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Lactational programming of glucose homeostasis: a window of opportunity

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Abstract

The window of lactation is a critical period during which nutritional and environmental exposures impact lifelong metabolic disease risk. Significant organ and tissue development, organ expansion and maturation of cellular functions occur during the lactation period, making this a vulnerable time during which transient insults can have lasting effects. This review will cover current literature on factors influencing lactational programming such as milk composition, maternal health status and environmental endocrine disruptors. The underlying mechanisms that have the potential to contribute to lactational programming of glucose homeostasis will also be addressed, as well as potential interventions to reduce offspring metabolic disease risk.

Introduction

David Barker's landmark epidemiologic study in the 1980s connected early life stressors to the development of ischemic heart disease in adult life (Barker *et al.* 1989). These initial studies led to the 'fetal origins of adult disease' hypothesis, which is based on the findings that undernutrition in pregnancy increases the long-term risk for adult diseases (Barker *et al.* 1989, Nijland *et al.* 2008). These discoveries have been replicated in human epidemiologic studies as well as studies with small and large animal experimental models (Nathanielsz 2006, Nijland *et al.* 2008, Padmanabhan *et al.* 2016). Because metabolic tissues are exquisitely sensitive to developmental stressors, developmental insults frequently alter metabolic outcomes in offspring manifesting as obesity, insulin resistance, abnormal blood glucose levels and diabetes (Devaskar & Thamocharan 2007).

Developmental programming studies have demonstrated that the adult function of organ systems can be organized during early life and that the critical windows of susceptibility to insults differ between different organ systems. The windows of susceptibility of the organs involved in programming and maintaining glucose homeostasis, the programming stressors, and the mechanism behind such programming, are important aspects to consider in the developmental origin of metabolic diseases. Organ systems involved in maintaining glucose homeostasis are susceptible to reprogramming throughout the stages of tissue differentiation and organ development, beginning during fetal life and often continuing through infancy.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

The ability to manipulate maternal and offspring diet in experimental animal models helps researchers gain key mechanistic insights into specific programming influences. In translating findings from animal models to humans, one must recognize that variations in the critical windows of organ development exist between precocial (e.g. monkeys, sheep, human) and altricial (e.g. mouse, rat) species (Fig. 1). Furthermore, while the *in utero* period is undeniably a period of critical organ development, the early postnatal window has an independent and significant contribution to long-term outcomes that is just beginning to be understood.

The lactation period is a critical window of susceptibility, as organ differentiation often continues during the early postnatal period. Lactational programming refers to programming that stems from an exposure that occurs during the period when the mother is nursing her infant, which may lead to changes in the nutrients, hormones or bioactive components in the milk. The ‘lactocrine hypothesis’ as described by Bartol connected changes in the milk-borne growth factor, relaxin, delivered to nursing offspring to programming of relaxin/insulin like family peptide receptor 1-positive target tissues in the female porcine reproductive tract (Bartol *et al.* 2008, Frankshun *et al.* 2011). Thus, alterations in milk composition can reprogram the developmental trajectory of organs leading to altered offspring outcomes in adult life (Bartol *et al.* 2013).

The period of lactation can be divided into a milk only phase in which offspring are fully dependent on maternal milk, followed by a mixed feeding/weaning period at which time complementary feedings are necessary to sustain infant growth (Langer 2008). The transition from milk exclusive to complementary food introduction differs by animal species (Langer 2008, Stringer *et al.* 2014, Wells 2014). For humans, milk is the only recommended substance for infant nutrition until at least 4–6 months of age, when exposure to complementary foods begins. Thus, in the early weeks of life for mammals this essential milk can serve as a significant programming agent. The role of milk intake during this period of programming cannot be viewed as the sole programming regulator, as maternal-infant interactions including care-giving and bonding during suckling also play key roles in early life programming (Hinde & Capitanio 2010, Macrì *et al.* 2011). The period of lactation provides a unique window of opportunity within the ‘first 1000 days’ to intervene and reduce lifelong metabolic disease risk from a public health standpoint. A better understanding of the developmental plasticity that occurs in metabolic tissues during this window is essential to develop interventions.

To address lactation-specific contributions to metabolic programming, this review will focus on animal and human studies that involve manipulations exclusively during the lactation period with documented effects on metabolic outcomes. Exposures during pregnancy are only included if a milk composition analysis was performed. This review will address factors influencing lactation and mechanisms by which lactational exposures program offspring metabolic tissues, highlighting sex-specific outcomes when they are reported. Table 1 summarizes the human and animal studies of lactational programming from groups that examined offspring metabolic endpoints. Sex-specific programmed effects and milk composition changes are noted in Table 1 when they have been reported.

Lactational/early postnatal window for programming of glucose homeostasis

The ability of mammals to maintain glucose homeostasis depends on the concerted functions of the brain, pancreatic islet cells, hepatocytes, myocytes and adipose tissues (Tirone & Brunicardi 2001). When glucose is ingested, it enters the circulation and is transported to the pancreas (Thorens & Mueckler 2010). The pancreatic beta cells then sense the glucose and secrete insulin, the major effector for glucose uptake by the body. Insulin stimulates glucose uptake in peripheral tissues including the liver, skeletal muscle and adipocytes followed by metabolism and/or storage of glycogen (Patti & Kahn 1998). When the demand on any of these organs becomes too high, compensatory actions take place to regain homeostasis (Cerf *et al.* 2012). This compensation may be defective if the differentiation of metabolic tissues is compromised (Shrayyef & Gerich 2010). Because the organs involved in maintaining glucose homeostasis continue differentiation and growth during the lactation period (Fig. 1), they are vulnerable to programming influences during the lactational window.

Exposures during the lactational window not only have programming effects, but may also have the potential to amplify the effects of *in utero* exposures on lifelong metabolic disease risk. Many studies have shown that while insults during fetal life may have programmed a 'thrifty' phenotype to promote short-term adaptations allowing for survival, a second insult occurring postnatally could unmask or amplify early programming through a 'second-hit' thus contributing to the development or severity of the metabolic dysfunctions (Gluckman *et al.* 2008, Padmanabhan *et al.* 2016, Puttabyatappa *et al.* 2016). For instance, overfeeding (second hit) of dams during lactation increased adiposity and glucose intolerance in rat offspring of maternal obesity (first hit), providing evidence for the importance of the independent contribution of the lactational window in programming of metabolic syndrome (Chen *et al.* 2008).

Lactational programming by early nutrient exposures

The importance of maternal milk as a programming agent was brought to light by studies demonstrating that excessive or deficient macronutrients, as well as global undernutrition or overnutrition during the critical suckling period contribute to long-term metabolic programming. In the sections below, we address the effects of specific manipulations during the lactation period on offspring metabolic tissues.

Undernutrition and overnutrition

Animal studies have used litter size manipulation to evaluate the effects of early postnatal nutrition with crowded litters modeling the impact of undernutrition during the lactation period. These studies in mice have demonstrated reduced body fat in young male and female and geriatric male offspring (Lopez-Soldado *et al.* 2006, Sadagurski *et al.* 2014). These models also show improvements in insulin sensitivity with both sexes having decreased fasting insulin levels and improved glucose tolerance (Sadagurski *et al.* 2014).

Small litters have been used to understand the effects of early overnutrition and have shown that male offspring have increased weight gain and fat mass as adults but did not develop

glucose intolerance until re-challenged with a high-fat diet (HFD) later in life (Glavas *et al.* 2010). Overnourishment during the lactational window also leads to hyperinsulinemia, impaired insulin signaling and impaired brown fat thermogenesis (Plagemann *et al.* 1992, Xiao *et al.* 2007, Bernardo *et al.* 2016). In these models, male offspring have increased circulating free fatty acids, which appear to underlie impaired glucose transporter function and elevated glucose levels (Bei *et al.* 2015). The increased circulating fatty acids involve palmitic acid, palmitoleic acid and oleic acid, which may serve as potential biomarkers for insulin resistance (Bei *et al.* 2015). Importantly, these models have substantiated an independent effect of overnutrition in the perinatal period, with exposure during the lactational window leading to glucose intolerance such as that seen in pups after gestational exposure to high-fat cafeteria style diet (Rajia *et al.* 2010).

