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Opinion

Exercised breastmilk: a kick-start to prevent childhood obesity?

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Exercise has systemic health benefits through effects on multiple tissues, with intertissue communication. Recent studies indicate that exercise may improve breastmilk composition and thereby reduce the intergenerational transmission of obesity. Even if breastmilk is considered optimal infant nutrition, there is evidence for variations in its composition between mothers who are normal weight, those with obesity, and those who are physically active. Nutrition early in life is important for later-life susceptibility to obesity and other metabolic diseases, and maternal exercise may provide protection against the development of metabolic disease. Here we summarize recent research on the influence of maternal obesity on breastmilk composition and discuss the potential role of exercise-induced adaptations to breastmilk as a kick-start to prevent childhood obesity.

Highlights

The period from conception to 2 years of age is the most critical period for pathophysiological disorders leading to childhood obesity.

Differences in breastmilk composition may play a role in the mother-to-child transmission of obesity.

Human milk oligosaccharides (HMOs) are identified as central breastmilk compounds linking maternal obesity to infant weight gain in early life, their effect potentially mediated by changes in the infant's gut microbiome.

Emerging data suggest that acute and chronic exercise can modify both the nutritional and non-nutritional bioactive constituents of breastmilk.

In mice, exercise training increased the abundance of the HMO 3′sialyllactose in milk, and this HMO was crucial in mediating improvements to metabolic health in mouse offspring. Whether these findings are translatable to humans is unknown.

Can exercise affect breastmilk composition? (Why wouldn't it?)

Exercise is a formidable regulator of overall systemic metabolism through both acute effects driven by individual exercise sessions and chronic adaptations. Exercise challenges whole-body homeostasis and affects multiple cells, tissues, and organs through the increased metabolic activity of contracting skeletal muscles. Moreover, the beneficial effects of exercise are not limited to adaptations within tissues, but instead stem from the integration of intertissue communication through various signaling molecules, hormones, and **cytokines** (see Glossary) collectively known as 'exerkines' [1]. Dramatic shifts are observed for more than 80% of annotated metabolites in the circulating **metabolome** in response to a single endurance exercise session of just 12 min, with beneficial alterations in metabolites from key metabolic pathways for obesity, insulin resistance, and inflammation [2]. These alterations may partly explain the broad benefits of exercise for cardiometabolic health. As little as 5 days of endurance training induced substantial changes in the serum metabolome, concomitant with improvements in aerobic fitness, glycemic control, and circulating lipid levels in men with overweight/obesity [3].

Recent studies have focused on the effects of maternal exercise on maternal and fetal outcomes. In humans, most studies demonstrate that exercise during pregnancy is safe and beneficial to both the mother and the fetus [4,5]. Specific benefits of maternal exercise in humans include increased rates of full-term delivery, normalized birth measures, reduced risk of macrosomia, and improved neurobehavioral abilities and cardiac autonomic health [5–9].

In rodents, numerous studies have identified the role of maternal exercise to improve the metabolic health of adult offspring. Studies have shown that maternal treadmill exercise and voluntary wheel running have similar effects in reducing body weight and fat mass and improving glucose metabolism and insulin sensitivity, even in the presence of a maternal high-fat diet [7,10–14]. The beneficial effects of maternal exercise on offspring metabolic health are not present in young animals, but instead in adult offspring. Importantly, these effects have been observed

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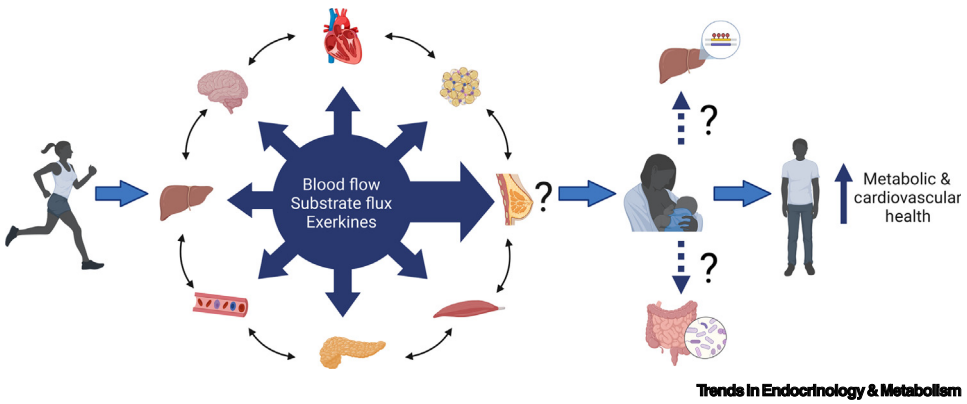

