 gestational weeks), and term (37–42 weeks) infants significantly affected breast milk protein content

and levels of individual proteins, while other macromolecules (e.g., lactose) and total energy content remained unchanged in the samples (Caldeo et al., 2021). In particular, higher protein levels were reported in preterm and very preterm milk samples at 0–7 days and 1–2 months post birth and plasmin activity (a major fibrinolytic protease) was higher in very preterm milk. This study shows that although maternal diet may not be a crucial determinant of energy providing proteins, alternate maternal factors and early life stress may modulate protein milk content and contribute to the dynamic and heterogeneous nature of human milk.

2.2. The effect of maternal diet on lipids

Human milk contains an outer milk fat globular membrane (MFGM) and a core portion of nonpolar lipids, including triglycerides, cholesterol esters, retinyl esters, and other lipophilic fats. Triglycerides are most sensitive to changes in maternal diet and constitute 98% of fatty acids in milk (Innis, 2014). Triglycerides can originate from maternal stores (long chain fats), dietary intake (medium chain fats), and *de novo* synthesis in the mammary glands (fats with <14 carbons) (Koletzko, 2016). Some of the earliest and seminal studies on MFGM and milk fatty acids reported that 1) levels of n-6 and n-3 omega fatty acids and mono-unsaturated fats in milk is directly dependent on maternal lipid consumption, 2) that dietary fatty acids are swiftly transferred into breast milk post dietary intake, and 3) increased consumption of fats can radically change the fatty acid composition of milk within 2–3 days (Bautista et al., 2016; Insull et al., 1959). *Trans*-fats and long chain poly-unsaturated fats (LC PUFAs) in breast milk are also directly correlated to maternal dietary intake (Innis, 2014; Jonsson et al., 2015; Samur et al., 2009) and metabolic status (Puentes et al., 2019). Rodent studies confirmed these earlier findings and illustrated that lactating rat dams on HFD had increased saturated fatty acids and lower n-3 PUFA in milk throughout lactation (Innis, 1991; Priego et al., 2013). Changes in fatty acid composition of milk due to increased maternal trans fatty acid consumption is implicated in altered behavior in rodent offspring. The Morris water maze is a behavioral test that assesses spatial and related forms of learning and memory on distal cues to navigate around the perimeter of an open swimming arena to locate a submerged escape platform (Vorhees and Williams, 2006). Spatial memory was affected in both male and female HFD offspring, albeit at different stages of post-natal development where a significant decrease in latency to find the escape platform was reported for males on day 4 of testing, whereas females were worse on day 2 (Santos de Souza et al., 2011). There was also reported aggregation of trans fatty acids in the hippocampus of offspring with HFD lactational exposure. Wuben et al. (2001) reported similar findings whereby offspring born to mothers that were on a 22% trans fatty acid diet during gestation and lactation exhibited significantly lower reversal learning in the water maze.

In humans, a compelling intersecting study characterizing the fatty acid composition of milk between US women (consuming mostly processed foods) and Bolivian women (consuming forager-horticulture diets with only 2% of energy generated from processed foods) reported that milk from Bolivian women had 50% lower levels of trans-fats and more than 3-fold higher DHA (Martin et al., 2012). Further, Puentes et al. (2019) analyzed how maternal obesity affected fatty acid profiles in breast milk (in particular DHA) and their association with infant growth and cognition. They used 78 mother-offspring dyads and reported that breast milk collected from mothers with obesity has increased saturated fats and n6:n3 ratio, lower levels of DHA, arachidonic acid, and alpha-linolenic acid, and infant cognition was directly influenced by the levels of these lipids in breast milk. DHA is a LC PUFA that is critically important for neurodevelopment (Zielinska et al., 2019). Although results are still inconclusive, recent studies have strongly suggested that breastfed children have increased cognition, better brain structural development, and greater grey and white matter compared to formula fed children. These positive effects have been attributed to LC PUFAs and carotenoids (especially lutein) in milk

(Deoni et al., 2013; Isaacs et al., 2010; Jing et al., 2010; Khedr et al., 2004). Nevertheless, strong experimental evidence supports the importance of milk-based DHA transfer during key periods of early postnatal development.

A study in baboons showed that DHA accumulates in high concentration throughout the neonatal CNS, particularly in grey matter of the basal ganglia and cerebral cortex in milk fed neonates but was significantly lower in formula fed neonates (Diau et al., 2005). Similar findings were reported in humans where exclusively formula fed infants were shown to have 15% lower DHA in the brain cortex (Makrides et al., 1994) and fortification of infant formula with DHA lead to improved developmental outcomes in offspring, including improved cognition and visual acuity (Lien et al., 2018). A notable functional trend in the CNS regions richest in DHA is that these brain regions are primarily associated with attention, motor control, and sensory integration. A recent human milk cohort study from Japan reported that the DHA concentration in human milk is influenced by maternal dietary intake, where increase consumption of grilled fish by lactating mothers lead to increased abundance of milk DHA (Ueno et al., 2020). Interestingly, milk DHA concentration in breast milk of Japanese women is reported to be historically higher than most other women, when controlled for DHA supplementation, due to sociodemographic factors. Further, recent studies in humans and laboratory animals suggest that even a small deficit in DHA can impair motor function and strongly encourages mothers to consume LC-PUFA enriched foods, such as salmon, and exclusively breastfeed for a minimum of 6 months with supplemental breastfeeding for up to 1–2 years (Champoux et al., 2002; Voigt et al., 2002). As per a community-based cohort study from South Dakota (USA), the key to ensuring pregnant and lactating women consume 200 mg of DHA per day is educating mothers about dietary DHA intake and their own levels. In a subset of 60 mothers, median breast milk DHA content increased from 0.19% to 0.22% post-education (Juber et al., 2016).

2.3. The effects of maternal diet on milk micronutrients

Milk micronutrients including, iron, vitamin A, zinc, vitamin B-6, vitamin B-12, vitamin D, folate, iodine, and selenium are sensitive to maternal nutrition (Innis, 2014). Iron is the most abundant trace element in the human body due to its close association with hemoglobin (60%), myoglobin (5%), heme and non-heme enzymes (5%) and transferrin (<1%). However, human breast milk has very little iron compared to maternal serum (0.8 µg/mL in colostrum and 0.2–0.4 µg/mL in mature milk) (Cai, 2015). Although the iron content in human milk is generally low, the biological importance of that small amount is substantial. Indeed, studies have shown that breast milk iron has high bioavailability (Saarinen et al., 1977) and for exclusively breastfed term infants with normal birth weight, the amount of iron received from breast milk is adequate to avoid iron deficiency during the first 6 months of life (Dewey and Chaparro, 2007). Iron deficiency in infants can interfere with the development of the central nervous system, myelination, neuronal and glial energy metabolism, and monoamine neurotransmitter function (Lönnerdal, 2017). Maternal diet is an important mitigator of iron levels in infants (Domellöf et al., 2004). The percentage of bodyfat in lactating women was negatively correlated to the concentration of iron in breast milk, meaning that women with overweight/obesity status generally have lower levels of breast milk iron (Mello-Neto et al., 2009). A similar association was also reported for vitamin A in breast milk in Brazilian and Kenyan cohort studies (Ettyang et al., 2005; Mello-Neto et al., 2009). Vitamin A in breast milk is necessary for growth, differentiation, immunological functions, and bone remodeling in infants (Tanumihardjo et al., 2016). Human milk minerals and their biological significance have been discussed in detail elsewhere (see Jenness, 1979; Boquien, 2018; Dror and Allen, 2018).

2.4. The effects of maternal diet on Human Milk Oligosaccharides (HMOs)

HMOs are highly sensitive to maternal BMI and diet. Lagström et al. (2020) reported a strong direct association between 2'FL levels and pre-pregnancy BMI as well as child height and weight z scores during the first 5 years in a model adjusted for maternal pre-pregnancy BMI, mode of delivery, birthweight z score, sex, and time. On the contrary, LNnT levels were inversely correlated. Given this was an observational study, the authors provide evidence for associations rather than causal relations. They postulate that the strong relationship between HMOs, maternal BMI, and child growth may involve the healthy development of the infant gut microbiota, given that HMOs are known to promote the growth of probiotic organisms such as *Bifidobacteria* spp. (Borewicz et al., 2019). Conversely, Seferovic et al. (2020) reported that maternal diet is a driver of milk HMO composition and short and long-term changes to maternal diet led to rapid alterations of individual HMOs in breast milk, when controlled for maternal genotype, BMI, diet, geography, mode of delivery, and maternal antibiotic use. Maternal obesity was also associated with lower levels of fucosylated and sialylated HMOs, that are critical for GI tract development and permeability (Saben et al., 2021). Sialylated HMOs also program cognitive development in the hippocampus and prefrontal cortex. Milk deficient in sialic lactose (6'SL) was associated with alterations in hippocampal electrophysiology, gene pathways regulating the serotonergic system, long-term and spatial memory, and learning in rodents and piglets (Hauser et al., 2021; Obelitz-Ryom et al., 2019; Oliveros et al., 2018; Wang et al., 2007). On the contrary, a recent cross-sectional analysis of HMO composition of vegan, vegetarian, and nonvegetarian lactating women showed that lactating women who consume plant-based diets do not produce different HMO profiles in breast milk (Neville et al., 2022). However, a majority of the participants in the study were reported to take dietary supplements. As such, the findings should be understood within the context of dietary supplementation. Future population-based studies involving ethnically diverse participants with varying maternal age, mode of delivery, and dietary preferences are required to understand the extent of HMO dependency on maternal diet and long-term neurodevelopmental consequences in offspring.