Nonhuman primate models of overnutrition have been characterized since the 1980s in the baboon infant (Mott & Lewis 2009). Studies of high-calorie formula from birth to 4 months showed that overfed females developed increased fat mass and fat cell volume at 5 years of age (Lewis *et al.* 1989). While the female offspring had an increase in all fat depots measured, males only had increases in specific depots with no overall weight change. Potential mechanisms suggested include increased insulin responses to meals and blunted cortisol responses in young offspring (Lewis *et al.* 1992). The impact of overnourishment during lactation has not been well defined or studied in humans.

Overall, rodent studies of overnutrition during the lactational window show a consistent increase in offspring body weight, fat mass and insulin resistance with some of this phenotype replicated in primate studies. Interestingly, only male rodent outcomes are reported while the phenotype seems to be more prominent in female primates. Importantly, changes in milk composition were not assessed in any of the rodent models. Understanding the changes in milk composition that result from these dietary manipulations of the dam is important to understand the basis of lactational programming.

Carbohydrate

Using an artificially prepared rat milk supplement, one rat study addressed the effects of a high-carbohydrate formula. Male rats reared on this high-carbohydrate formula developed persistently elevated insulin levels and increased body weight (Aalinkeel *et al.* 2001). Isolated islets from the high-carbohydrate pups showed an exaggerated insulin response *in vitro*, a risk factor for beta cell stress (Aalinkeel *et al.* 2001). Pancreatic islets also had an increase in insulin content due to increased insulin biosynthesis with elevated mRNA levels for preproinsulin and transcription factors related to insulin synthesis (Srinivasan *et al.* 2000, 2001). The offspring also had programming of increased appetite due to hypothalamic changes, altered lipogenesis in adipose tissue and disrupted insulin signaling in the liver and skeletal muscle (Hiremagalur *et al.* 1993, Srinivasan *et al.* 2013).

A human study, while finding no significant variance in breast milk sugars (glucose, fructose and lactose) between collections at 1 and 6 months postpartum, found a direct relationship between fructose content in breast milk at 6 months and infant weight, weight for length, lean mass and fat mass at age 6 months (Goran *et al.* 2017). Taken together, the findings

from these experimental animal and human studies stress that high early postpartum carbohydrate intake increases offspring growth trajectory and adiposity.

Protein

Animal models have shown that both high- and low-protein diets during the early postnatal period increase susceptibility for metabolic syndrome in adulthood. A study of mouse dams on 40% high-protein diet during lactation found that their litter mass was lower than controls and this was coupled with a decrease in the dam's mammary gland mass and milk lactose (Kucia *et al.* 2011). In a rat model that compared pups receiving rat milk, low-protein cow's milk or high-protein cow's milk after early weaning from exclusive rat milk (postnatal day 14), female pups on the high-protein cow milk developed increased fat, hyperphagia and lower insulin secretion while males from this group had lower body protein (Rodrigues *et al.* 2017). This study also showed higher corticosterone levels in the high-protein cow's milk group after 1-week exposure. These results provide evidence that a high-protein diet during lactation can influence mammary gland function and milk composition, with long-term impacts on offspring growth. The difference in outcomes in these models may relate to the length of exposure. The exposure to high protein in the mouse model occurred throughout lactation, while in the rat model exposure began only at mid lactation.

Low-protein diets have been more extensively studied than high-protein diets. Maternal malnourishment using a protein-free diet during the first 10 days of lactation in rats led to increased plasma insulin levels in suckling offspring (Moura *et al.* 2002). Differences in insulin levels between groups subsided after weaning onto a normal diet but resurfaced when animals were re-challenged with a protein-free diet (Moura *et al.* 2002). Similarly, a 10% casein low-protein maternal diet during lactation decreased offspring body weight and serum glucose levels in adult males (Morimoto *et al.* 2012). Studies examining isolated pancreatic islets from these programmed offspring *in vitro* showed increased insulin secretion upon stimulation with high glucose on postnatal day 36 but impaired insulin secretory responses at 3 and 15 months (Morimoto *et al.* 2012). These results indicate that there may be latent programmed abnormalities that only become evident when an additional stressor is imposed, providing further support for the two-hit hypothesis (Tang & Ho 2007, Padmanabhan *et al.* 2016).

The EU Childhood Obesity Programme, a randomized controlled trial that compared high- and low-protein formula to breast milk, found a lower BMI at 2 years of age in the low-protein-fed group while the high-protein-fed group had more rapid weight gain with increased fat mass and persistently elevated BMI at 6-year follow-up (Koletzko *et al.* 2009, Escribano *et al.* 2012, Weber *et al.* 2014). Overall, these results indicate that changes in early protein levels are directly related to infant growth and body weight. In addition, studies from animal models provide evidence for an impact on pancreatic beta cell function, which has not been explored in detail in human cohorts. While milk composition was not assessed in the low-protein animal models, the clinical trial results indicate that lower protein intake during the lactation period could provide an intervention strategy to alter lifelong obesity risk in offspring.

Fat

Several animal studies have shown a negative impact of HFD during lactation on infant metabolic outcome. A cross-fostering rat model evaluated offspring of rats fed a control versus HFD during gestation, which were then suckled by either control or HFD-fed dams. Male and female pups nursed by HFD dams had significantly elevated body weight, glucose intolerance, insulin resistance and elevated triglyceride and leptin levels (Masuyama & Hiramatsu 2014). Mouse studies of dams fed a HFD during lactation showed that offspring had increased weight and fat mass, glucose homeostasis irregularities, impaired insulin secretion mediated by a decrease in parasympathetic innervation of the pancreatic beta cells and impairment in brown adipose tissue adrenergic signaling (Vogt *et al.* 2014, Liang *et al.* 2016). Cross-fostering studies have shown that HFD in the mother during suckling has an additive and independent impact on the offspring metabolic phenotype over a gestational exposure (Sun *et al.* 2012, Masuyama & Hiramatsu 2014). Importantly increases in milk insulin, glucose, triglycerides and leptin have been documented in these models with the changes in insulin being directly implicated in the hypothalamic and beta cell outcomes (Vogt *et al.* 2014). To date, there is no available information about HFD confined to lactation in humans.

Fatty acids

The levels of certain fatty acids in milk are influenced by dietary fat exposures during lactation, and this nutrient change is carried on to the nursing pups (Oosting *et al.* 2015). Murine studies have shown that a maternal diet rich in long-chain omega-3 polyunsaturated fatty acids (LCPUFAs) during lactation is associated with decreased weight, fat mass and adipocyte size in pups (Korotkova *et al.* 2002a, Oosting *et al.* 2010). Conversely, diets with an increased ratio of omega-6 to omega-3 LCPUFAs promoted offspring weight gain and adiposity (Korotkova *et al.* 2002a, Hadley *et al.* 2017). Milk analysis in these models has identified changes that may facilitate an understanding of potential programming agents. In a mouse model of obesity during gestation and lactation, obese dams had reduced medium chain PUFA levels (Saben *et al.* 2014). Analysis of milk from dams fed a diet high in arachidonic acid and docosahexaenoic acid (DHA) had higher omega-6 milk content (Hadley *et al.* 2017), while dams given an essential fatty acid-deficient diet produced milk with increased leptin (Korotkova *et al.* 2002b). Rodent experiments with developmental exposures to omega-3 fatty acids have shown that they limit adipocyte hypertrophy and inflammation, while omega-6 fatty acids stimulate adipocyte proliferation and adipogenesis (Massiera *et al.* 2003, Oosting *et al.* 2010). In a nonhuman primate macaque model of maternal long-term HFD feeding, breast milk was found to have increased insulin but lower protein, DHA and eicosapentanoic acid levels (Grant *et al.* 2011). Offspring of these HFD mothers had increased fat mass and decreased lean body mass.

