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Non-nutritive bioactive components in maternal milk and offspring development: a scoping review

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Review

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Abstract

Lactation is a critical time in mammalian development, where maternal factors shape offspring outcomes. In this scoping review, we discuss current literature concerning maternal factors that influence lactation biology and highlight important associations between changes in milk composition and offspring outcomes. Specifically, we explore maternal nutritional, psychosocial, and environmental exposures that influence non-nutritive bioactive components in milk and their links to offspring growth, development, metabolic, and behavioral outcomes. A comprehensive literature search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines. Predetermined eligibility criteria were used to analyze 3,275 papers, and the final review included 40 primary research articles. Outcomes of this review identify maternal obesity to be a leading maternal factor influencing the non-nutritive bioactive composition of milk with notable links to offspring outcomes. Offspring growth and development are the most common modes of programming associated with changes in non-nutritive milk composition due to maternal factors in early life. In addition to discussing studies investigating these key associations, we also identify knowledge gaps in the current literature and suggest opportunities and considerations for future studies.

Background

Maternal milk is a heterogeneous biological fluid that is tailored to meet the developmental, digestive, and immune needs of offspring and is the sole source of nutrition for most newborn mammals.[1–3] The World Health Organization (WHO) recommends that infants should be exclusively breastfed for a minimum of 6 months to receive the optimal benefits of maternal milk.[4] Milk is rich in nutritive components, including carbohydrates, proteins, lipids, vitamins, and minerals, which have been discussed in relation to offspring development elsewhere.[1,2,5–10] Milk also contains non-nutritive bioactive components, including growth and neurodevelopmental factors, hormones, active enzymes, peptides, a complex microbiota, immune factors, as well as non-coding RNA (microRNA – miRNA) encapsulated in milk-derived exosomes, which play roles in immune maturation, metabolism, overall health and developmental outcomes of offspring.[11–18]

Maternal milk composition varies across lactation stages, milk fractions, circadian cycle, and even temporally within a single feed, exhibiting compositional differences between foremilk and hindmilk.[1,2,19,20] The first fluid produced by mammary gland epithelial cells soon after delivery, known as colostrum, is rich in non-nutritive factors, including hormones, growth factors and immune components (e.g., lactoferrin, leukocytes, and immunoglobulins).[2,8,21] In humans, colostrum is replaced by transition milk approximately 60 hours to 5 days post birth and lasts for about 10 days to 2 weeks post-partum, after which mature milk production is initiated.[2,22,23]

Studies in human and animal models suggest that non-nutritive components in maternal milk contribute to early life developmental programming. Developmental programming refers to cellular and biochemical processes that lead to long-term functional changes as a result of a stimulus and/or insult during a critical period of development.[24] For example, maternal nutrition and psychosocial stress exposure during prenatal and/or early postnatal period can affect the overall growth and cognitive development of offspring, as well as increase the risk of disease later in life.[25–27] Non-nutritive bioactive compounds in milk enhance offspring survival by promoting the healthy development of the immune system and intestinal microbial colonization.[2,14,28–31] Emerging evidence also suggests that these bioactive components in milk may help

protect infants against acute infections, neuroinflammation and systemic inflammation, and metabolic diseases, including obesity, hypertension, and/or type I and II diabetes.[1,2,12,32,33]

There is considerable evidence that perinatal (e.g., the combined period of prenatal and postnatal life) maternal overnutrition and psychosocial stress play a role in shaping metabolic and neurodevelopmental outcomes in the offspring.[34,35] For example, in rodent models, a maternal diet high in saturated fats and complex sugars leads to increased offspring bodyweight,[34] elevated levels of inflammation in visceral adipocytes,[36] increased liver steatosis in males,[36] and increased anxiety-like behavior that persists into adulthood.[37,38] In humans, maternal obesity is associated with an increased risk of childhood asthma, and higher infant weight-for-length and Body Mass Index (BMI) at birth.[39,40] However, the milk of mothers with obesity was found to contain high levels of insulin and leptin, which may provide some benefit to the developing offspring,[41] as increased levels of milk insulin and leptin reduce intestinal inflammation and increase intestinal barrier function.[42]