2.5. The effects of maternal diet on milk-derived extracellular vesicles and milk transcriptome

Supplementation of infant formula with MEVs prevent the development and progression of necrotizing enterocolitis (NEC), a debilitating intestinal disease largely affecting premature babies (5–7%), where chronic intestinal inflammation leads to necrosis and creation of perforations (holes) in the gut (Alganabi et al., 2019). Although independent of its association with prematurity, maternal nutritional status is a major antenatal risk factor for prematurity and adverse outcomes associated with prematurity, including systemic inflammation, development of NEC, neurodevelopmental deficits, and behavioral anomalies in children (Carmichael et al., 2017; Helderma et al., 2012; Singh et al., 2016; van der Burg et al., 2015). A recent study by Hock et al. (2017) illustrated that rat MEVs when supplemented into intestinal epithelial cells increased viability, enhanced proliferation, and simulated stem cell activity in a NEC model. Similarly, Miyake et al. (2020) illustrated using intestinal organoids, that human MEVs lead to attenuation of inflammation and *in vivo* a significant reduction of NEC induced mucosal injury, inflammation, and mucous production. These findings are corroborated by other *in vitro* and *in vivo* studies showing beneficial and pro-survival properties of MEVs (Gao et al., 2019; He et al., 2021; Li et al., 2019).

The question remains, how do MEVs convey beneficial effects to the recipient and is it the small non-coding RNA cargo that mitigates biological functions given human milk is one of the richest sources of miRNAs? Abuaiash et al. (2020b) attempted to address this question

using a mHFD (60% saturated fats) Long Evans rat model, where they characterized the abundance of candidate milk miRNAs (miRNA-148/152 family) in the brain of female offspring with perinatal mHFD exposure at postnatal day 7, immediately after the stress hyporesponsive period. They found that exposure to mHFD altered the abundance of miRNA 148/152 levels in the stomach milk and the brain following milk feeding and that these changes in milk miRNA levels were directly associated with DNA methylation patterns in the neonatal brain. In particular, they reported reduced miRNA 148-3P levels in the brain, increased DNA methyltransferase 1 (DNMT1) transcript abundance, increased DNMT1 enzymatic activity, and a global increase in DNA methylation. miRNA-148-3P is a direct post-transcriptional regulator of DNA methyltransferase enzymes and control DNMT translation, insulin signaling, and adipogenesis (Goedeke et al., 2015; Huff et al., 2020; Mirra et al., 2018). They also assessed genome-wide DNA methylation at single nucleotide resolution using reduced representation bisulfite sequencing (RRBS) in the same females. Gene ontology analysis of differentially methylated regions identified cellular processes relating to organismal development, neurodevelopment, gene expression, metabolism, inflammation, cell secretion, and signal transduction in the brain. Similarly, a human cohort study involving 30 normal weight and 30 overweight mothers-infant dyads at 1-, 3-, and 6-months post-partum found that the abundance of miRNA-148a is negatively associated with infant weight, fat mass, and fat-free mass at 1-month post-partum. Moreover, Pomar and colleagues investigated the impact of cafeteria-diet feeding during lactation on miRNA levels in breast milk and found that a cafeteria diet leads to substantial alterations in milk miRNA levels, and this may alter the translation of target transcripts and potentially affect offspring phenotype (Pomar et al., 2019). A cafeteria diet involves feeding experimental animals a choice of human food items to stimulate energy intake (Rothwell and Stock, 1988). Studies have also reported direct associations between mHFD, changes in milk miRNA content, and transcriptional changes in offspring. In particular, Huff and colleagues showed that mHFD not only affected the mRNA and miRNA content of the secreted milk, but also showed evidence of changes in the duodenal proteome of offspring as a direct result of the transcriptional changes (Huff et al., 2020). Cheng and colleagues investigating the effect of mHFD on the mid-lactation transcriptome in C57BL6 mice, reported that mHFD alters the expression of genes involved in inflammation, lipid metabolism, and immune responses in mid-lactation mammary glands (Cheng et al., 2018). Overall, these studies illustrate that maternal diet influences the composition of MEVs and milk miRNAs and these changes could shape developmental outcomes in offspring.

2.6. The effects of maternal diet on maternal care provisions and lactation performance

Human and rodent studies demonstrate that maternal nutritional status greatly impacts maternal care behavior and lactation dynamics (Connor et al., 2012). As an example, mHFD induces maternal prolactin resistance. Prolactin is a hormone released by the anterior pituitary gland in response to stimuli (e.g., suckling), stress, reproduction, ovulation, and lactation (Bole-Feysot et al., 1998). Prolactin is critical for mammary gland development and milk production (Kelly et al., 2001; Ormandy et al., 1997), as well as for regulating maternal care behaviors in humans and rodents (Dobolyi et al., 2014; Lucas et al., 1998). Increases in prolactin resistance as a result of mHFD led to a 33% reduction in milk volume, approximately 10% reduction in the glandular tissue area of the mammary glands that promote mammapoiesis, and a decrease latency to retrieve pups back into the nest in the mHFD group, compared to control dams (Buonfiglio et al., 2016). No statistically significant differences between control and mHFD dams were reported for other maternal care behaviors such as latency to crouch over the pups to initiate feeding or latency to contact the pups. Further, initiation of lactation was shown to be delayed in mHFD mothers, with a notable decrease in intact alveolar units that are important for

lactogenesis (Buonfiglio et al., 2016). There were also significant decreases in the mRNA expression of milk protein genes, including glucose transporter 1 (GLUT1) and keratin 5 (K5), and a significant increase in cell markers that indicate premature mammary gland involution such as 5-HT (7) receptor (Hernandez et al., 2012). Mammary gland involution is the process by which lactocytes are actively removed from the mammary gland when they become redundant, typically post-weaning (Watson, 2006). They also reported elevated levels of the pro-inflammatory cytokine interleukin-6 and tumor necrosis factor alpha in the mammary glands.

In terms of maternal care behavior, interesting results were reported by Purcell et al. (2011) and Abuaiish et al. (2018) in mHFD dams compared to control dams (Abuaiish et al., 2018; Purcell et al., 2011a). Generally, mHFD dams spend more time nursing their pups and mHFD offspring consume more milk during the first postnatal week. A seminal study on nutrition and maternal care provisions by Bertino (1982) reported similar findings, where rodent dams on a high fat and high protein diet (HPD) exhibited increased postural nursing, pup grooming, and spent more time attending to the litter compared to control dams (Bertino, 1982). This is likely a compensatory measure to alleviate the effects of delayed lactation and changes in nutritive and non-nutritive components of maternal milk that is crucial for promoting early-postnatal development (Eisha et al., 2022).

2.7. Benefits of breastfeeding for offspring metabolic health

Although studies have associated maternal diet and metabolic status with changes in select milk components, exclusive and/or supplemented breastfeeding is proposed as a solution to attenuate risks of developing obesity/overweight status in children. We recognized this discrepancy and explored the literature for evidence-based studies to determine if breastfeeding can help reduce obesity and adipogenesis in the mother and/or offspring and how that compares to exclusive formula feeding. This is an important area to explore because, according to reports, women with obesity have higher chances of earlier formula supplementation and are at increased risk for premature breastfeeding cessation (Marshall et al., 2019; Hauff et al., 2014; Donath and Amir, 2008; Kitsantas and Pawloski, 2010). This is largely due to mammary gland hypoplasia, reduced stromal tissues (Flint et al., 2005), flattened areolas, edema (Katz et al., 2010), and hormonal dysfunction that delays lactogenesis (ex: prolactin deficiency) (Buonfiglio et al., 2016). However, formula does not mimic the bioactive non-nutritive profiles of milk that is dynamic and heterogeneous and is catered to meet the developmental demands of offspring (Martin et al., 2016).