Randomized controlled trials in human have shown that dietary interventions can increase breast milk omega-3 LCPUFAs and reduce breast milk omega-6 to omega-3 LCPUFA ratio (Helland *et al.* 2008, Much *et al.* 2013). This has been correlated with a lower infant plasma omega-6-to-omega-3 ratio (Much *et al.* 2013, Sherry *et al.* 2015). Higher breast milk omega-3 LCPUFAs have been associated with increased skinfold thickness and BMI at 1 year (Much *et al.* 2013) and increased BMI at 7 years (Helland *et al.* 2008). The results for

increased omega-6-to-omega-3 ratio have been conflicting with studies reporting a positive association with 2-month weight-for-length z-score (Panagos *et al.* 2016) and 4-month body fat percentage (Rudolph *et al.* 2017) with another study reporting a negative association with waist circumference at age 1 year (Much *et al.* 2013). In terms of DHA supplementation, one study using infant formula supplemented with DHA found a small negative association between DHA status at 16 weeks of age and weight at 1 and 2 years (Makrides *et al.* 1999). A lactation exclusive randomized controlled trial found that a 2.5-fold increase in breast milk DHA content was associated with a significantly higher BMI and waist circumference at 2.5 years (Lauritzen *et al.* 2005), but no significant anthropometric differences on follow-up at 7 years (Asserhøj *et al.* 2009).

Human investigations on the influence of maternal diet and maternal supplementation have confirmed that some milk fatty acids are responsive to dietary intake. In the rodent studies the impact of omega-3 supplementation on offspring weight is beneficial, while in primate and human studies, it seems to be detrimental or neutral depending on the specific fatty acid supplement. One limitation of the human growth outcome studies is that not all infants were exclusively breastfed. Clearly, the influence of milk fatty acids is complex in primates and warrants additional carefully controlled long-term studies with detailed milk analysis to determine the effect of changes in milk fatty acid on offspring metabolic tissues.

Maternal health influences on lactation

Maternal metabolic and nutritional status during both pregnancy and lactation has been demonstrated to influence infant outcomes. We will review the impact of maternal metabolic disease states on offspring outcomes with a focus on the effects of maternal disease on lactation and breast milk content.

Maternal diabetes

Animal models with cross-fostering have been used to study the effects of maternal diabetes exclusively during the lactational window, independent of gestational influences. For this model, control rat pups were cross fostered to one of two groups: control or streptozotocin induced diabetic dams at day 1 of birth. Offspring fostered to diabetic dams were found to have a lower growth rate than control offspring; however, adult metabolic outcomes were not studied (Fahrenkrog *et al.* 2004).

The effect of diabetes in humans was studied by Plagemann *et al.* examining a cohort of mothers with preexisting type 1 or gestational diabetes mellitus (Plagemann *et al.* 2002). Infants were fed either exclusively by their diabetic mother's breast milk or with a mixture of diabetic breast milk and banked donor breast milk. Infants who received exclusive breast milk from a mother with diabetes had increased infant body weight with a correlation found between increased diabetic milk intake in the first week of life and increased blood glucose levels at 2 years of age, a dose-dependent protective effect of donor milk against obesity at age 2 years (Plagemann *et al.* 2002). When considering the effect of breastfeeding versus formula, a study of mothers with gestational diabetes reported a decreased risk of overweight in offspring at age 5 years if mothers exclusively breastfed for more than 3 months (Schaefer-Graf *et al.* 2006). This protective effect was most prominent in offspring

of obese mothers, indicating that breastfeeding may protect from risk of overweight in specific populations after *in utero* programming. A limitation of this study was that breastfeeding history was from retrospective recall.

Human studies of maternal metabolic states have also examined breast milk fat and fatty acid composition. In a study of milk from mothers with insulin-dependent diabetes, there was an overall reduction in medium chain PUFAs and reduced omega-3 PUFA derivatives thought to result from altered fatty acid metabolism (Jackson *et al.* 1994). An additional study demonstrated an increase in omega-6 PUFAs in the serum of mothers with a recent history of gestational diabetes (Fugmann *et al.* 2015). This is of interest in that a link between plasma nonesterified fatty acids and human milk fatty acid profiles has been established (Torres *et al.* 2006).

Maternal obesity

Over 50% of human pregnancies are complicated by maternal overweight or obesity (Gynecologists ACoOa 2013). Using an animal model to study the influence of maternal obesity, Gorski *et al.* used cross-fostering to compare the differences between obese and lean dams during lactation (Gorski *et al.* 2006). This study found that offspring from obese dams fostered to lean dams maintained an obese phenotype, but had improved insulin sensitivity compared with those fostered to obese dams. Thus, providing a lean maternal environment to offspring predisposed to an obese phenotype does not attenuate adiposity, but may provide an intervention for the development of insulin resistance. Offspring of lean dams cross-fostered to obese dams developed obesity and insulin resistance when fed a high-energy diet in adulthood. The obese dams were found to have increased insulin and altered fatty acid profiles in their milk (Gorski *et al.* 2006).

In a rhesus macaque model, mothers with increased weight produced milk with lower EGF levels. EGF is a bioactive factor found in human and experimental animal milk that is thought to play a role in the development of the neonatal intestine, pancreas and liver (Donovan & Odle 1994). Higher milk EGF levels during peak lactation have also been found to be associated with increased infant body mass in males and females (Bernstein & Hinde 2016).

While obesity limited to the lactational window is not a clinical condition that exists, increased energy intake and obesity during lactation should be viewed as exerting additional influences on long-term programming of offspring metabolism. Human studies have revealed alterations in breast milk composition in mothers with obesity. The DARLING (Davis Area Research on Lactation, Infant Nutrition and Growth) study identified that maternal body weight for height positively correlated with milk lipid concentration in healthy mothers (Nommsen *et al.* 1991). Milk insulin and leptin levels have also been found to be higher in the milk of mothers with overweight or obesity (Fields & Demerath 2012, Young *et al.* 2017a). A significant inverse relationship between breast milk insulin levels and infant weight and lean mass was also demonstrated (Fields *et al.* 2017). Increasing maternal BMI has been linked to increased milk omega-6/omega-3 LCPUFA ratio and decreased omega-3 PUFAs (Panagos *et al.* 2016). Milk from obese mothers also had decreased levels of carotenoids and Vitamin D (Panagos *et al.* 2016). Studies have not examined exclusive

lactational exposure to milk from mothers with obesity; however, a follow-up study of the offspring of the Nurses' Health Study II demonstrated a dose-dependent decrease in childhood risk of overweight with exclusive breastfeeding even in mothers with obesity (Mayer-Davis *et al.* 2006). Taken together, these results indicate that maternal obesity influences human breast milk composition, which in turn has the potential to influence infant growth and fat accrual. Additional longitudinal studies with glucose and insulin measures would be needed to understand long-term effects on glucose homeostasis and metabolic functioning.

Maternal inflammation

Inflammation often coexists with obesity; however, while there are studies examining the impact of inflammation during pregnancy and lactation (Segovia *et al.* 2015, Dudele *et al.* 2017), no published studies examine the effect of maternal inflammation exclusively during lactation. A mouse study examining the effects of programming from a western style diet used cross-fostering to isolate the lactational impact. Maternal diet during lactation impacted the level of saturated fatty acids in the milk, which in turn increased offspring expression of inflammatory genes in the skin, intestines and liver during the suckling period (Du *et al.* 2012). In human studies, breast milk from obese mothers has been shown to have elevated inflammatory markers (Fields & Demerath 2012), and a pro-inflammatory fatty acid profile that were found to be associated with infant growth and adiposity at 1 month of age (Panagos *et al.* 2016). Further studies of the impact of maternal inflammation during lactation on offspring metabolic outcomes and the role played by the increased inflammatory markers in the breast milk are needed, especially in mothers with metabolic disease.

Maternal stressors and exposures during lactation

In addition to nutrient exposures other maternal exposures such as stress, cigarette smoking, alcohol and environmental contaminants during the lactational window may also influence offspring metabolic phenotypes.