Maternal anxiety during gestation as well as psychological and social stress are associated with a slower rate of cognitive development (lower scores on the mental development index of the Bayley Scales of Infant Development) in human infants over the first postnatal year.[43] In addition, maternal psychosocial stress is correlated with lower levels of milk bacterial diversity at 3 months postpartum,[44] which may contribute to a subsequent decrease in infant gut microbiome diversity.[45] While still debated,[46] there is evidence that this decreased complexity of the neonatal gut microbiome is associated with elevated risks of gastrointestinal, autoimmune, and metabolic disorders in adulthood.[47,48] Although the compositional changes of non-nutritive components in milk due to maternal obesity and nutritional status is well-established,[49–57] less is known about how maternal psychosocial stress during the pre-gestational/gestational/post-gestational periods impact milk composition.[58,59] Also, while a majority of studies with human subjects has statistically controlled for anthropometric and demographic covariates, including maternal height, age and ethnicity, these measurements have not been investigated as independent variables that could potentially alter non-nutritive milk composition. This is particularly important because milk composition varies across demographics. For instance, maternal age and ethnicity are highly correlated with fat content in milk.[60,61]

This scoping review was designed to provide a comprehensive overview of studies that have investigated non-nutritive bioactive components in milk associated with maternal factors and/or physiological and behavioral outcomes of offspring. In addition to a focus on the human literature, we did not exclude model organisms during the screening process to avoid missing relevant literature that fit within the scope of our study. Model systems that have been investigated in lactation biology research are highly heterogenous and span non-human primates, rodents, bovine, and other mammals. We categorized the primary literature into different species to aid in elucidating knowledge gaps in lactation biology. We attempted to characterize emerging knowledge concerning the most studied maternal factors that play roles in altering the non-nutritive bioactive components of maternal milk, along with their associations with offspring outcomes during early childhood that can potentially persist into adulthood.

Methods

This scoping review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines.[62]

Search strategy

A comprehensive literature search was performed using the databases MEDLINE, PubMed, EMBASE and the Web of Science, with "and/or" combinations of the following keywords: mammalian milk, lactation biology, maternal factors, and offspring developmental programming. The literature search was last updated on August 5th, 2020. All records were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and duplicates were removed from the library.

Exclusion/eligibility criteria and article selection

Title and abstract screening were conducted by two, independent reviewers (IJ and SE), with disagreements resolved by a third independent reviewer (SW). During the abstract and title screening phase, articles were excluded if one or more of the following criteria were met: 1) Primary language is not English; 2) Not peer-reviewed; 3) Sole focus on metabolic, nutritional, and immune stress affecting maternal health as opposed to mother-offspring dyads or maternal factors contributing to changes in milk composition; 4) Do not link changes in milk composition with either maternal factors or offspring outcomes.

Remaining articles were subcategorized into four species-specific databases (human, rodent, bovine, and other mammals). We included studies that spanned human and non-human models, because many previously published studies used several non-human mammalian model systems to investigate different aspects of lactation biology that were relevant to our research objective. For instance, numerous studies have investigated the mechanistic and molecular mechanisms of milk derived exosome uptake and transfer using rodent, bovine, and marsupial milk. However, studies that have investigated non-nutritive milk components in relation to maternal factors and/or offspring outcomes mainly used human and/or rodent models. Further, differences in milk composition have been reported across mammals.[63] As such, we decided to include all relevant studies rather than to exclude non-human model systems, and used four subcategories to differentiate human studies from studies of rodents, bovines, and other mammals.