What do evidence-based studies tell us about the impact of maternal obesity and breastfeeding? *In vivo* studies on rodents and human cohorts have illustrated that milk feeding provides short and long-term pro-survival benefits to offspring and under select maternal stress, can even lead to a “rescue phenotype” that reverts *in utero* exposures. A cross-sectional study involving 2515 mother-offspring dyads from 9 different Greek rural and urban regions were used to evaluate the role of breastfeeding on maternal and childhood bodyweight and obesity. The study found that 68% of women exclusively breastfed their children for a minimum of 4 months and this was associated with a two-fold lower risk for maternal and childhood overweight/obesity for 2-5 years from delivery, independent of maternal age, education, and socioeconomic status (Mantzorou et al., 2022). Additionally, a study of 1330 infants as part of the Western Australian Pregnancy Cohort (Raine) reported that the age at which exclusive breastfeeding was stopped and the age at which formula was introduced played a significant role in the trajectory of BMI from birth to adolescence. Interestingly, they found that infants who were exclusively breastfed for more than 4 months but were introduced to formula later had BMIs in the healthy range, whereas infants who experienced mixed feeding (breast milk and formula) at less than 4 months had higher BMIs and unhealthy dietary behaviors at adolescence (Chivers et al., 2010). Similar findings were also reported

by a recent scoping review that critically analyzed 25 studies spanning 12 countries and a total of 226,508 participants on the risk of childhood obesity and breastfeeding. They found a dose response effect between breastfeeding duration and reduced risk of childhood obesity. The authors commendably conducted a sensitivity analysis to minimize variability in BMI categorization of the mothers and children across the 25 studies. They also defined the differences between “exclusive breastfeeding”, “ever breastfed”, “never breastfed”, and “mixed fed” to reduce ambiguity in vernacular used across studies (Yan et al., 2014). These findings are corroborated by several other studies that identify breastfeeding as a protective factor for childhood obesity and cardiometabolic dysfunction (Ferreira et al., 2010; Labayen et al., 2012; Metzger and McDade, 2010).

Therefore, although maternal metabolic status may shape select components of milk, exclusive milk feeding (directly from the breast or pump-and-feed) is highly recommended for mothers. We also stress that it is vital to provide tailored breastfeeding support for mothers with obesity in the hospital, immediately post-birth, with modified feeding and latching positions and tips to increase milk let-down. Indeed, studies have found that breastfeeding education and support is strongly associated with higher rates of breastfeeding initiation, successful latching, and continued exclusively breastfeeding (Pérez-Escamilla et al., 2016; Fair et al., 2019).

3. The effect of immune stressors on breastfeeding

3.1. What happens to the body during illness?

Severe inflammation due to pathogens, physical injury, or chronic health conditions can cause or contribute to what is colloquially known as illness. Illness is characterized by fever, general malaise, and exhaustion as the body uses energy to generate an immune response. Inflammation concentrated in a specific area of the body leads to the experience of common symptoms of sickness, such as a sore throat or a runny nose. When a virus, bacteria, or other pathogen enters the body, the immune system responds by deploying inflammatory cells, including macrophages and lymphocytes (B cells, T cells, natural killer cells) that are responsible for ingesting harmful foreign particles and mobilizing immune defenses to minimize damage to the body (Hirayama and Nakase, 2017; Medzhitov, 2010). Macrophages produce cytokines, which are molecules that help orchestrate these inflammatory responses (Duque and Descoteaux, 2014). Cytokines are found in breast milk and are able to cross the placental and blood brain barriers (Dawod and Marshall, 2019; Iqbal et al., 2012; Wu et al., 2017). In addition to the cytokine response, B cells work to ensure that the body is prepared to defend itself against reinfection in the future. Antibodies are proteins made by B cells that can identify and neutralize previously encountered pathogens. However, neonates are unable to produce many of these immune responses. The neonatal immune system is bolstered by antibodies and other immunological factors transferred through breast milk (Witkowska-Zimny and Kaminska-El-Hassan, 2017).

Inflammation during perinatal life has been linked to preterm birth, low birth weight, disrupted infant development and later life health impacts, and increased maternal morbidity and mortality (Shafiq et al., 2021; Hirshberg and Srinivas, 2017). The recent spread of SARS-CoV-2, the virus that causes Coronavirus disease (COVID-19), has led to a renewed interest in the consequences of illnesses that occur during pregnancy and lactation. Due to the novelty of this virus, early in the pandemic physicians struggled to provide guidance to pregnant and lactating individuals asking how to care for themselves and their children. Similar to viruses such as influenza and Zika (Antoniou et al., 2020; Wang et al., 2021; Yu et al., 2022), we now know that undergoing COVID-19 during pregnancy can be detrimental to the health of the mother as well as the developing fetus (Wei et al., 2021; Atyeo et al., 2021; Edlow et al., 2022). Fortunately, studies show that immunity to many pathogens, including COVID-19, is passed to the developing fetus

through the placenta *in utero* and through breast milk after birth, and that breast milk does not transmit the virus to the baby (Quitadamo et al., 2021; Atyeo et al., 2021; Duncombe et al., 2021; Narayanaswamy et al., 2022; Young et al., 2022). This highlights how a developing immune system can be supported through breastfeeding. Indeed, genomic, and proteomic data confirm that people who have received an mRNA COVID-19 vaccine and/or contracted the illness transmit antibodies to their offspring through milk; therefore, people with COVID-19 should be encouraged to breastfeed (Zhu et al., 2021; Bauerl et al., 2022). The CDC recommends mothers with diagnosed Covid-19 infections, who choose to continue breastfeeding, wash hands before breastfeeding and wear a mask while nursing (CDC, 2022).

3.2. How does illness influence maternal and neonatal health?

Most people will endure acute illnesses without experiencing long-term consequences. However, individuals are more vulnerable to the effects of pathogens during critical periods of early development, including during pregnancy, lactation, and neonatal life (Yu et al., 2022). The immune system undergoes adaptations during these periods to account for the health of the baby in addition to the self (Groer et al., 2015; Aghaeepour et al., 2017). For example, a delicate balance must be struck so that a pregnant person's immune system does not attack the developing fetus (PrabhuDas et al., 2015). While these adaptations allow for the general success of the pregnancy, they also lead to an increased risk of complications and illness in both the baby and the birthing person when exposed to pathogens (Yu et al., 2022). In addition, the baby's immune system is immature during gestation and the early lactational period, and therefore unable to launch effective defenses against many infectious agents. Studies show that illness during pregnancy can alter neurodevelopment; fetuses exposed to the Zika virus *in utero* are born with smaller than normal brains (Antoniou et al., 2020). Infection during pregnancy is also associated with an increased risk for the offspring to develop neurodevelopmental disorders in later life, including autism and schizophrenia (Estes and McAllister, 2016; Han et al., 2021). A recent study of 7772 births found that 6.3% of the 222 babies exposed to SARS-CoV-2 *in utero* were diagnosed with a neurodevelopment disorder in the first year of life, whereas only 3% of unexposed babies received a diagnosis during the same period (Edlow et al., 2022). Maternal inflammation during pregnancy has also been linked to changes in brain connectivity and deficits in cognitive measures, such as working memory among toddlers (Rudolph et al., 2018).

This risk of illness continues into the postnatal period when sepsis, an extreme inflammatory response to infection, accounts for over 20% of maternal deaths in the United States (Hensley et al., 2019). Infection in neonates also has long term consequences on neurodevelopment and behavior (Stoll et al., 2004; Rand et al., 2016). Rand et al. (2016) found that babies born prematurely who experienced an infection while hospitalized were more likely to have motor impairments, attention deficit hyperactivity disorder (ADHD), and delays in cognition at nine years of age, compared to preterm infants that did not experience infection. In a longitudinal study that followed participants into adulthood, Lapidaire et al. (2022) showed that neonatal infection in preterm infants was linked to lower scores on IQ tests at age seven and age thirty. Neonatal sepsis in babies with low birth weight has also been associated with behavioral problems in preschool aged children, especially among males (Giordano et al., 2022). Unfortunately, illness during the early neonatal/lactational period is common, especially in low resource settings (Karolinski et al., 2010; Hussein et al., 2011). Health issues can sometimes necessitate separation of the caregiver and baby. However, uncoupling during this critical developmental interval can have detrimental effects on a baby's ability to breastfeed and bond with their caretaker (Bartick et al., 2021). A physician should be consulted, but it is often safe to continue breastfeeding while ill, as long as precautions are taken to prevent transmission (see section 3.7). If it is possible to continue breastfeeding or expressing milk for bottle feeding, breast milk can

provide crucial immune support to babies exposed to infections in early life.

3.3. Antibodies in breast milk

Individuals develop antibodies against pathogens they are exposed to, whether through vaccination or infection. These antibodies are then passed to offspring *in utero* and through breast milk after birth (Lönnerdal, 2013). Recent studies demonstrate that neutralizing antibodies are present in babies breastfed by a parent that was either previously infected by or vaccinated for SARS-coV-2 (Duncombe et al., 2021; Young et al., 2022; Narayanaswamy et al., 2022). The primary protective antibody found in human breast milk is SIgA (Hurley and Theil, 2011; Andreas et al., 2015). Although present in milk at concentrations much lower than SIgA, immunoglobulin (Ig) G and IgM also help to protect against infections in neonates (Akhter et al., 2021). SIgA and IgM are associated with the mucosal immune system, which protects the mucosal membranes of the intestines and respiratory system (Brandtzaeg, 2003; Brandtzaeg, 2010). When a breastfeeding person has an infection, antibody levels are elevated in their breast milk (Groer et al., 2004). For this reason, breastfeeding allows babies to ward off infections such as COVID-19 and Giardia (Fatimah et al., 2022; Tellez et al., 2003; Verd et al., 2021). IgG, the least abundant antibody in breast milk, is anti-inflammatory and helps to tag foreign pathogens for elimination by phagocytes (Agarwal et al., 2011).