Stress

Postpartum maternal stress has been reported to have negative consequences for lactogenesis and lactation duration (Dewey 2001, Lau 2001). A stress response may result in altered hormone production. One impact is on glucocorticoids, which not only play a role in the stress response, but also in mammary gland development, lactogenesis and in milk production. Cortisol and cortisone are present in milk and are transferred to the neonate through absorption by the intestinal epithelium leading to gut maturation and through the intestinal barrier into the offspring blood stream leading to systemic effects (Macrì *et al.* 2011, Hinde *et al.* 2015, Hollanders *et al.* 2017). Studies on the level of glucocorticoids in breast milk and their relationship to infant metabolic outcomes during the lactational window in animal and human models show inconsistent results potentially related to the difficulty of sampling and variations in analytical techniques (Pundir *et al.* 2017).

In a red squirrel model of exposure to high-density cues to induce physiological stress while rearing litter, female squirrels had increased glucocorticoids and their offspring had an

accelerated postnatal growth rate (Dantzer *et al.* 2013). A study of the rhesus macaque evaluated glucocorticoid levels in breast milk and their influence on offspring temperament and growth and found breast milk cortisol levels were positively associated with infant weight gain (Hinde *et al.* 2015).

Human studies of stress are more complicated, as a single stress is difficult to isolate from compounded factors (Dozier *et al.* 2012). These stressors not only influence maternal health, but may also have an impact on breast milk composition (Kondo *et al.* 2011) and childhood development (Lau 2001). In a small prospective study of childhood BMI percentiles over 2 years in relation to maternal breast milk cortisol level at 3 months, increased cortisol levels were associated with lower BMI percentile at age 2 years and decreased rapid early BMI gain in girls (Hahn-Holbrook *et al.* 2016). In a study of preterm deliveries, a time where increased maternal stress is expected, higher cortisone levels were found in breast milk when delivery was after 30 weeks compared to earlier gestation delivery but infant metabolic outcomes were not measured (Pundir *et al.* 2018). Additional human studies would need to be performed to further understand the impact of breast milk glucocorticoid levels on infant growth outcomes and metabolic programming mechanisms, given these conflicting results.

Smoking

Maternal smoking and nicotine exposure during pregnancy have been linked to several negative fetal hormone and metabolic outcomes (Tweed *et al.* 2012). However, many women who smoke may quit during pregnancy but resume after delivery (Rockhill *et al.* 2016, Logan *et al.* 2017). Smoking relapse after birth may program for adverse metabolic outcomes independent of programming in the gestational period. Studies have confirmed that nicotine does transfer into human breast milk, even if smoking occurs in a separate environment (Santos-Silva *et al.* 2011). During lactation, offspring are exposed to nicotine directly through mother's milk as well as indirectly through environmental exposure as second hand or passive smoke exposure. Both methods have been independently evaluated (de Oliveira *et al.* 2010, Santos-Silva *et al.* 2013) to determine offspring metabolic outcomes.

In the direct model of nicotine exposure, nicotine is infused into dams during lactation to simulate the blood nicotine levels seen in average human smokers. While offspring have a lower concentration of blood nicotine than dams, they have a much higher concentration of nicotine than control pups. When these offspring are examined as adults, offspring exposed to nicotine show significantly increased body weight, whole body and visceral adiposity and fasting insulin levels compared to controls (de Oliveira *et al.* 2010). In the indirect model of nicotine exposure, mother and offspring are placed in a smoking chamber to simulate the effects of environmental tobacco smoke exposure. At weaning, blood nicotine levels were elevated in offspring exposed to tobacco smoke, while blood insulin levels were significantly lower than controls. As adults, offspring exposed to tobacco smoke showed a significantly higher total body fat than controls. Unlike the direct model findings, second hand exposed rats were found to have hyperglycemia with normal insulin levels in adulthood (Santos-Silva *et al.* 2013). While there are no human data to reflect the impact of smoking during the lactation period alone, studies of infant feeding and growth have revealed a negative

association between maternal smoking and infant linear growth (Makrides *et al.* 1999), although an association with long-term metabolic disease is less clear.

Alcohol

Gestational consumption of alcohol may lead to deleterious effects on neonates, including the development of metabolic syndrome (Tavares do Carmo *et al.* 1999, Murillo-Fuentes *et al.* 2003, Ting & Lutt 2006). Studies focused on maternal postnatal consumption of alcohol and infant metabolic outcomes, however, are rare. Chen and Nyomba compared the results of prenatal and postnatal maternal alcohol abuse using rats to model mothers who resume heavy alcohol consumption during lactation (Chen & Nyomba 2004). At 16 weeks of age, male offspring had higher glucose responses on glucose tolerance tests than controls, similar to offspring with prenatal ethanol exposure (Chen & Nyomba 2004). The postnatal ethanol-exposed animals also had decreased insulin sensitivity similar to the prenatal exposure group. Given the outcomes demonstrated in these limited animal studies, clinical interventions to limit maternal smoking and alcohol consumption may need to be extended to the lactation period.

Nonnutritive sweeteners

Artificial sweeteners have become commonplace in western food and drink as a substitute for sugar. In an animal model of nonnutritive sweetener exposure during lactation, female lactating mice were exposed to saccharin in water for 21 days after birth (Parlee *et al.* 2014). In this study, female offspring experienced decreased weight gain that emerged during the third postnatal week, while male offspring showed increased body weight with age. In adulthood, male saccharin exposed offspring showed decreased fat mass and increased lean mass, with changes in visceral adipocyte size; however, female mice did not follow this pattern (Parlee *et al.* 2014).

In a human study of nonnutritive sweetener consumption during lactation, Sylvetsky *et al.* (2015) found that saccharin, sucralose and acesulfame potassium, but not aspartame, were all detected in human breast milk. However, further research is needed to understand the impact of these nonnutritive sweeteners on long-term metabolic outcomes in the offspring.

Environmental toxins

It is becoming increasingly clear that developmental exposures to environmental contaminants have lasting effects on metabolic tissues and have endocrine disrupting potential (Heindel *et al.* 2017). Studies have documented the presence of environmental toxins in breast milk thus introducing the possibility of lactational programming (Solomon & Weiss 2002). Chemicals that persist in the environment even after regulation to ban them are concerning if they are lipophilic, as they are likely to accumulate in the adipose tissue over time. Indeed, higher levels are thought to reach breast-fed infants than would be accounted for by daily exposure, an aspect reviewed by Lehmann *et al.* (2014). A study of 633 women found breast milk to be a route of exposure to perfluoroalkyl acids in breast-fed infants (Mondal *et al.* 2014). In another study measuring 121 endocrine disrupting chemicals in breast milk, a higher prevalence of persistent chemicals were found in samples obtained in Denmark compared to those obtained in Finland (Krysiak-Baltyn *et al.* 2010). To what

extent country-specific differences in lactational exposure to persistent organic chemicals are associated with differences in metabolic health, such as that reported for testicular cancers (Skakkebaek *et al.* 2007, Krysiak-Baltyn *et al.* 2010, Antignac *et al.* 2016) remains to be determined.

Studies addressing the impact of exposure to environmental chemicals exclusively during the lactational window are sparse. Most studies testing the impact of exposure to environmental chemicals have focused on the perinatal window. In these studies it is difficult to distinguish the effects of gestational impact from lactational impact. In one cross-fostering study, Bisphenol AF administered to rats only during the postnatal window was found to transfer thorough breast milk to the offspring and decrease the growth of male pups during suckling (Li *et al.* 2016). When considering the impact of polychlorinated biphenyls (PCBs), trends found between human breast milk PCB concentrations and infant growth outcomes are conflicting. One study showed a correlation between increased breast milk levels of beta-hexachlorocyclohexane (β -HCH), an agricultural pesticide, at 1 month after birth and reduced infant weight gain up to age 6 months (Criswell *et al.* 2017). However, another found no significant difference between infant growth measures at 6 months and 1 year and increased PCBs in human milk at 3 months postpartum (Pan *et al.* 2010). A large analysis of multiple European birth cohorts demonstrated a negative association between postnatal PCB-153 exposure and change in infant weight for age z-score from birth to 24 months (Iszatt *et al.* 2015). This field of research centering on the impact of lactational exposure to endocrine disrupting chemicals is beginning to expand and presents an opportunity to investigate the long-term metabolic consequences from such exposures.