Subsequently, the remaining articles were subjected to full-text screening. As per abstract and title screening, two independent reviewers (IJ and SE) conducted this analysis, and a third independent reviewer (SW) resolved disagreements. The following criteria were used to determine eligibility of the full-text articles towards the scoping review. Studies that contained the following criteria were included: 1) Primary literature; 2) A primary focus on non-nutritive bioactive components of milk as opposed to nutritive components; 3) Report experimentally validated physiological and psychological outcomes in offspring as opposed to conducting only *in vitro* experiments and/or *in-silico* predictions; 4) Research topics investigating non-nutritive bioactive components in milk and relating them to maternal factors and/or offspring outcomes (Table 1); 5) Experimental methodologies for milk exosome isolation and characterization adhering to the guidelines put forth by the International Society for Extracellular Vesicles (ISEV), where applicable.[64]

Data collection and extraction

Data extraction was conducted for all articles that remained post full-text screening. A comprehensive and detailed excel inventory was created as a data charting form and the extractable variables were jointly developed by three reviewers (IJ, SE and SW).

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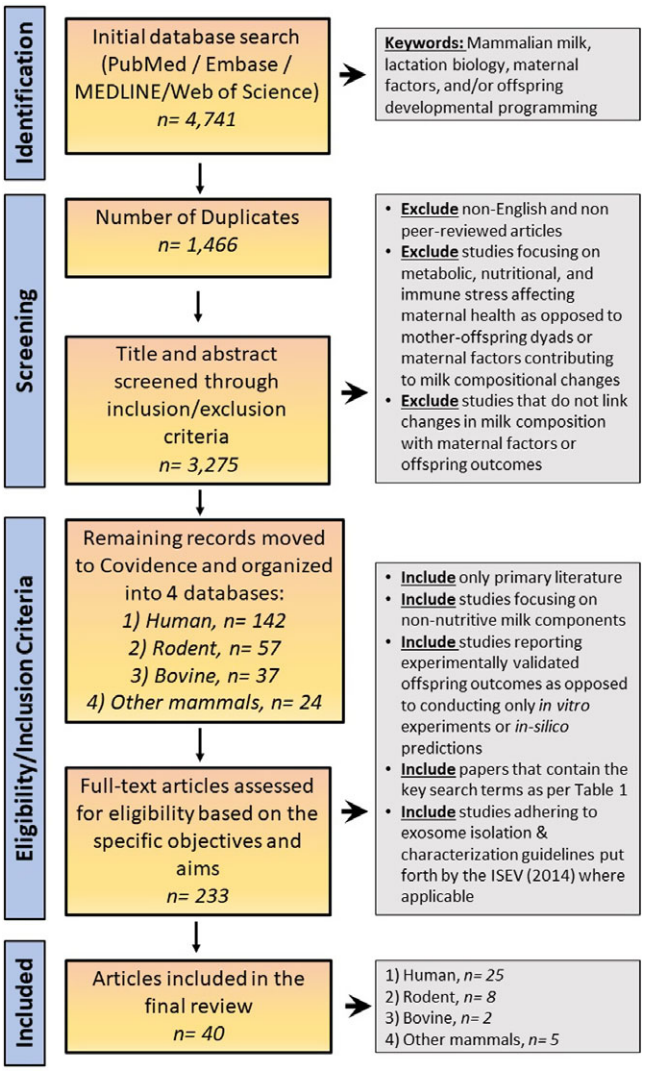

Fig. 1. PRISMA-ScR flow chart illustrating screening and eligibility criteria for article selection.

Table 1. Search terms and strategy

Non-nutritive bioactive components in maternal milk
Growth and neurodevelopmental factors
Cytokines
Chemokines
Hormones
Enzymes
Microbiota
Immune factors
Milk-derived exosomes
microRNA
Maternal factors
Nutrition
Psychosocial
Environmental
Anthropometry
Offspring outcomes
Growth
Neurodevelopment
Metabolism
Immunity
Microbiome
Behavior

Note: We searched for primary literature that included non-nutritive bioactive components in maternal milk AND linked that to maternal factors AND/OR offspring outcomes. We used multiple search terms (individually and in combination) for each category, and we included papers that contained at least one of the search terms.

Extracted data included study characteristics (author, year of publication, country and doi), subtopic categorization based on overarching research objectives, maternal factors in relation to non-nutritive lactation biology and developmental outcomes of offspring. Two reviewers (IJ and SE) independently extracted and inputted data based on the distinct categorical variables developed.