The maternal gastrointestinal tract contains bacteria that will seed the gut microbiota of the infant, and many of the SIgA and IgG antibodies in breast milk are directed against these microbes (Brandtzaeg, 2010; Sanidad et al., 2022). Studies in mice have shown that failure to receive SIgA or IgM through breast milk in early life is associated with abnormal microbial communities and increased susceptibility to gut inflammation later in life (Rogier et al., 2014; Sanidad et al., 2022). The gut interacts with the brain, and gastrointestinal inflammation has been linked to the development of mental illness, including autism, schizophrenia, anxiety, and depression (Clapp et al., 2017; Severance et al., 2015; Kim et al., 2022). In summary, antibodies passed through breast milk are important for the baby's current and future health.

3.4. Other immunological factors in breast milk

In addition to antibodies, breast milk contains oligosaccharides, cytokines, and other immunological factors that confer protection to the infant (Erney et al., 2000; Oddy et al., 2003; Quitadamo et al., 2021). When a breastfeeding caretaker becomes infected during the postnatal period, the number of leukocytes in milk rises to confer active immunity in the infant, a response that returns to baseline levels upon recovery (Hassiotou et al., 2013). Breast milk leukocytes destroy harmful microorganisms and secrete antimicrobial agents, including antibodies and cytokines, to protect the infant (Witkowska-Zimny and Kaminska-El-Hassan, 2017; Hassiotou et al., 2013). Human milk feeding, whether directly from the birthing person or from milk provided by a donor bank (a service that collects, screens, and dispenses by prescription donated human breast milk), has been shown to decrease the likelihood of neonatal infection and subsequently improve cognitive performance in adulthood (Lapidaire et al., 2022). HMOs may directly support cognitive development (Sprenger et al., 2022; see Section 2.4). Increased breast milk sialyllactose, an HMO that contains sialic acid, during infancy was also associated with greater language and cognitive development in toddlers (Oliveros et al., 2021; Cho et al., 2021). Sialic acid is important for synapse formation and neural transmission (Schnaar et al., 2014), which may account for the differences in cognitive performance between breastfed and non-breastfed populations.

3.5. Can a sick baby change the immunological composition of breast milk?

Breast milk not only changes when the caretaker is ill, but it also changes composition when the baby is sick. If an infant becomes infected before their breastfeeding caretaker, the IgA concentration in breast milk does not change, but the number of white blood cells (macrophages and leukocytes) and tumor necrosis factor- α (TNF- α) in the milk are increased (Riskin et al., 2012; Hassiotou et al., 2013). Macrophages and leukocytes in human milk have been shown to kill potentially harmful pathogens such as *Escherichia coli*, *Staphylococcus aureus*, *Giardia lamblia*, and *Candida albicans* (Robinson et al., 1978; Honorio-França et al., 1997; França-Botelho et al., 2006). TNF- α is secreted from macrophages and elevated levels have been shown to downregulate expression of lipid processing proteins, including lipoprotein lipase which is necessary for converting triglycerides into fatty acids and glycerol for transport into mammary cells (Walker et al., 2022). This immune response in breast milk is present even when the mother remains asymptomatic when their baby is sick (Hassiotou et al., 2013). While it cannot be discounted that changes in breast milk occur because the lactating person is themselves fighting off an infection (although asymptomatic), the breast milk changes may be a physiological response catered towards the needs of the infant to combat infection. It is hypothesized that the health status of the infant is transmitted to the breastfeeding person through the baby's saliva when nursing (Hassiotou et al., 2013). This transfer could occur at the end of milk ejection when pressure is decreasing and a small amount of milk and saliva flow backward into the breast (Ramsay et al., 2004), triggering a localized immune response in the breast milk. Due to these dynamic immune functions, breast milk provides considerable protection during the neonatal period. In addition, infants may breastfeed at more frequent intervals while sick, which can help reduce the risk of dehydration (Paintal and Aguayo, 2016) and increase caretaker and infant interaction and bonding. Oxytocin is a peptide hormone that allows for milk let-down ejection, but also promotes bonding and decreases stress through reduction of the stress steroid hormone cortisol (Krol and Grossmann, 2018). For this reason, breastfeeding can provide both immune and emotional support for an infant during illness.

3.6. Preclinical models of maternal immune activation

In preclinical animal models, maternal immune activation (MIA) can be simulated by administering the bacterial endotoxin lipopolysaccharide (LPS; Borrell et al., 2002) or the viral mimic polyinosinic: polycytidylic acid (Poly I:C) to rodent dams. LPS stimulates a bacterial-like innate immune response by activating Toll-like receptor 4, which promotes the release of proinflammatory cytokines such as interleukin (IL)-1 β and IL-6 (Ashdown et al., 2006). Similarly, Poly I:C stimulates a viral-like innate immune response by activating Toll-like receptor 3 (Matsumoto and Seya, 2008). These models of MIA result in transient sickness phenotypes characterized by low activity levels, reduced feeding and grooming, fever, and piloerection (Dantzer, 2001; Fortier et al., 2004).

While numerous studies have investigated the effects of gestational MIA on offspring health and development (Bao et al., 2022), few studies have examined the effects of MIA occurring during the lactational period. Nascimento et al. (2015) found that LPS administered on postnatal day 3 caused rat dams to retrieve their pups more slowly and decreased the frequency of ultrasonic vocalizations among pups on postnatal day 5, suggesting that interactions between the mother and her pups were altered by MIA. DeRosa et al. (2022a) administered LPS to dams on postnatal day 10 and performed transcriptome analyses on breast milk to examine potential changes in gene expression after MIA. Results indicated that genes responsible for oxytocin and glucocorticoid signaling were differentially expressed between dams that were exposed to LPS and those that were not. Genes related to glucocorticoid signaling were generally downregulated, while genes related to oxytocin were upregulated in MIA dams. They also found that the quality of maternal

care did not differ between MIA and control dams during the sickness period. Interestingly, licking and grooming of pups the following day was drastically increased among MIA dams. This is notable as rat offspring that receive high levels of licking and grooming during the neonatal period have reduced blood corticosterone levels in response to acute stressors in adulthood, compared to offspring of low licking and grooming dams. Furthermore, increased licking and grooming is associated with greater glucocorticoid receptor expression in brain areas that provide negative feedback to the HPA axis, governing stress hormone production and release (Liu et al., 1997). Essentially, the heightened maternal care offered through elevated licking and grooming the day following MIA challenge could have long-lasting effects on offspring stress responsivity (Denenberg, 1964; Meaney and Szyf, 2005). In the DeRosa et al. (2022a) study, the upregulation in oxytocin could be responsible for the increase in pup-licking observed the day after MIA challenge and may serve as a compensatory mechanism to prevent undesirable effects of MIA on offspring. Pups in this study still went on to display altered behavior on measures of mechanical allodynia, sensorimotor gating, and social behavior, but it is possible that this compensatory increase in maternal care helped decrease the magnitude of these effects.

Other studies have also investigated the effects of LPS-induced MIA on milk nutrition and content. Ling and Alcorn (2010) found that LPS administered to rat dams on postnatal days 4, 11, and 18 affected milk production and quality by downregulating milk precursor molecules such as glucose, L-carnitine, and fatty acid transporters in mammary glands. Glucose and fatty acids are needed to produce sufficient levels of lactose, oligosaccharides, and triglycerides in the milk (Cheema et al., 2021; Ramiro-Cortijo et al., 2020) while L-carnitine is necessary for neonates to use fatty acids as energy substrates (Borum et al., 1987). Therefore, downregulation of these precursor molecules could have a detrimental effect on milk nutrition, which could impact neonatal development. DeRosa et al. (2022a) administered LPS on postnatal day 10 and observed an immediate increase in the stress steroid hormone corticosterone in milk samples, which returned to baseline levels by the following day. On postnatal day 11, triglycerides and percent creatinotrit, an indicator of fat concentration and energy content of milk, were reduced in milk of LPS-treated dams, suggesting that the nutritive components of milk were decreased in response to MIA. Compared to offspring of untreated dams, offspring of LPS-treated dams went on to have greater body weights in adolescence, which is correlated with poor early life nutrition (Lalanza et al., 2014).

Breast milk also contains microbes that help populate neonatal gut bacteria (Pannaraj et al., 2017). DeRosa et al. (2022a) showed that microbiome communities in milk were affected by MIA. Analysis revealed nine differently abundant taxa on postnatal day 10 and six on day 11. Among the taxa identified, *Pseudomonadaceae* and *Christensenellaceae* were more abundant on day 10 in the milk of MIA dams compared to unexposed dams. *Pseudomonadaceae* has been shown to be elevated in the large intestine of pregnant mice with low blood triglycerides (Connor et al., 2018). Additionally, Hibberd et al. (2019) reported a negative correlation between *Christensenellaceae* and blood triglyceride levels in humans. Doerfler et al. (2022) found that a majority of breast milk cells die during digestion in the stomach, but commensal bacteria, proteins, and antibodies may be more resilient and therefore able to survive in the neonate. In a study of adults, microbiome differences were present in individuals that were breastfed as babies compared to those that had never been breastfed, demonstrating the long-lasting effects of breast milk on microbial communities (Ding and Schloss, 2014). The formation of the gut microbiome during infancy has long term effects on the health and immunity of the individual (Pannaraj et al., 2017). Perturbations in the gut microbiome have been associated with chronic diseases, including autoimmune diseases, gastrointestinal inflammatory conditions, and neurological illnesses (Vijay and Valdes, 2022). As such, it is important to investigate the effects of lactational MIA on microbial communities in offspring.