Mechanisms of lactational programming

Molecular mechanisms at the level of offspring tissue identified in lactational programming experiments include oxidative stress, inflammation, methylation changes, histone modifications and altered axonal migration (Fig. 2), similar to mechanisms identified in *in utero* programming (Berends & Ozanne 2012). While the specific mediators of these changes are not known, alterations in the levels and actions of hormones present in the milk, including insulin, leptin and cortisol have been implicated (Badillo-Suárez *et al.* 2017) along with altered breast milk microRNA levels (Munch *et al.* 2013). Exposure to excessive nutrients during lactation has been shown to induce oxidative stress and increase reactive oxygen species in the livers of male rat offspring (Conceicao *et al.* 2013). In this rat model of postnatal overfeeding there were higher levels of malondialdehyde, a marker of oxidative stress and reduced levels of antioxidants including catalase, superoxide dismutase and glutathione peroxidase in the livers of male offspring (Conceicao *et al.* 2013). Reactive oxygen species have been linked to attenuated insulin signaling, particularly in the liver in rodent models (Hirosumi *et al.* 2002, Conceicao *et al.* 2013). Elevations in milk reactive oxygen species have also been linked positively with infant weight-for-length z-score up to age 6 months (Young *et al.* 2017b). Epigenetic changes may occur in response to postnatal nutritional influences, leading to programming. Longer duration of breastfeeding in humans has been linked with global methylation changes, along with methylation changes of promoters for genes important for metabolic homeostasis (Hartwig *et al.* 2017). For instance, longer duration of breastfeeding was found to be associated with a decrease in leptin

promoter methylation in human blood samples of 17-month-old babies (Obermann-Borst *et al.* 2013). Neonatal feeding of high-carbohydrate formula increased hypothalamic neuropeptide Y (an orexigenic neuropeptide) mRNA expression, decreased promoter methylation at several CpG sites and increased histone acetylation in female rat offspring (Mahmood *et al.* 2013). This same group also demonstrated a decrease in skeletal muscle *Glut4* transporter mRNA in adult male offspring from the high-carbohydrate group. This decrease in *Glut4* transporter mRNA was accompanied by an increase in *Slc2a4* (encoding insulin-related glucose transporter 4) promoter methylation (Raychaudhuri *et al.* 2014). Another component of breast milk involved in regulation of gene expression is microRNA. These small noncoding RNAs are thought to transfer undigested from human milk into the infant blood stream (Kosaka *et al.* 2010, Alsaweed *et al.* 2015). Some of the specific species of microRNAs detected in human breast milk are altered in response to maternal HFD during lactation (Munch *et al.* 2013). It is important to note that changes in the milk likely lead to the deleterious responses in offspring tissues, but more work needs to be done to understand the specific mediators of these effects.

Interventions during the window of lactation

Interventions during the critical periods of infant development, like the lactational window, offer a key area for future research to identify potential strategies to target long-term metabolic risk prevention. Current intervention work has focused on the areas of calorie restriction, exercise intervention, and nutritional supplementation.

Maternal exercise during lactation

Maternal exercise during the lactation period has numerous physiological benefits for both mother and baby (Bane 2015). However, most of the research has focused on maternal postpartum metabolic health (Dewey *et al.* 1994, Lovelady *et al.* 2000) rather than on infant outcomes from maternal exercise. A perinatal study by Ribeiro *et al.* provides a preliminary insight into the metabolic benefits of maternal perinatal exercise (Ribeiro *et al.* 2017). Using an animal model, this study evaluated the effects of maternal low-intensity exercise during both pregnancy and lactation and postnatal overnutrition on adult male offspring metabolic outcomes (Ribeiro *et al.* 2017). In both normal litter and small litter (overnutrition) offspring of exercised dams, a reduction in fasting insulin and a decrease in adiposity were observed compared to both normal litter and small litter offspring of sedentary dams. Human studies of the effect of exercise interventions on milk composition and offspring metabolic health could provide more valuable evidence in this area.

Offspring dietary changes and supplementation

Studies examining dietary interventions during the lactational window are few. Postnatal dietary interventions during the suckling period may offer a method to realign metabolic abnormalities developed as a neonate. The limited number of available intervention studies do not yet support human applications. Prebiotic fiber offers one form of dietary modification that has been linked with a reduction in body fat and glucose levels (Reid *et al.* 2016). We found no animal or human clinical studies that focus exclusively on probiotic intervention during the lactational window and offspring metabolic outcomes. However,

Luoto *et al.* looked at probiotic supplementation (*Lactobacillus rhamnosus*) during the perinatal period, from 4 weeks before birth to 6 months postpartum (Luoto *et al.* 2010). At 4 years of age, children perinatally supplemented with probiotics showed a trend to reduced BMI (Luoto *et al.* 2010). These results suggest potential for a dietary supplement to be beneficial for metabolic health and highlight the need for further investigation of such supplements during the lactation period.

Non-dietary interventions

Since milk bioactive factors are thought to play a role in programming, investigations into bioactive factor supplements as interventions to prevent metabolic disease have been undertaken. Leptin supplementation offers one such potential intervention during suckling, given its roles in central appetite and energy regulation and adipogenesis. Leptin is present in breast milk but not in commercial formulas and has been proposed to result in signals of satiety in newborns (Badillo-Suárez *et al.* 2017). A human study examining Filipino women showed higher milk leptin in mothers with increased body fat and an inverse relation between milk leptin levels infant weight and BMI at 1 year of age (Quinn *et al.* 2015). Patterson *et al.* found that large litter rearing decreased circulating leptin levels by the second postnatal day and reduced weight gain by postnatal day 8 in male and female pups of diet-induced obese rats (Patterson *et al.* 2010). In a rat model of neonatal supplementation with oral leptin, long-term outcomes included lower body weight in adulthood and improved insulin sensitivity in male offspring (Sánchez *et al.* 2008). When leptin was provided as an oral intervention in a rat model of HFD, male offspring had improved body weight, lower leptin receptor abundance in adipose tissue, increased expression of genes involved in fat oxidation and lipogenesis, along with decreased liver fat accumulation (Picó *et al.* 2007, Priego *et al.* 2010). When leptin was supplemented subcutaneously to pups in a model of maternal undernutrition, there was decreased weight gain in pups and normalized glucose, insulin and leptin concentrations compared to pups not receiving supplementation (Vickers *et al.* 2005). GLP-1, an incretin hormone, plays a role in glucose homeostasis by increasing beta cell insulin secretion as well as promotes satiety via hypothalamic actions (Badillo-Suárez *et al.* 2017). Animal models of early postnatal intervention with GLP-1 receptor agonists have demonstrated decreased adipose tissue and improvements in glucose tolerance and liver insulin sensitivity in mouse (male and female), rat (male) and sheep (sex not reported) models (Raab *et al.* 2009, Gatford *et al.* 2013, Rozo *et al.* 2017). Further work is needed in order to better characterize benefits vs risks in order to consider translation of these findings from animal models into human studies.

Conclusions

Despite the broad range of exposures covered in this review, common outcomes of early stressors during the lactational window are programming of insulin responsiveness in insulin sensitive tissues; feeding behavior via changes in hypothalamic circuits and leptin action; adipocyte number and specific adipose depot expansion and pancreatic beta cell glucose responsiveness. Animal models of macronutrient excess or global overnutrition during the lactational window lead to dramatic 10–40% increases in offspring body weight often with increases in visceral fat, while findings in large human intervention trials revealed more

modest impacts on weight, weight for length, waist circumference or BMI. Other common patterns that emerge from these studies are the occurrence of physiologic changes during the exposure, which then seem to resolve only to be unmasked when a second stressor is applied later in life. Additionally, in rodent models of lactational programming the phenotype is often more severe in male offspring whereas the primate females tend to have stronger metabolic perturbations. Finally, these studies have demonstrated that there is indeed an independent contribution of the lactation period to long-term metabolic health and that the impact of lactational stressors can be as significant as an *in utero* stressor.