Results

Study selection

A total of 4,741 journal articles were identified after the primary search. One thousand four hundred and sixty-six duplicates were removed using the Covidence reference manager and the 3,275 papers that remained were subjected to first round eligibility screening. Upon completion, 233 articles met the first eligibility criteria and were organized into four databases based on the species that was investigated, where the human database contained 142 entries, rodent contained 57, bovine contained 37, and the other category involving all other mammals contained 24. Fifteen papers were repeated across multiple species at this stage of screening. Finally, 40 articles passed the second round of full-text eligibility screening and were used in the final review (Fig. 1). The final collection of 40 papers did not have repeating entries.

Study characteristics and categorization

The final selection of 40 primary research articles that remained post-screening and eligibility testing were categorized into two overarching research objectives, with a third category that linked both objectives, across four different species (Table 2). Fourteen papers (35.0%) pertained to maternal factors influencing non-nutritive bioactive components in milk, 13 papers (32.5%) related to non-nutritive components of milk impacting offspring development, and 13 papers (32.5%) linked maternal factors altering non-nutritive bioactive milk components and, in turn, alterations in offspring outcomes. Of the 40 papers, 25 papers (62.5%) were in humans, 8 papers (20.0%) were in rodents, 2 papers (5.0%) in bovine and 5 papers (12.5%) were in other mammals.

Analysis and synthesis of results

Of the 40 remaining papers, 13 papers (32.5%) characterized non-nutritive bioactive components in milk in relation to maternal

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factors impacting developmental outcomes of offspring (Table 2 – Category 3; Table 3). Within this category, six papers (46.1%) were in human, five papers (38.5%) were in rodent, and two papers (15.4%) were in other mammals, specifically rhesus macaques (*Macaca mulatta*). As reported in Table 3, 11 studies (84.6%) investigated maternal overweight or obesity status, which was associated with altering non-nutritive bioactive milk components and impacting offspring outcomes. Maternal gestational stress, metabolic syndrome (gestational diabetes mellitus), social rank, and parity were investigated by only four studies (30.1%). Two of these studies were included in multiple categories since they investigated more than one maternal factor (e.g., obesity, gestational stress and metabolic syndrome). In addition, weight, growth, and development were the most common offspring outcomes that were explored across all 13 papers with respect to maternal factors and non-nutritive milk composition. Five papers (38.4%) measured offspring body fat/adiposity, four papers (30.8%) pertained to offspring metabolism, and two papers (15.4%) examined offspring behavior. Finally, two papers (15.4%) assessed other offspring outcomes, such as microbiome, intestinal, and adipose tissue inflammation.

Supplementary Table 1 contains a complete list of all 40 papers identified in the final selection of primary literature included in this scoping review, along with a short description of each paper's main findings/focus.

Discussion

The overall objective of this scoping review was to explore the current literature pertaining to maternal factors, including nutritional status, psychosocial stress, and environmental factors that may influence non-nutritive bioactive composition in milk, and thereby impact developmental trajectories in offspring (e.g., physiological, neurological, metabolic, and behavioral outcomes). Numerous studies have investigated distinct aspects of this topic and the associations between individual maternal factors, lactation biology, and/or offspring outcomes. However, potential causal relationships and associations between maternal factors, changes in non-nutritive milk composition, and early life programming effects in offspring remain poorly understood.