3.7. Summary of recommended guidelines for breastfeeding during illness

To our knowledge, in humans, infections have not been shown to directly influence milk quality (i.e., milk nutrition and production), but primary and secondary symptoms of illness, such as loss of appetite and stress, may influence milk nutrition and volume produced (Innis, 2014; Dewey, 2001a). However, due to the host of immunological benefits, the CDC recommends that individuals continue to breastfeed, if possible, while experiencing illnesses such as the flu, COVID-19, or diarrhea. Furthermore, due to the importance of continued breastfeeding and bonding, the Academy of Breastfeeding Medicine recommends that infants and caretakers not be separated if either is hospitalized (Bartick et al., 2021). Indeed, physical touch and the oxytocin released during breastfeeding can provide much needed comfort and stress reduction for the baby as well as the caretaker during times of illness (Krol and Grossmann, 2018). However, precautions should be taken to prevent vertical transmission of pathogens. For example, current CDC recommendations suggest that individuals with active COVID-19 infections wash their hands for at least 20 s with soap and water prior to breastfeeding and wear a mask while breastfeeding or within 6 ft of the baby. Individuals experiencing illness may also choose to express breast milk, in which case precautions should also be taken while pumping milk and bottle feeding the baby. A mask should be worn, and hands should be cleaned before touching the breast pump, which should also be cleaned and not shared with others. If available, one may choose to have a healthy caregiver feed the expressed breast milk to the baby to minimize the risk of transmission. Importantly, some viruses, including human immunodeficiency virus (HIV), human T-lymphotrophic virus I (HTLV-I), and cytomegalovirus (CMV), can be transmitted through breast milk, so breastfeeding and milk expression should be avoided or initiated with caution among individuals positive for these viruses (Lawrence and Lawrence, 2004; Lawrence, 2011). The CDC recommends that individuals with HIV, regardless of antiretroviral treatment or viral load, avoid breastfeeding if alternatives are available. Antiretroviral therapy for HIV can greatly reduce, but not eliminate, the risk of transferring the virus to the baby (Fernández-Luis et al., 2022). Studies show that CMV passed through breast milk can lead to a severe sepsis-like syndrome in very low birth weight babies, so it is recommended that caretakers pasteurize their milk to reduce, but not eliminate risk, or provide pasteurized milk from a donor (Osterholm and Schleiss, 2020). For HTLV-I, studies show that the risk of transmission was not increased by breastfeeding for babies less than six months of age but breastfeeding after 6 months was associated with increased risk of transmission, perhaps due to reductions in maternal milk antibodies in mature milk compared to colostrum (Boostani et al., 2018).

In summary, breast milk provides neonates with essential immune system support tailored to their needs. When a breastfeeding caregiver or neonate becomes ill, breast milk provides the antibodies and immunological factors needed to combat ailments now and in the future. Illness can lead to stress and questions about the safety and efficacy of breastfeeding, but in most cases, breast milk will only aid in recovery and return to good health.

4. Physiological intersection of psychological stress and milk

Psychogenic stress may originate from a wide variety of sources during pregnancy and lactation. Labor and vaginal delivery or delivery via caesarian section are major medical events with variation in recovery and complications, cortisol levels, and self-reported maternal stress. After delivery, poor sleep, parenting stress, experiencing a traumatic event, and acute or chronic mental or physical health issues can increase psychological stress. Anxiety and mood disorders, including depression, adversely affect mental and physical well-being and are linked to dysregulation of the physiological stress response system and changes in immune profile (Otte et al., 2016; Tafet and Nemeroff, 2020). For example, post-partum depression (PPD) is a common disorder associated

with HPA dysregulation during reactivity tests in several studies (García-Leal et al., 2017). PPD symptoms 15 days after birth are also positively associated with prenatal maternal hair cortisol levels, a retrospective biological measure of chronic cortisol output, during the first and third trimesters (Caparros-Gonzalez et al., 2017). Not all studies report associations between serum cortisol levels and depression and anxiety-like symptoms, so associations between depression or anxiety and milk composition may also be reflective of other physiological states associated with these conditions (Dombrowska-Pali et al., 2022; Patacchioli et al., 1992). Measures of maternal psychogenic stress are shown to influence milk quantity, let-down, and select milk components in human and animal studies with effects on infant development (Nagel et al., 2022). Notably, the biological mechanisms underlying the effects of psychogenic stress on milk quality may be through changes in hormones that affect milk synthesis and secretion directly or through secondary effects, such as changes in maternal diet, exercise, immune status, or infant-directed behavior.

The hormonal regulation of milk synthesis and milk let-down overlaps with the physiological responses to psychological stressors. The HPA axis is activated with the perception of stress or a threat ultimately elevating circulating glucocorticoids, primarily cortisol in humans. Cortisol levels in saliva, blood, urine, feces, or hair are commonly used as biological measures of stress. After release from the adrenal gland, glucocorticoids exert their effects throughout the body by regulating the immune, reproductive, and neurobiological systems. Cortisol also affects metabolism by facilitating release of glucose, fatty acids, and amino acids from endogenous storage into circulation (Vegiopoulos and Herzig, 2007). While the HPA responses to acute stress are physiologically protective, chronic stress can lead to pathophysiology and damage to healthy systems with increased allostatic load (McEwen, 2017; McEwen and Wingfield, 2003). Thus, acute stressors, such as those associated with critical periods of perinatal development, likely have different physiological effects compared to chronic stressors that are experienced for long periods before and after birth. Different stress types and durations lead to disparate underlying physiology and likely modulate milk composition in unique ways.

Oxytocin, a nonapeptide released by hypothalamic neurons to enable milk let-down during lactation, also attenuates HPA activity in response to stress (Onaka et al., 2012). In fact, one study found that breastfeeding mothers have lower salivary cortisol after feeding compared to mothers using mixed feeding methods and the length of breastfeeding was negatively associated with the degree of cortisol decrease in healthy participants (Mizuhata et al., 2020). Others have reported a reduction in depression symptoms at 3 months postpartum among mothers who continue breastfeeding (Figueiredo et al., 2014). On the contrary, maternal stress may interfere with normal oxytocin release, impairing milk ejection during nursing (Dewey, 2001b; Ueda et al., 1994). Psychological stressors that activate the HPA axis acutely or chronically may affect select milk components by altering physiological processes responsible for milk synthesis and milk ejection.

4.1. The effects of psychological stress on milk volume, secretory activation, and breastfeeding frequency

The first studies examining the effects of maternal stress on milk focused on milk volume and secretory activation, described as the initiation of copious milk secretion. Chen et al. (1998) found a negative association between maternal exhaustion during labor and delivery and breastfeeding outcomes (breast fullness, milk volume, feeding frequency) during the first 2 postnatal weeks. Similarly, a composite stress score comprised of several self-reported surveys 1 and 4 days after delivery was negatively associated with milk volume, duration of first feeding, and feeding frequency, but positively associated with initiation of lactation after controlling for age, epidural use, and post-delivery stress score (Doulougeri et al., 2013). Maternal depression scores are also negatively associated with milk quantity and delayed latency of first

feeding mothers of premature infants (Feldman and Eidelman, 2003). Low milk volume was also related to lower infant cognitive skills, an effect moderated by maternal touch which was also reduced in the group of mothers producing the lowest volumes of milk (Feldman and Eidelman, 2003). The association between reduced milk volume and stress extends to animal models, where four consecutive days of stress induced through daily limited dam-pup contact or intrusion by a male led to lower milk intake in Sprague-Dawley rat pups (Lau and Simpson, 2004).

Comparable findings are reported by studies measuring cortisol as a biological marker of stress; Maternal salivary cortisol during active labor is negatively associated with postpartum breastfeeding success (Karakoyunlu et al., 2019); moreover, maternal (but not neonatal) postpartum hair cortisol and higher perceived stress are associated with later onset of secretory activation (Caparros-Gonzalez et al., 2019). Similarly, dexamethasone, a synthetic glucocorticoid, treatment caused reduced oxytocin and prolactin secretion during lactation, less arched-back nursing, and lower pup body weight 2 h after administration in Wistar rats (Vilela and Giusti-Paiva, 2011). The effects of stress on milk volume may extend beyond the first week after delivery. For instance, increased maternal depressive and anxiety symptoms are associated with earlier termination of breastfeeding (Fallon et al., 2016; Hatton et al., 2005). Moreover, one or two maternal stressful events, particularly emotional or traumatic events, in the 12 months before birth reduces likelihood of initiating breastfeeding and increases likelihood of ceasing breastfeeding by four weeks postpartum (Kitsantas et al., 2019). Furthermore, a study of first-time mothers showed that disturbed sleep during the past week was associated with lower milk volume intake by infants, although there were no direct associations between milk volume and self-reported stress (Carrega et al., 2020). Collectively, these studies provide evidence that psychological self-reported stress and HPA measures of stress in the perinatal period may reduce milk production, secretory activation, and infant feeding frequency following birth. In addition to the possibility that HPA activation differences may be a driving factor behind reduced breastfeeding in those experiencing elevated depression or anxiety, other factors, such as prescribed medications that contraindicate breastfeeding may cause those mothers individuals to cease breastfeeding, affect sleep habits, or lead to other lifestyle changes that may indirectly affect breastfeeding behaviors.