With the rising incidence of obesity, diabetes and hypertension, understanding the windows of susceptibility that contribute to developmental programming are vital to identify important time periods to target intervention strategies. The lactational window has been shown to be a critical window for establishment of body composition, insulin sensitivity and beta cell mass accrual and is a period of greater plasticity of metabolic tissues than later in life. In addition, the lactation period offers a time for intervention such that gestational insults may be ameliorated in offspring at risk for poor metabolic outcomes. The programming influences of altered breast milk nutrient, hormone and bioactive factor composition, maternal health and environmental toxin exposures are an area that is only beginning to unravel. Breast milk research is made more complex because milk composition has been shown to change over time, as well as with maternal age, parity, multiple births and infant gender in animal and human studies (Michaelson *et al.* 1994, Hinde 2009, Hinde *et al.* 2009, Powe *et al.* 2010, Thakkar *et al.* 2013). Significant future research with a focus on the lactational window is necessary to understand specific mechanisms that change offspring metabolic trajectory taking into account the complex maternal influences on breast milk.

Of the studies reviewed, few examine a specific lactational stressor with detailed milk composition studies and long-term offspring metabolic phenotyping. Animal studies offer the opportunity to address this gap and pinpoint mediators of programmed outcomes to isolate milk changes, rather than changes in bonding, as causative factors. Animal models are not a perfect proxy for human lactation given variations in organ developmental time frames, plasticity and capacity to buffer deleterious exposures, therefore, further large human cohort studies are also needed to understand the short- and long-term impacts of lactational stressors. Such studies could identify biomarkers of metabolic outcomes with the goal of eventually targeting interventions to the lactational window and develop clinical recommendations to advise lactating mothers. While breast milk has extensive benefits to the newborn that cannot be undervalued, a greater understanding of the influence of altered milk composition could allow for early maternal lifestyle interventions and infant personalized nutrition interventions to optimize long-term metabolic health.

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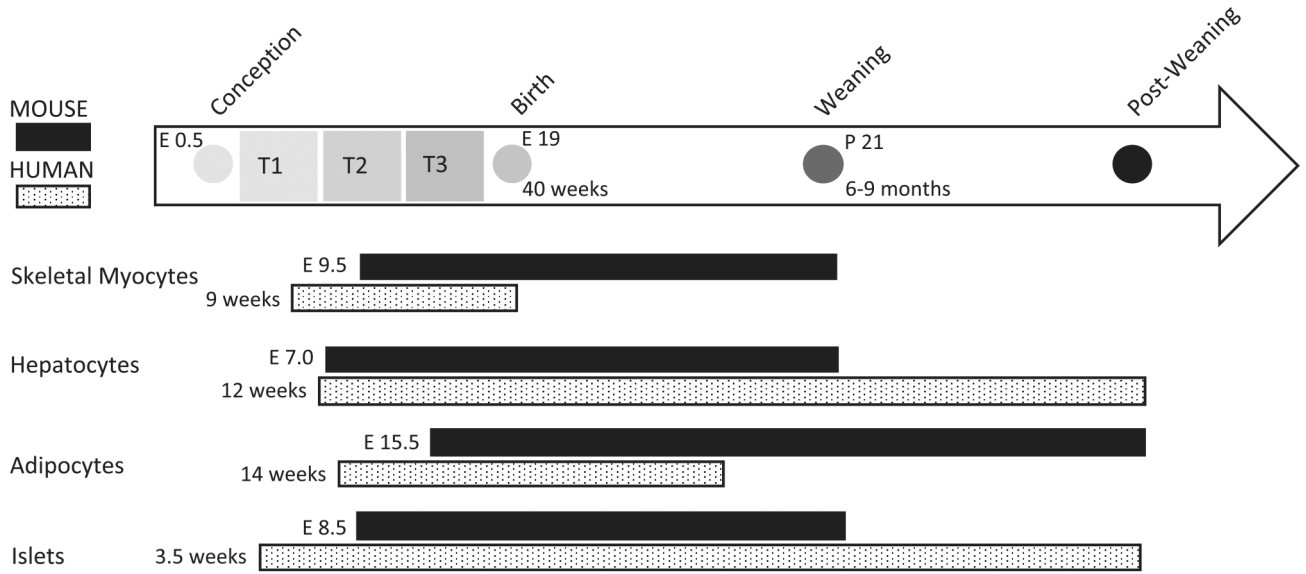
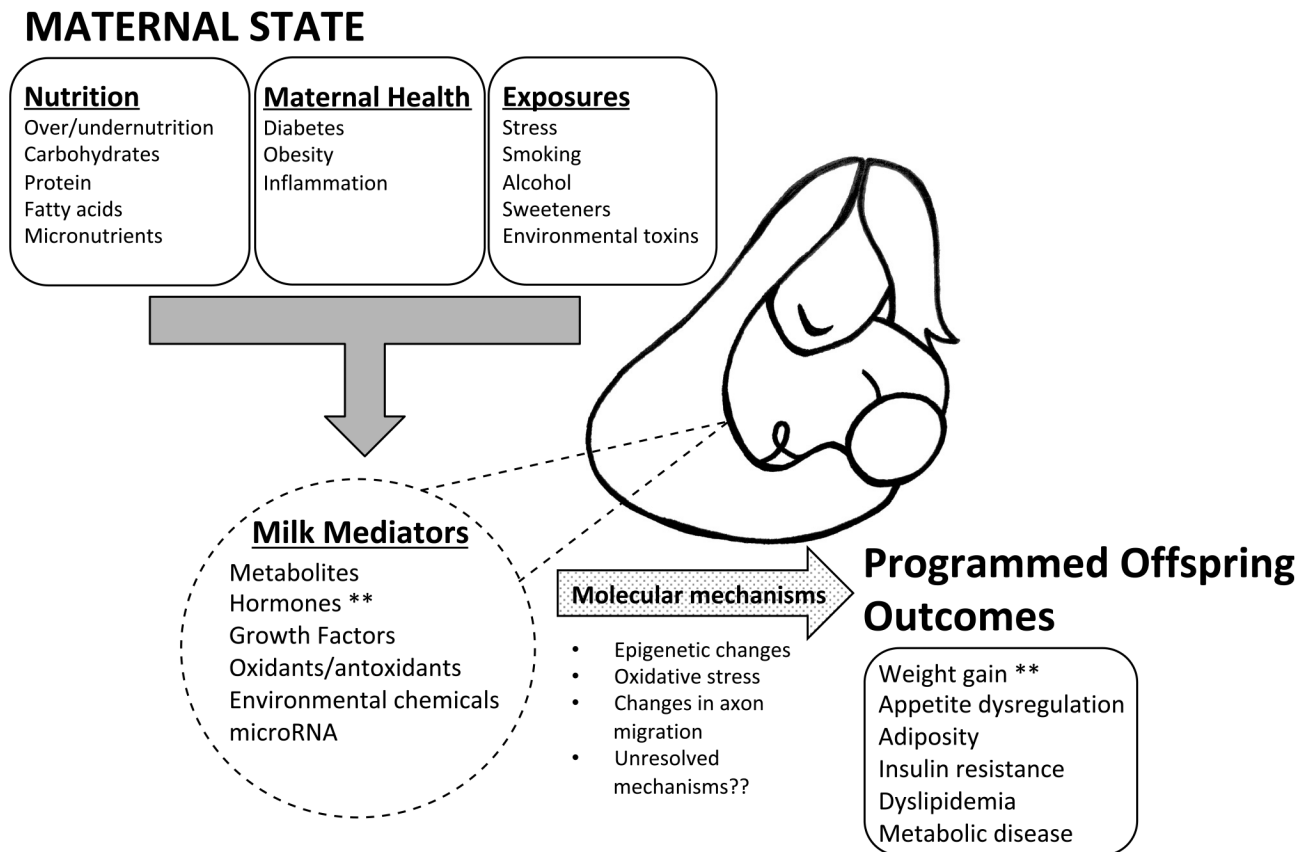


Figure 1.
 Timelines for mouse and human metabolic tissue development.