Maternal factors influencing milk composition and offspring developmental trajectories

Maternal factors, including nutritional status, metabolic disorders, and/or psychosocial stress appear to play important roles in shaping non-nutritive milk composition (explored across 14 papers; Table 2), which in turn may influence the development and early life programming of offspring (explored across 13 papers; Table 2). Maternal nutritional status was the most investigated maternal factor reported to influence lactation biology and offspring outcomes. In particular, there is evidence that maternal obesity status (BMI > 30 kg/m^2) alters miRNAs,[65] immune components,[66] pro-inflammatory fatty acid,[50] and carotenoid levels[50] in milk. These bioactive compounds are critical for offspring growth[39], visual and neural development,[50] intestinal microbiota diversity and metabolic health.[42] Moreover, human and laboratory rodent studies have demonstrated that the initiation of lactation was delayed in mothers that were on a high fat diet,[67,68] including disruption of mammary gland morphology and a notable decline of intact alveolar units that are essential for lactogenesis.[67] Several rodent studies also reported that mothers exposed to a high fat diet during pregestation, gestation, and lactation, exhibited increased nursing behaviors, where time spent in "arched-back"[69] and "blanket"[70] nursing increased during the dark phase of the circadian cycle. "Arched-back" nursing is a type of maternal care behavior, where the mother arches her back while nursing pups to allow more access to the teats, and "blanket" nursing is where the dam uses her body to lay over the pups while nursing.[71,72] We previously postulated that the percent increase in time spent nursing may be a compensatory lactation-specific behavior to combat impaired milk production, prolactin insensitivity[73] or delayed milk production due to increased mammary gland inflammation.[67,70] Several human studies have shown that maternal obesity alters hormonal and immune components in milk, and that being obese and/or overweight during the pre-gestational period is associated with increased bodyweight and alterations in the metabolic profile of offspring during early childhood.[39,74,75] For example, higher maternal post-pregnancy BMI was associated with increased levels of milk adiponectin, a hormone that affects development by regulating lipid metabolism, reducing pro-inflammatory cytokines and improving insulin sensitivity in offspring.[76–79] Other studies reported that adiponectin levels in maternal milk from healthy lactating women were found to be positively correlated with adiponectin in infant serum[80] and inversely associated with growth and weight gain during early infancy.[79,81] Another study reported that infants who were partially breastfed (defined as the combined use of maternal milk and formula) by mothers with obesity had elevated levels of insulin and adiponectin and lower levels of IGF-I (insulin growth factor 1) in the blood at 9 months of age compared to infants partially breastfed by normal weight mothers.[74] Thus, the higher concentration of blood adiponectin reported in offspring who were born to as well as partially breastfed by mothers with obesity may indicate a positive, lactation-specific metabolic adaptation to prenatal maternal obesity exposure.

Maternal psychosocial stress is another prominent factor that may influence cortisol levels in milk,[82] which in turn has been associated with offspring development and behavioral trajectories. A study in rhesus macaques reported a positive correlation between increased maternal milk cortisol levels and changes in male offspring temperament, including increased activity, boldness, confidence and curiosity.[83] Higher milk cortisol was also associated with increased social interactions in female macaques at 4–8 months of age.[84] However, another study in rhesus macaques found that cortisol levels in milk were positively correlated with nervous temperament, and negatively correlated with confident temperament in offspring.[85] A study in humans reported a protective effect of increased milk cortisol exposure during early childhood, where increased milk cortisol levels were associated with decreased childhood obesity.[86] However, there is other evidence that higher milk cortisol levels are associated with increased fear reactivity in female infants at 3 months[87] and 8 months of age.[88] Despite mixed findings on the beneficial/deleterious effects of increased milk cortisol transfer across mother-offspring dyads, these studies illustrate the manner in which maternal psychosocial stress may alter milk composition and offspring behavior.

Additional studies in humans and other mammals reported that maternal immune status, group rank, and parity also influence not only cortisol, but adiponectin, growth factors and secretory immunoglobulin levels in milk.[83,89,90] Gestational age and mode of delivery are two other maternal factors associated with altered milk composition.[91] Specifically, Carney et al.[91] reported that the expression profiles of milk miRNAs in lipid and skim fractions differed in preterm delivery compared to term birth. They found that two miRNAs showed increased transcript abundance, and six

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Table 2. Overarching research topics and categorization of the articles included in the final review ($N = 40$)