4.2. The effects of psychological stress on cortisol in milk

Not only are elevated glucocorticoids capable of inhibiting milk production and initiation of breastfeeding, but they can also affect offspring directly by altering cortisol levels in milk (Stead et al., 2022). Circulating glucocorticoids may enter the mammary gland from the bloodstream by passive diffusion (Hollanders et al., 2019). Several studies report strong correlations between milk cortisol levels and maternal serum cortisol levels, with cortisol decline over the first few days following vaginal and caesarean delivery (Dombrowska-Pali et al., 2022; Patacchioli et al., 1992; Sullivan et al., 2011). There is also an established link between self-reported psychological stress and milk cortisol concentrations. For example, milk cortisol levels were positively associated with self-reported maternal hostility and neonatal performance on the Neonatal Behavioral Assessment Scale autonomic stability cluster 1–2 weeks after delivery (Hart et al., 2004). Preterm birth, which is generally associated with elevated maternal stress, was positively associated with milk cortisol levels in a Finish cohort, as part of the Steps to the Healthy Development and Well-being of Children study (Pundir et al., 2019). Another study took a more comprehensive approach to account for circadian changes in cortisol by taking repeated milk and saliva samples across a 24-hour period in a sample of mothers recruited from a maternity ward with increased risk of psychological distress. Cortisol in saliva and milk were highly correlated, showed a monophasic rhythm, and the area under the curve relative to ground was lower in mothers seeking care compared to control mothers. Together, this indicated a lower overall cortisol output for mothers at risk for

psychological distress. However, there were no differences between groups on other measures of rhythmicity (Romijn et al., 2021).

Increased cortisol in milk from psychological stress can impact infant development as glucocorticoids can pass into the infants' circulation after milk ingestion and cross the epithelial intestinal barrier (Agostoni et al., 2001). Once in the circulation, glucocorticoids are capable of crossing the blood brain barrier and are likely involved in guiding neural, intestinal, microbiome, and metabolic maturation in the infant (Cottrell and Seckl, 2009; Hollanders et al., 2017; Cottrell and Seckl, 2009; Hollanders et al., 2017). Elevated cortisol levels in milk are associated with higher scores on the Negative Affectivity dimension of the Infant Behavior Questionnaire measure of infant temperament in girls but not boys (Grey et al., 2013). Conversely, Confident factor scores, which includes positive loadings of active, bold, confident, curious, and playful traits of temperament in male rhesus monkeys were found to be positively related to milk cortisol concentrations (Sullivan et al., 2011). On the other hand, another study found maternal milk glucocorticoid concentrations predicted more Nervous and less Confident temperaments in male and female infant rhesus macaque offspring independent of milk energy (Hinde et al., 2015). A third study found that milk cortisol was also predictive of impulsivity in male and female rhesus offspring and total play frequency in female offspring (Dettmer et al., 2018). Higher cortisol in milk has been associated with reduced body mass index percentage at two years old, an effect particularly strong in human girls (Hahn-Holbrook et al., 2016), and positively correlated with infant adiposity and infant head circumference in the first year (Pundir et al., 2020). These studies highlight the potential for milk cortisol, and by extension maternal psychological stress levels, to pass on signals by which mothers provide environmental cues to their infants and influence behavior and brain development.

4.3. The effects of psychological stress on milk immune factors

Stress effects on inflammation and immune factors in milk are known to be important for the development of the infant immune system postpartum (discussed in more detail in Section 3). Several studies have examined immune components of milk in relation to maternal stress with particular attention to SIgA, an antibody essential to immune function of mucous membranes and considered a primary source of active and passive immunity in the neonatal period. SIgA appears to be influenced by different types of maternal stress. For instance, milk SIgA levels were negatively associated with negative Profile of Mood States (e.g., depression-dejection, tension-anxiety), General Health Questionnaire mental health scores, and state and trait anxiety scores, and depression symptoms within two weeks postpartum (Hart et al., 2004; Kawano and Emori, 2015). Milk SIgA is also negatively associated with postpartum-specific stress (but not general stress or negative affect) and self-reported perceived stress scores 4–6 weeks after delivery (Groer et al., 2004; Moirasgenti et al., 2019). Milk SIgA levels in the first two weeks postpartum are positively associated with infant alertness and attention directed to auditory and visual stimuli, suggesting positive benefits of higher SIgA on infant cognitive development (Hart et al., 2004).

While less explored, other immune components in milk may also be affected by maternal stress. Breast milk-borne transforming growth factor-beta (TGF- β), another immune component found in milk important for mucous membranes, was higher in mothers reporting higher levels of depression symptoms (Kondo et al., 2011; Shariat et al., 2017). In addition, another study found positive associations between state anxiety and depression and TGF- β (Abedinia et al., 2017). A more comprehensive examination of immune components in milk at 2, 6, and 12 weeks, did not find strong relationships between 22 immune components that were measured in milk and several self-reported measure of maternal stress, although null findings may be due to the relatively small sample size and low overall levels of self-reported stress in this study (Aparicio et al., 2020). Conversely, a study that investigated

relationships between several self-report types of psychological stress and ten immune components found in milk, measured from a sample of 85 African American mothers, reported that as perceived stress increased, EGF, milk macrophage inflammatory protein-1-alpha, and TNF α levels were decreased on postnatal day 3. Moreover, maternal salivary cortisol was positively related to EGF on postnatal day 9 (Thibeau et al., 2016). Both studies found that levels of immune components in milk generally decreased over time. Together these studies show that increased maternal psychological stress leads to changes in select immune components in milk, but the type of stress and its duration determines which immune components of milk are affected and to what degree.

4.4. The effects of psychological stress on lipids

Glucocorticoids are involved in lipid metabolism, so changes in circulating glucocorticoids may have implications for fat content in milk (Lee et al., 2014). Contradictory results pertaining to maternal psychology and milk fatty acid composition have been reported. A few studies reported no relationship between milk glucocorticoid levels and total fat content in milk at 1 and 2.5 months (Hollanders et al., 2019; Linderborg et al., 2020). Likewise, anxiety levels of mothers whose infant was hospitalized was unrelated to milk macronutrient composition, including fat, the day after hospital admission or one week after discharge (Soffer et al., 2020). On the other hand, Juncker et al. (2022) found concentrations of total fatty acids, PUFAs, and n-6 PUFA in milk were lower in the mothers whose newborns were hospitalized for at least two days compared to control mothers during the first postpartum month. Mothers whose infant was hospitalized had higher perceived stress scores but limited changes in hair or salivary cortisol was reported compared to control mothers (Juncker et al., 2022). Others have found significant relationships between milk cortisol and individual fatty acids. Milk cortisol has been reported to be positively associated with saturated fatty acids, lauric acid and myristic acid, monounsaturated fatty acids (eicosenoic acid, and docosenoic acid), and positively associated with the saturated fatty acid palmitic acid (Linderborg et al., 2020). Keim et al. (2012) found a negative relationship between depressive symptoms and DHA concentration, but no other fatty acids in milk less than 20 weeks postpartum. The differential effects of psychological maternal stress and milk cortisol on fatty acids is underscored by a comprehensive comparison of 62 metabolites in milk samples from mothers with high milk cortisol, high levels of prenatal psychological distress, or low levels of both distress and cortisol. High prenatal distress was associated with higher acetate, formate, propionate, caprate, and hypoxanthine and lower methanol whereas high milk cortisol was associated with higher 2-oxoglutarate, capylate, pyruvate, caprate, and lactate (Kortensniemi et al., 2021). The effects of maternal stress on lipid content in milk have received considerably less attention in studies using rodent models. Purcell et al. (2011) looked at total lipid, sugar, protein, and water content in milk from Sprague-Dawley rats on P21 exposed to a prenatal variable stress paradigm during the second half of pregnancy. There were no differences in these measures of milk composition, although milk from stress dams also fed a HFD had higher levels of insulin in milk (Purcell et al., 2011). These studies paint a complex picture of the relationship between stress and fatty acids in milk that may be influenced simultaneously by other maternal factors and anthropometric features, such as maternal immune activation, maternal diet, HPA dysregulation and the microbiome, and should be investigated further in carefully controlled animal experiments.