** Increased milk insulin in dams fed a high fat diet mediates impaired glucose tolerance and an obese phenotype in offspring (Vogt *et al.* 2014)

Figure 2. Proposed mechanisms of developmental programming during the lactation period. Copyright Gregg Lab, reproduced with permission.

Table 1

Summary of animal and human nutrient and environmental exposures during lactation.

Programming influence	Author	Species	Breast milk composition	Sex differences	Metabolic outcomes and mechanisms
Undernutrition	Sadagurski <i>et al.</i> (2014)	Mouse	Not evaluated	Both male and female mice became insulin sensitive at different time points in adulthood (later in females). Males only had reduced beta cell mass and proliferation rate	Reduced body fat and perigonadal adipocyte size, increased lean body weight, lower fasting leptin, increased insulin sensitivity in pups of a crowded litter
	Lopez-Soldado <i>et al.</i> (2006)	Rat	Triacylglycerol concentration lower in dams with large litters	Males had decreased lumbar and epididymal adipose weights. Lower weight, reduced VLDL-TG (adult)	Decreased total weight and adipose weight (males), increased insulin sensitivity in pups of a large litter
Overnutrition	Glavas <i>et al.</i> (2010)	Mouse	Not evaluated	Male rats studied exclusively	Increased body weight, increased fat deposits (visceral, epididymal, retroperitoneal) and hyperleptinemia with hypothalamic leptin resistance. As an adult, insulin resistance and obesity developed when challenged with a high-fat diet
	Bernardo <i>et al.</i> (2016)	Mouse	Not evaluated	Male mice studied exclusively	Increased body weight and visceral fat, increased liver weight with hyperinsulinemia and hyperglycemia. Impaired insulin signaling in the heart with mild mitochondrial structure abnormalities
	Plagemann <i>et al.</i> (1992)	Rat	Not evaluated	Male rats studied exclusively	Increased body weight gain persisting into adulthood, increased systolic blood pressure and elevated basal insulin level
	Xiao <i>et al.</i> (2007)	Rat	Not evaluated	Male rats studied exclusively	Increase in body weight, increased food intake, impaired brown adipose tissue thermogenic response to cold stimulus
	Rajia <i>et al.</i> (2010)	Rat	Not evaluated	Male rats studied exclusively	Increased weight and white adipose tissue on chow diet in small litter and impaired glucose tolerance and liver fat on adult HFD re-challenge in the small litter offspring
	Bei <i>et al.</i> (2015)	Rat	Not evaluated	Male rats studied exclusively	Adult insulin resistance, increased free fatty acid and increased triglycerides levels, increased body weight and white adipose tissue. Impaired insulin signaling with downregulation of GLUT4 receptors in adipose tissue and skeletal muscle
	Lewis <i>et al.</i> (1989)	Primate	Not evaluated	Female baboons had increased fat mass and adipocyte volume; overfed males had no weight change but increased fat in visceral and subcutaneous depots	Obese phenotype (female) baboons, potentially mediated by increased adipocyte volume
	Lewis <i>et al.</i> (1992)	Primate	Not evaluated	Female baboons studied exclusively	Early increased insulin secretion in response to meals but not at later time points. Early blunted cortisol responses that resolved by 18 weeks of age. Increased weight in females after puberty and no change in fat cell volume

	Programming influence	Author	Species	Breast milk composition	Sex differences	Metabolic outcomes and mechanisms
	Carbohydrate	Early outcomes: Srinivasan <i>et al.</i> (2000, 2001)	Rat	Not evaluated	Sex differences not analyzed or male rats exclusively studied	Hyperinsulinemia related to increased GLP-1 and GLP-1 receptor mRNA with increased downstream signaling pathway activity; increased activity of protein kinases that mediate insulin secretion in offspring islets; increased insulin biosynthesis with increased PDX1 levels with increased mRNA of factors regulating <i>Pdx1</i> expression HCD, offspring developed increased body, perigonadal fat pad and liver weights; increased liver fat, increased adipocyte size in epididymal tissues and increased lipogenic enzyme activity (Hiremagalur <i>et al.</i> 1993). Offspring also showed increased basal and stimulated insulin levels with underlying increases in <i>Glut2</i> and preproinsulin mRNA, along with upstream factors that regulate preproinsulin transcription (Aalinkel <i>et al.</i> 2001). Pair feeding after HCD reduced weight gain and serum hormones normalized, however islets remained hypersecretory (Srinivasan <i>et al.</i> 2013)
		Adult outcomes: Hiremagalur <i>et al.</i> (1993), Aalinkel <i>et al.</i> (2001), Srinivasan <i>et al.</i> (2013)				
		Goran <i>et al.</i> (2017)	Human	Breast milk sugars measured	No effect of infant sex	Breast milk fructose composition at 6 months related to increased infant growth in weight, lean mass and fat mass
Protein		Kucia <i>et al.</i> (2011)	Mouse	Decrease in milk lactose content with high-protein diet	Similar outcomes for males and females	A maternal high-protein diet during lactation showed reduced litter mass linked to decreases in mammary gland mRNA levels with impaired lactation
		Moura <i>et al.</i> (2002)	Rat	Not evaluated	Sex differences not analyzed	Maternal low-protein diet led to increased offspring plasma insulin and leptin during lactation and decreased during adulthood during a re-challenge protein-free diet
		Morimoto <i>et al.</i> (2012)	Rat	Not evaluated	Male rats studied exclusively	Rat offspring with maternal protein-restriction showed increased islet insulin secretion <i>in vitro</i> at weaning but impaired insulin secretion after glucose challenge as adults
		Rodrigues <i>et al.</i> (2017)	Rat	Not evaluated	Female rat pups nursed on high-protein cow's milk developed increased fat, hyperphagia and lower insulin secretion. Males had lower overall body protein	Female rats developed hypoinsulinemia and normoglycemia while males showed unchanged insulin levels and hyperglycemia when nursed on a high-protein cow's milk diet, potentially mediated by estrogen and prolactin
		European Childhood Obesity Trial: Koletzko <i>et al.</i> (2009), Escribano <i>et al.</i> (2012), Weber <i>et al.</i> (2014)	Human	Not evaluated	Analysis adjusted for sex	At age 2 years, infant fed a higher protein diet had increased Wt/L Z-score and increased weight (Koletzko <i>et al.</i> 2009). Increased weight gain velocity and fat mass for first 6 months of life and a higher BMI at 12, but not 24 months for infants given high-protein formula (Escribano <i>et al.</i> 2012). Children given high-protein formula showed increased BMI at 6 years of age and 2.4 times the risk of obesity as compared to the low-protein group (Weber <i>et al.</i> 2014)
Fat		Vogt <i>et al.</i> (2014)	Mouse	Increase in milk glucose and insulin content from dams fed a high-fat diet during lactation	Male mice studied exclusively	A maternal HFD during lactation showed an obese phenotype and impaired glucose tolerance in offspring, mediated by an impairment of axonal projections to the PVH area of the hypothalamus and decreased parasympathetic innervations of the pancreatic beta-cells