Research objective	Total papers, *n* (%)	Human, *n* (%)	Rodent, *n* (%)	Bovine, *n* (%)	Other, *n* (%)	Citations
1. Maternal factors influencing non-nutritive bioactive components of milk	14 (35.0)	12 (85.7)	2 (14.3)	–	–	(O'Rourke *et al*., 2018), (Carney *et al*., 2017), (Kugananthan *et al*., 2017), (Munch *et al*., 2013), (Thibeau *et al*., 2016), (Xi *et al*., 2016), (D. Chen *et al*., 1998), (Fujimori *et al*., 2016), (Groer *et al*., 2004), (Mirza *et al*., 2019), (Browne *et al*., 2019), (Aparicio *et al*., 2020), (Pomar *et al*., 2019), (Hernandez *et al*., 2012)
2. Non-nutritive bioactive components of milk influencing offspring development	13 (32.5)	7 (53.8)	1 (7.7)	2 (15.4)	3 (23.1)	(Grey *et al*. 2013), (Munblit *et al*., 2017), (Berger *et al*., 2020), (van Rossem *et al*., 2019), (Nolvi *et al*., 2018), (Hahn-Holbrook *et al*., 2016), (Willumsen *et al*., 2003), (Melo *et al*., 2009), (Lee *et al*., 2018), (Li *et al*., 2019), (Ma *et al*., 2017), (Sullivan *et al*., 2011), (Dettmer *et al*., 2018)
3. Maternal factors altering non-nutritive bioactive components of milk that in turn influence offspring outcomes	13 (32.5)	6 (46.1)	5 (38.5)	–	2 (15.4)	(Lemas *et al*., 2016), (Panagos *et al*., 2016), (Young *et al*., 2017), (Ellsworth *et al*., 2020), (Zamanillo *et al*., 2019), (Yu *et al*., 2018), (Oben, *et al*., 2010), (Bautista *et al*., 2016), (Monks *et al*., 2018), (Y. Chen *et al*., 2017), (Purcell *et al*., 2011), (Hinde *et al*., 2015), (Bernstein & Hinde, 2016)
Total papers *n* (%)	40 (100.0)	25 (62.5)	8 (20.0)	2 (5.0)	5 (12.5)	

miRNAs showed decreased transcript abundance in both fractions of preterm milk, when compared to term milk. In addition, six miRNAs in maternal milk were correlated (three positively and three negatively) with mode of delivery.[91] None of the expression profiles of the milk miRNAs examined in the study were associated with maternal age, race, or ethnicity.[91]

Limitations in the current literature

We identified several common limitations in studies of human lactation to date. First, limited number of studies included large heterogeneous populations representing a wide range of ethnicities, socioeconomic status, and pre-gestational and gestational BMIs. Although it may be challenging to include multi-ethnic populations due to limitations in funding as well as difficulties in the recruitment of mothers belonging to underrepresented groups, the lack of diversity in these datasets limits the generalizability of the interpretations relating to lactation biology and offspring development. Interestingly, the few studies that included diverse populations reported differences in milk composition among ethnic groups as a function of regional maternal diets and breastfeeding practices.[92,93] Second, a large proportion of studies lack detailed descriptions of the methods used for milk collection and analysis, including the time of milk collection, use of breast pumps, the interval from last feeding to the time of sample collection, storage and processing steps, and lactational age. Consideration of these factors is critically important for studies that use human milk, especially human mature milk since there are notable differences in bioactive composition as mature milk is produced over a longer period of time, ranging from 4 to 6 weeks post-partum until the end of the lactation period.[2] In addition, milk collected at the beginning of a feed (foremilk) contains lower fat and higher cellular content compared to the milk collected at the end of the feed (hindmilk).[19] Efforts to standardize the methods, protocols, techniques for milk sample collection and processing by following the technical guidelines set forth by the ISEV (referred to as the Minimal Information for Studies of Extracellular Vesicles, MISEV) could serve to limit these potential confounds.[64]