Although multiple cortisol measures in saliva or blood collected throughout the day can provide an idea of overall circadian patterns of cortisol production, and hair cortisol is reflective total chronic HPA output, neither measure is informative about dynamic HPA reactivity to acute stress. A recent study sought to disentangle the effects of chronic stress and the HPA response to an acute laboratory stressor on milk composition in a group of 146 Polish breastfeeding mothers at

approximately 5 months postpartum. Chronic perceived stress over 6 months prior to sample collection (Recent Life Changes Questionnaire) was associated with reduced fat and energy density of milk and the content of medium and long-chain saturated fatty acids. On the other hand, higher cortisol response to a one-minute cold pressor test was related to higher fat, lower lactose, and higher long chain unsaturated fatty acid content in milk (Ziomkiewicz et al., 2021). These results suggest that elevated glucocorticoids may facilitate fat synthesis in milk in the short term in response to acute stress, but prolonged HPA activation has the opposite effect, perhaps due to exhausted resources for fat production.

4.5. The effects of psychological stress on micronutrients

There is limited evidence of maternal psychological stress on micronutrients. Postpartum depression did not affect vitamin B-6 levels in milk approximately a week after delivery (Boylan et al., 2002). Two studies examined the relationship between maternal psychopathologies and sodium levels in milk, which may be informative about mammary gland permeability and, by extension, lactation volume. The first study found no association of sodium levels with depression, but a significant positive association with anxiety symptoms (Ozbek et al., 2008). The second study found higher sodium levels and higher sodium/potassium ratios in mothers with postpartum depression (Demirgoren et al., 2017). These preliminary studies help us understand how maternal stress affects micronutrient levels in milk, but more work looking at other micronutrients (i.e., vitamins B-1, B-7, B-2, D, K, ions, mineral salts) is needed.

4.6. The effects of psychological stress on milk microRNAs

Effects of psychogenic stress on milk miRNAs are starting to be explored. A study published in 2020 looked at MEV-miRNA profiles in relationship to scores on two self-reports of maternal distress: Life Stressor Checklist-Revised and Crisis in Family Systems-Revised. The number of MEV-miRNAs present was negatively associated with lifetime stress scores. Expression level of MEV-miRNAs differed with stress type; 8 MEV-miRNAs for lifetime stress and 17 MEV-miRNAs for family crisis score showed significant associations. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed that the differentially expressed MEVs from both stress variables were related to fatty acid metabolism and Hippo signaling pathway, which integrates biochemical cues from the cellular environment to regulate cell proliferation, cell differentiation, and organ growth (Bozack et al., 2021). Disparate profiles for the two stress scores may indicate differential effects of chronic *versus* more recent stress experienced during pregnancy. A second study showed that milk miR-148a, which is known to indirectly affect tight junction proteins in the intestinal barrier in addition to epigenomic programming, expression 1 month postpartum was negatively associated with negative mood scores and positively associated with positive mood scores (Chiba et al., 2022).

4.7. The effects of psychological stress on the microbiome

The gut microbiome is affected by stress and stress-induced changes to the maternal gut microbiome may influence the lactational microbiome. The first study to look at the effects of psychological stress on the microbiome in milk at 2, 6, and 12 weeks postpartum found high self-reported maternal psychosocial stress was associated with lower bacterial diversity starting at 3 months, although there were no differences in relative abundances on major bacterial genera (Browne et al., 2019). Stress, depression, and anxiety scores were also associated with dissimilar bacterial profiles, indicating divergent influences of these variations of stress (Browne et al., 2019). Another recent study by Deflorin et al. (2022) found that prenatal anxiety levels concerning birth and pregnancy were negatively correlated with *Alphaproteobacteria* while

postnatal state anxiety scores were negatively associated with *Alphaproteobacteria*, *Propionibacteriales*, *Cutibacterium*, and *Pseudomonas* in milk collected during the first 5 days postpartum. Furthermore, milk cortisol levels were positively associated with alpha diversity and negatively associated with *Staphylococcus* in milk (Deflorin et al., 2022).

5. The effect of enrichment and support on breastfeeding

The maternal environment can clearly influence breastfeeding dynamics and milk production. Importantly, studies show that individuals with emotional, social, and physical support at home and in the workplace experience greater breastfeeding efficacy (Uludağ and Öztürk, 2020; Vilar-Compte et al., 2021). Uludağ and Öztürk (2020) found that perceived emotional, physical, and social support from a spouse was correlated with increased feelings of breastfeeding sufficiency. Likewise, Vilar-Compte et al. (2021) showed that workplace interventions, such as designated breastfeeding/breast milk expression areas, support from co-workers, and flexibility to work from home increased the duration of breastfeeding and decreased premature introduction of non-breast milk supplemental nutrition. This finding is significant because increased breastfeeding duration has been shown to promote secure attachment between babies and their caretakers and enhance performance on neurocognitive tests later in childhood (Tharner et al., 2012; Lopez et al., 2021).

The effect of the environment was also evident during the recent COVID-19 pandemic, when many caretakers faced stressful circumstances along with disrupted work and home life. Some parents reported a positive impact of COVID-19 on breastfeeding due to increased time at home, extended maternity leave, and greater frequency and duration of feeding (Brown and Shenker, 2021; Pacheco et al., 2021). However, other parents reported a negative impact of COVID-19 due to isolation and lack of support that led to early cessation of breastfeeding. Brown and Shenker (2021) found that women from historically marginalized populations and lower resource settings were more likely to report experiencing a more difficult breastfeeding experience, a finding that has also been reported among breastfeeding parents outside of the COVID-19 pandemic (Temple Newhook et al., 2017; Mathews et al., 2014). Taken together, comfortable, and supportive environments with access to resources positively impact breastfeeding outcomes. In turn, continued breastfeeding may promote long-term bonding and secure attachment between caretakers and their babies (Krol and Grossmann, 2018; Linde et al., 2020). Indeed, Tharner et al. (2012) found that breastfeeding duration in the first six months of life was positively correlated with maternal sensitive responsiveness and reduced the risk of a disorganized *versus* secure attachment classification between mothers and their fourteen-month-old babies. Maternal sensitive responsiveness is the ability of the caretaker to perceive signals from their infant and respond to them appropriately and promptly. Caretakers that scored low on maternal sensitive responsiveness were more focused on their own needs and only responded to very pronounced signals from the infant, often unsuccessfully or incompletely. Although not all studies have demonstrated a direct relationship between breastfeeding and attachment quality (Britton et al., 2006), evidence suggests that breastfeeding is associated with enhanced maternal sensitivity, which has been linked to improved attachment quality between caretakers and their babies (Britton et al., 2006; Krol and Grossmann, 2018).

5.1. The effects of interventional support on breastfeeding

Several studies have investigated the impact of stress reducing therapies on breastfeeding outcomes. Azizi et al. (2020) delivered stress management counseling to forty-six pregnant women in a randomized controlled study over the course of four sessions and found that women in the treatment condition experienced greater breastfeeding efficacy one and four months after giving birth, compared to women in the control condition. Another study evaluating mothers of infants in the

neonatal intensive care unit (NICU) showed that participation in a progressive muscle relaxation protocol followed by a guided imagery protocol was associated with higher milk production and milk fat content during the first 6 days of the study, compared to mothers that received standard hospital support (Keith et al., 2012). Other work extended these findings by showing that a relaxation intervention completed across several weeks reduced maternal self-reported stress, reduced milk cortisol, improved infant sleep, and increased infant weight gain and body mass index (Shukri et al., 2019).

The therapeutic potential of music during perinatal period has also been investigated. Düzgün and Özer (2020) performed a meta-analysis and found that music interventions are an effective method for increasing milk production. Jayamala et al. (2015) showed that listening to music while expressing milk was associated with decreased salivary cortisol, reduced self-reported maternal stress level, and increased milk expression compared to sessions without music, highlighting the importance of environmental conditions while breastfeeding. In this study, participants were seated in a comfortable and quiet room where they listened to slow, instrumental flute music or no music during eight, thirty-minute breastfeeding sessions (four sessions with music, four without). During the music sessions, music was played on earbuds at the participant's preferred volume for 15 min prior to initiation of milk expression and then for another 15 min during milk expression. Differences across musical genres were not investigated in this work, but music that an individual perceives as calming and relaxing could conceivably produce similar results.