	Programming influence	Author	Species	Breast milk composition	Sex differences	Metabolic outcomes and mechanisms
		Liang <i>et al.</i> (2016)	Mouse	Increase in milk triglyceride levels	Male mice studied exclusively	A maternal HFD during lactation showed increased body weight and fat mass in adults with impaired glucose tolerance and insulin sensitivity and an abnormal brown adipose tissue response to cold
		Sun <i>et al.</i> (2012)	Rat	Increase in milk leptin and fat content at postnatal day 21	Similar results in males and females	Rat pups cross-fostered to dams fed HFD during pregnancy and lactation showed greater adiposity with an increase in subcutaneous fat, increased plasma leptin, elevated insulin levels associated with a reduction in STAT3 response to leptin in the hypothalamus
		Masuyama and Hiramatsu (2014)	Rat	Not evaluated	Male rats showed an increased leptin surge compared to females	Rat pups cross-fostered to dams fed HFD during lactation showed increased fat mass gain, food intake, glucose intolerance and insulin resistance along with increased mRNA expression of leptin, triglycerides and adiponectin
Fatty acids		Oosting <i>et al.</i> (2010)	Mouse	Increase milk n-3 LC-PUFAs in dams supplemented with n-3	Male mice studied exclusively	Mice fed an n-3 rich postnatal diet showed a 30% reduction in fat accumulation when challenged in adulthood with a western style diet
		Korotkova <i>et al.</i> (2002a, b)	Rat	Increase in milk leptin and saturation PUFAs in dams fed EFAD. No difference in leptin level with n-3 and n-6 supplementation	Sex differences not analyzed	Decreased serum leptin levels and leptin mRNA in inguinal white adipose tissues of offspring suckling to dams on EFAD. Pups receiving high-n-3 diet developed lower body weight, inguinal fat pad weight, adipocyte size and serum leptin. Pups receiving increased ratio n-6/n-3 PUFA had increased body weight, inguinal fat pad weight and adipocyte size
		Hadley <i>et al.</i> (2017)	Rat	Dams supplemented with a combination ARA and DHA diet had milk with increased ARA and DHA	Male mice studied exclusively	Offspring cross-fostered to dams supplemented with a combination ARA and DHA diet showed increased body weight
		Grant <i>et al.</i> (2011)	Primate	Decrease in milk protein, DHA, EPA levels and increase insulin	Sex differences not analyzed	Offspring developed increased body fat and lower lean body mass when maternal diet was supplemented with omega-6. Infant DHA level at 16 weeks had a minor negative association with weight at age 1 and 2 years
		Makrides <i>et al.</i> (1999)	Human	Not evaluated	Analysis adjusted for sex	Fish oil supplementation associated with a 0.65 kg/m ² increase in BMI at age 2-5 years
		Lauritzen <i>et al.</i> (2005), Asserthøj <i>et al.</i> (2009)	Human	Not evaluated	Analysis adjusted for sex	Maternal erythrocyte DHA level positively associated with offspring BMI and waist circumference (Lauritzen <i>et al.</i> 2005). At age 7 the association no longer remained (Asserthøj <i>et al.</i> 2009)
		Helland <i>et al.</i> (2008)	Human	Measured PUFAs in breast milk	Analysis adjusted for sex	Alpha-linoleic acid levels in breast milk sampled at 3-months positively correlated with child BMI at 7 years
		Much <i>et al.</i> (2013)	Human	Maternal n-3 supplementation and reduced ARA intake showed a reduced n-6 to n-3 ratio	Analysis adjusted for sex	Breast milk DHA and n-3 fatty acids have a positive relationship with infant body fat subcutaneous to pre-peritoneal ratios at 6 weeks of age
Maternal diabetes		Fahrenkrog <i>et al.</i> (2004)	Rat	Not evaluated	Sex differences not analyzed	Reduced growth rate (weight and length) in offspring of diabetic dams potentially due to malprogramming of the hypothalamus. No difference in plasma insulin, leptin concentrations
		Plagemann <i>et al.</i> (2002)	Human	Not evaluated	Sex differences not analyzed	Infants of diabetic mothers receiving banked breast milk as supplementation were protected against obesity at 2 years old

Programming influence	Author	Species	Breast milk composition	Sex differences	Metabolic outcomes and mechanisms
Maternal obesity	Schaefer-Graf <i>et al.</i> (2006) Gonski <i>et al.</i> (2006) Bernstein and Hinde (2016) Mayer-Davis <i>et al.</i> (2006) Fields <i>et al.</i> (2017)	Human Rat Primate Human Human	Not evaluated Diet-induced obese dams had higher insulin and decreased total PUFAs Milk growth factors measured Not evaluated, retrospective report Insulin and leptin levels increased with increased BMI	Sex differences not analyzed Male rats studied exclusively Increased female offspring growth rate with lower milk EGF-receptor Analysis adjusted for sex Maternal BMI correlates with higher human breast milk insulin levels for mothers who gave birth to female infants	Offspring of obese mothers with gestational diabetes had a decreased risk of childhood overweight if they were breastfed >3 months Improved insulin sensitivity with maintained obese phenotype in offspring of obese dams fostered to lean dams. Lean dam offspring then given a high-energy diet developed obesity and insulin resistance Lower EGF and EGF-receptor in increased weight mothers. Higher EGF and EGF-R associated with increased infant body mass Self-report of exclusive breast feeding to 6 months associated with an odds ratio of 0.75 for overweight in children age 9-14 years High-milk leptin associated with decreased infant length and fat mass at 6 months
Stress	Dantzer <i>et al.</i> (2013) Hinde <i>et al.</i> (2015) Hahn-Holbrook <i>et al.</i> (2016)	Squirrel Primate Human	Not evaluated Higher milk cortisol with stress. Measured milk fat, protein, sugars Cortisol is found in human breast milk	Sex differences not analyzed Females more sensitive to milk cortisol in relation to temperament scores In females, decreased rapid early BMI gain linked to cortisol breast milk levels	Accelerated offspring postnatal growth rate with maternal physiological stress At 1 month, infant growth was highest with higher milk cortisol and milk energy peaked Increased milk cortisol associated with lower BMI at 2 years
Smoking	de Oliveira <i>et al.</i> (2010) Santos-Silva <i>et al.</i> (2011) Santos-Silva <i>et al.</i> (2013) Tavares Do Carmo <i>et al.</i> (1999)	Rat Rat Rat Rat	Dams treated with nicotine infusion had milk with higher lactose and energy content. Cotinine levels were similar in milk and plasma Smoke-exposed dams showed milk with increased lactose and triglycerides Not evaluated Maternal ethanol intake decreases milk production	Male rats studied exclusively Male rats studied exclusively Sex differences no analyzed Male rats studied exclusively	Offspring with increased body weight, adipocyte hypertrophy, insulin and leptin levels as adults when exposed to nicotine directly, possibly related to reduced protein in leptin signaling Pups had lower total fat, hyperinsulinemia, hypertriglyceridemia
Alcohol	Chen and Nyomba (2004) Parlee <i>et al.</i> (2014)	Rat Mouse	Not evaluated Not evaluated	Sex differences no analyzed Male rats studied exclusively In males, decreased fat mass and adipocyte size, improved glucose tolerance with saccharin lactational exposure	In adulthood, pups exposed to smoke had increased total and visceral fat mass, dyslipidemia, increase leptin and adiponectin Decreased body weight and brain weight, higher serum triglyceride/free fatty acid, beta-hydroxy-butyrate levels, decreased plasma glucose in ethanol exposed pups Decreased pup birth weight, increased triglycerides, insulin resistance with ethanol exposure Saccharin exposure was linked to initial reduced body weight that persisted in females
Nonnutritive sweeteners					

Programming influence	Author	Species	Breast milk composition	Sex differences	Metabolic outcomes and mechanisms
Environmental toxin	Li <i>et al.</i> (2016)	Rat	Bisphenol AF concentration not measured in milk	Males rats studied exclusively	Bisphenol AF was transferred to pups during lactation and found in the testes with increased testosterone levels, altered gene expression in cell differentiation and meiosis. Decreased body weight of male pups
	Criswell <i>et al.</i> (2017)	Human	Breast milk PCBs, poly-brominated diphenyl ethers, organochlorine pesticides, β -HCH levels	Results adjusted for child sex	Increased milk β -HCH correlated with reduced infant weight gain at 6 months
	Pan <i>et al.</i> (2010)	Human	Breast milk PCBs, pesticides	No effect after co-variate analysis with infant sex	Breast milk chemical levels had no impact on infant growth
	Izatt <i>et al.</i> (2015)	Human	Not evaluated	Sex differences not reported	Postnatal PCB-153 exposure associated with about a 140 g weight deficit at the age of 2 years compared to those with lower exposures

ARA, arachidonic acid; β -HCH, beta-hexachlorocyclohexane; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EFAD, essential fatty acid deficient diet; HCD, high-carbohydrate diet; HFD, high-fat diet; LCP/FA, long-chain omega-3 polyunsaturated fatty acids; PCBs, polychlorinated biphenyls; VLDL-TG, very low density lipoprotein triglyceride; BMI, body mass index; EGF, epidermal growth factor; PCB, polychlorinated biphenyl.