Limitations of this scoping review

While we have attempted to provide a comprehensive analysis of the current literature on the biological associations between maternal factors, lactation biology and developmental outcomes in offspring, this scoping review is not without limitations. Despite compiling 40 papers from four different databases, we may have missed relevant studies in our search. Only peer-reviewed, primary literature published in English was included in our search criteria. A few published studies required specialty permission and journal subscriptions that limited our ability to access the full-print version to apply the exclusion and inclusion criteria. Moreover, the anthropometric controls, such as maternal obesity, used as fixed variables in epidemiological studies varied widely, and many studies investigated only one or two maternal factors at distinct timeframes. For instance, while some studies examined maternal pre-gestational obesity,[39,42,50] others investigated maternal gestational or post-gestational obesity.[11,74] This imposed limitations on our ability to draw clear conclusions from such findings concerning the roles of specific factors.

Conclusion

There is strong evidence that maternal factors, including nutritional status, psychosocial stress, and environmental factors, influence the non-nutritive bioactive components in milk, which are associated with developmental trajectories in offspring. These outcomes include early life growth, weight, height, language, and emotional development. Studies using non-human models have provided important information concerning the mechanistic role of non-nutritive bioactive components of milk on offspring development. Understanding the association between milk composition

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Table 3. Non-nutritive bioactive components in milk linking maternal factors with offspring outcomes

			Offspring outcomes							
							Inflammation			
Maternal factors	Milk components	Species	Growth[b]/ Development[c]	Metabolism	Body fat/ adiposity	Microbiome	Intestine	Adipose tissue	Behavior[d]	Citations
Obesity[a]	Hormones (Insulin, leptin, adiponectin)	Human	1, 2, 3, 4		1	1	1			(Lemas *et al*., 2016)[1], (Ellsworth *et al*., 2020)[2], (Zamanillo *et al*., 2019)[3], (Yu *et al*., 2018)[4]
		Rodent	5, 6, 7	5, 6, 8	5, 6, 7			6	7	(Bautista *et al*., 2016)[5], (Monks *et al*., 2018)[6], (Purcell *et al*., 2011)[7], (Oben *et al*., 2010)[8]
	microRNAs	Human	3							(Zamanillo *et al*., 2019)[3]
		Rodent	9	9						(Y. Chen *et al*., 2017)[9]
	Carotenoid	Human	10		10					(Panagos *et al*., 2016)[10]
	Inflammatory cytokines and markers	Human	11							(Young *et al*., 2017)[11]
Gestational stress	Hormones (Insulin, leptin, adiponectin)	Rodent	7		7				7	(Purcell *et al*., 2011)[7]
Metabolic syndrome (Gestational diabetes mellitus)	Hormones (adiponectin, ghrelin, insulin)	Human	4							(Yu *et al*., 2018)[4]
Social rank and parity	Hormone (cortisol, adiponectin), epidermal growth factor and transforming growth factor	Rhesus macaques	12, 13						13	(Bernstein & Hinde, 2016)[12], (Hinde *et al*., 2014)[13]

[1–13]Numerical values in "Offspring outcomes" correspond to the references listed in the "Citations" column.
[a]Characterization of obesity in human studies: overweight: BMI > 25 kg/m^2, and obese: BMI > 30 kg/m^2.
[b]Growth: Z-scores for weight-for-age, length-for-age, head circumference-for-age, weight-for-length, body muscle index.
[c]Development: brain, immunity.
[d]Behavior: nervous and confident temperament, milk ingestion.

and offspring developmental outcomes is essential in the development of strategies to enhance maternal nutrition and mitigate risk factors, leading to the improved health of both the mother and offspring. Milk compositional analysis may also inform enhancement of the quality of infant formula, given that exclusive breastfeeding is not feasible for all mothers due to health and/or lactational complications. Future studies with an increased ethnic and socioeconomic diversity of participants, a more extensive collection of participant phenotypes, and more standardized procedures for human milk collection, processing, storage, and analysis will enhance the generalizability and reproducibility of knowledge in this emerging field of research.

Supplementary materials. For supplementary material for this article, please visit https://doi.org/10.1017/S2040174422000149

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Conflicts of interest. The authors declare that they have no competing or financial interests.

Ethical standards. None.

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