Vianna et al. (2011) delivered a more varied form of musical therapy that consisted of pre-recorded and live music played on a variety of instruments. Ninety-four mothers in the NICU participated in hour long sessions 3 times a week. Sessions began with a verbal expression period in which mothers were allowed to talk about themselves and their babies for 5–10 min, followed by 20–30 min of time when mothers were allowed to request music or play instruments themselves. The sessions ended with 15–20 min of classical lullabies and 5 min of free conversation. Results showed that more mothers in the music therapy group were still breastfeeding at the first follow up appointment, compared to mothers that were not in music therapy. However, this effect had disappeared by the 60-day check-up appointment. Another study investigated the influence of listening to traditional lullabies on breast milk volume in 100 mothers in the NICU (SefidHaji et al., 2022). In addition to volume, this study measured concentrations of triglycerides, cholesterol, total protein, and albumin in three groups of mothers during breastfeeding classes in the NICU for 6 days after birth. The first group was a control group that sat in a quiet room for 15 min prior to breastfeeding for another 15 min. Mothers in the second group listened to a lullaby for 15 min before initiating breastfeeding, and for another 15 min while breastfeeding. The third group of mothers was the same as the second group, except that they were given a photo of their babies to look at while listening to the lullabies and breastfeeding. Results showed that breast milk volume and concentrations of triglycerides, cholesterol, albumin, and total protein were significantly greater in the third group that listened to music while looking at a photo of their baby compared to the lullaby only group. The lullaby only group scored significantly higher on these measures compared to the quiet room control group. These findings suggest that lullabies, especially in combination with a visual aid, can improve lactation output and quality (SefidHaji et al., 2022). Lastly, Chawanpaiboon et al. (2021) administered a musical intervention to three groups of women that underwent caesarean sections. In the first group, caesarean section was performed in the absence of music; in the second group, caesarean section was performed while listening to a song about the joys of breastfeeding (repeated twice for a total of 7 min and 40 s play time); in the third group, the same song was played during caesarean section and replayed during breastfeeding on the first and second days postpartum. Results showed that individuals in the music groups did not have higher rates of exclusive breastfeeding at 6 months, compared to those in the no music group. However, mothers

who stayed in a private ward of the hospital had greater success at exclusive breastfeeding compared to those in a shared ward, suggesting that the quiet of a private room may be the leading factor contributing to early breastfeeding success.

The act of breastfeeding itself has also been shown to decrease stress (Groer, 2005; Hamdan and Tamim, 2012). Therefore, while a comfortable, stress-free environment is conducive to breastfeeding, the anxiolytic effects of breastfeeding are reinforcing and may increase the likelihood of continuing the behavior in the future. In a study of two hundred and sixteen breast-feeding individuals, formula-feeding individuals, and controls, Groer (2005) found that breastfeeding people reported significantly less perceived stress than formula feeding caretakers. Furthermore, breastfeeding women scored lower on the Edinburgh Postnatal Depression Scale (EPDS) at two months postpartum and were less likely to be diagnosed with postpartum depression (PPD) at four months postpartum than non-breastfeeding women (Hamdan and Tamim, 2012). Evidence suggests that reduced stress and depression in breastfeeding individuals may be due to increased release of oxytocin (Matsunaga et al., 2020). Oxytocin is released during skin-to-skin contact (Vittner et al., 2018) and its release during breastfeeding has been shown to promote bonding and inhibit stress signaling mechanisms (Pierrehumbert et al., 2012). Studies show that suckling decreases cortisol as well as adrenocorticotrophic hormone (ACTH), which causes the release of cortisol from the adrenal cortex (Chiodera et al., 1991; Handlin et al., 2009). Furthermore, decreases in ACTH were greater with increased oxytocin levels and during longer bouts of breastfeeding (Handlin et al., 2009). In summary, stress can decrease breastfeeding initiation and success, but the act of breastfeeding itself can have immensely beneficial effects on the mental health of caretakers and the bond between them and their babies.

5.2. Preclinical models of enrichment support on lactation

Animal models can provide useful insights into the molecular mechanisms underlying benefits of supportive environmental interventions. In addition, these models offer a controlled setting that allows for observation across the entire trajectory of development. However, few studies have examined the effects of environmental enrichment on milk quality and breastfeeding behaviors. DeRosa et al. (2022b) investigated this question by housing and breeding one group of rats in standard conditions and another group of rats in environmental enrichment (EE), which consisted of larger cages with ramps leading to different levels of the cage, and access to toys, tubes, chew bones, and extra nesting materials. In this study, maternal behaviors were evaluated, and milk samples collected from rat dams on postnatal days 1 and 10 to investigate the effect of EE on milk quality. Compared to dams in standard housing conditions, EE dams spent less time nursing, but their milk had increased levels of triglycerides. Cross fostering showed that pups fed by EE dams weighed more than those fed by mothers housed in standard conditions. Social behaviors were measured in pups on postnatal day 21; cross-fostering showed that male offspring postnatally housed in EE were more social than those postnatally housed in standard housing, regardless of their mother of origin. Gene expression analysis revealed that genes related to oxytocin were upregulated in the milk of EE dams compared to standard housed dams, suggesting that more oxytocin was released during breastfeeding, supporting social bonds between EE dams and their pups. The increased nursing observed in standard housed dams could be indicative of overfeeding or of metabolic differences in the quality of milk that necessitates increased feeding to deliver sufficient nutrition to offspring. In either case, dams in standard housing conditions have been observed to assume a 'press posture' in which they press the ventral portion of their body against the side of the cage, presumably to hide their teats from their offspring (Cramer et al., 1990; Gaskill and Pritchett-Corning, 2015). DeRosa et al. (2022b) noted that while the 'press posture' was displayed by standard housed dams, it was not observed in EE conditions. This was suggestive that dams in

standard housing conditions may be experiencing difficulty obtaining rest in between nursing bouts. This idea is supported by another study in which standard housed rat dams were provided with a small loft area in their cages, which they could use as a private escape. In this study, Ratuski and Weary (2021) found that rat dams with loft access spent around 27% of their time in the loft away from their litters during the first postnatal week. By the third week, rat dams were spending around 52% of their time in the loft. Taken together, it appears that rat dams prefer to have space and time to rest away from their pups if given the opportunity. Importantly, increased time off of the nest does not negatively impact offspring as EE dams are more efficient with their caregiving duties resulting in socially and cognitively enhanced offspring (Connors et al., 2015).

DeRosa et al. (2022b) also found that milk from EE dams contained a greater diversity of species in the gut microbiome than the milk of standard housed dams. Analysis revealed that the abundance of forty-four taxa differed between the housing conditions, and thirty-eight of those taxa were more abundant in the milk of EE dams. EE dams expressed a greater abundance of *Christensenellaceae*, *Ruminococcaceae*, *Lachnospiraceae*, *Erysipelotrichaceae*, and *Peptococcaceae*, which have been shown to influence lipid metabolism and body mass index through changes in levels of short-chain fatty acids (Waters and Ley, 2019; Vacca et al., 2020; Magzal et al., 2022). A balanced diet and greater microbial diversity in the gut during infancy have been linked to better cognitive performance in adolescence, suggesting that gut health enhances brain development early in life (Nyaradi et al., 2015; Carlson et al., 2018). Furthermore, a more active lifestyle was linked to increased *Peptococcaceae* and *Erysipelotrichaceae* in a study of older adult humans (Magzal et al., 2022). In contrast, *Streptococcaceae*, a taxon that has been implicated in intestine-related health problems such as dyspepsia and rotavirus infections (Chen et al., 2017a, 2017b; Sohail et al., 2021) was more abundant in the milk of standard housed dams compared to EE dams. In summary, breast milk of EE dams promotes microbial communities that support healthy physical and social development in offspring.

5.3. Summary and guidelines of environmental considerations to support breastfeeding

Environmental factors can affect breastfeeding and milk let-down (Dewey, 2001a; Jayamala et al., 2015). The CDC recommends that breastfeeding individuals find a quiet, private, and comfortable place to breastfeed or express milk. External aids, such as counseling or relaxing music, may also help caretakers to reduce stress and improve breastfeeding outcomes (Azizi et al., 2020; Jayamala et al., 2015). For caretakers in the workplace, the United States Department of Labor has mandated by law that employers provide breastfeeding individuals break time to express milk in a private, non-bathroom space for one year after the child's birth. Environmental conditions can affect breastfeeding success and longevity, so it is important for breastfeeding individuals to seek comfortable and supportive environments at home and in the workplace (Uludağ and Öztürk, 2020; Vilar-Compte et al., 2021). It is also important for caretakers to take breaks to care for themselves, which will ultimately allow them to provide better care for their babies (Ratuski and Weary, 2021; DeRosa et al., 2022b). From a larger perspective, cultural and policy-driven parenting and breastfeeding contexts can directly affect parenting stress with implications for breastfeeding (Swanson and Hannula, 2022).

6. Overall conclusions

Due to the numerous reported benefits of breastfeeding, the CDC and WHO recommend early initiation and exclusive breastfeeding during the first 6 months of life. Breast milk provides infants with the nutrition needed to grow and foster healthy brain development, while also supplying the necessary building blocks to develop their own immune

system and microbial communities (Krol and Grossmann, 2018; Quitadamo et al., 2021). That said, perinatal stressors in the form of maternal dietary, immune, or psychological status can change the nutritive and non-nutritive components of maternal milk, impacting both the short and long-term developmental outcomes of offspring. While current scientific evidence supports that lactation can be protective against maternal nutritional and immune stressors, evidence for the benefits of lactation in response to psychological stressors has been divided. For individuals who are unable to breastfeed or choose not to, there are options to explore including expressing milk to bottle feed, receiving milk from human donor banks, or feeding with fortified formula. Recent advances provide exciting new possibilities for both breast milk and formula supplementation. Moreover, there is growing evidence that environmental enrichment interventions and support tools can be used to improve the quality and volume of breast milk as well as related offspring developmental outcomes. The act of breastfeeding itself can provide caretakers with stress relief and an opportunity to bond with their baby. Together, this highlights the importance for future studies to focus on therapeutic lactational interventions designed to counteract perinatal stressors in support of maternal and infant health and development.

Data availability

No data was used for the research described in the article.

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