Figure 1. Exercise induces multiple molecular adaptations in the heart, adipose tissue, pancreas, skeletal muscle, circulation, liver, and brain directly and via interorgan crosstalk. Few data are currently available for exercise-induced adaptations in human breastmilk, but exercise may induce adaptations to breastmilk that can mediate whole-body metabolic and cardiovascular health in the offspring. The underlying mechanisms of such effects are unclear, but it is likely that breastmilk mediates improvements in the offspring's liver and microbiome. Figure was created with BioRender.com.

across species and strains of rodents (C57BL/6 mice, ICR mice, and Sprague–Dawley rats) [7,10,15,16]. The mechanisms underlying the beneficial effects of maternal exercise on offspring metabolism are only beginning to be elucidated, but we hypothesize that there are many factors involved. These include **epigenetic modifications** to metabolic tissues in the offspring, adaptations to the placenta, and changes to the offspring metabolome [7,11,17]. Little is known, however, about how exercise affects human breastmilk or whether exercise-induced breastmilk modifications affect infant health (Figure 1).

The interplay between maternal lifestyle, breastmilk composition, and infant health is an emerging field of research, with maternal smoking, body mass index (BMI), gestational diabetes, and diet all influencing breastmilk composition [18–22]. Maternal diet can alter breastmilk composition, with demonstrated differences between carbohydrate-rich and high-fat diets and between different types of carbohydrates [22]. However, there is currently no experimental evidence that lifestyle-induced breastmilk modifications affect infant obesity risk. One behavioral factor that has not been well studied in this context is exercise. Herein we review recent evidence for differences in breastmilk composition in response to maternal physical activity and metabolic health, the importance of breastmilk composition for infant obesity risk, and the potential role that exercise can have in making the milk less obesogenic. This topic is timely, in light of the increasing prevalence of childhood obesity and of recent advances in technology that now allow much more detailed analyses of breastmilk. We suggest that exercised breastmilk may be a kick-start to prevent childhood obesity (Figure 2, Key figure).

The origins of childhood obesity and early-life nutrition

Childhood obesity is reaching alarming proportions in many countries and poses an urgent challenge to healthcare systems. Between 2006 and 2016, 18% of European children aged 2–7 years were overweight or obese [23], while 13% of US children aged 2–5 years were obese in 2013–2016 [24]. Obesity affects a child's immediate health and quality of life, and children with obesity are five times more likely to remain obese as adults compared with those without childhood obesity [25]. Maternal pre-pregnancy BMI is a strong risk factor for childhood obesity, accounting for up to 21% of the **population attributable risk** [26], implying strong mother-to-child transmission.

Glossary

Common polygenic obesity: the results of hundreds of genetic variations that each has a small effect. The heritability of polygenic obesity follows a pattern that is similar to other complex traits and diseases. Polygenic obesity is classically considered as a different disease than monogenic obesity, which is typically a rare, early-onset, and severe type of obesity involving either chromosomal deletions or single-gene defects.
Cytokines: is a broad category of small proteins that are important in cell signaling and that help to control inflammation in the body.
Epigenetic modifications: heritable changes in phenotype not involving changes to the genetic code itself. Epigenetic modifications include DNA methylation (the process by which methyl groups are added to the DNA molecule and thereby typically repress gene transcription), histone modifications (a post-translational modification to histone proteins that alters chromatin structure or recruits histone modifiers that can impact gene expression), and noncoding RNAs such as miRNAs.
Gut microbiota dysbiosis: an imbalance in bacterial composition, changes in bacterial metabolic activities, or changes in bacterial distribution within the gut. A dysbiotic microbiota can compromise the gut barrier, resulting in a negative impact on the host immune system and metabolism.
Human milk oligosaccharides (HMOs): a group of structurally complex carbohydrate-based polymers. With around 200 different HMOs identified to date, HMOs are the third most abundant solid component in breast milk, after lactose and lipids.
Metabolome: the complete set of small molecules in a biological sample (e.g., a cell, an organ, a tissue, a biofluid, an entire organism).
miRNA: microRNA; a type of noncoding RNA molecule, meaning that it is not translated into protein. miRNAs are smaller than other types of RNA and can bind to mRNAs to inhibit specific protein production.
Population attributable risk: the proportion of the incidence of a disease that is due to an exposure; the difference between the risk in the total population and that in unexposed individuals.

Key figure

Maternal exercise during lactation may decrease childhood obesity risk, mediated via exercise-induced improvements in breastmilk composition

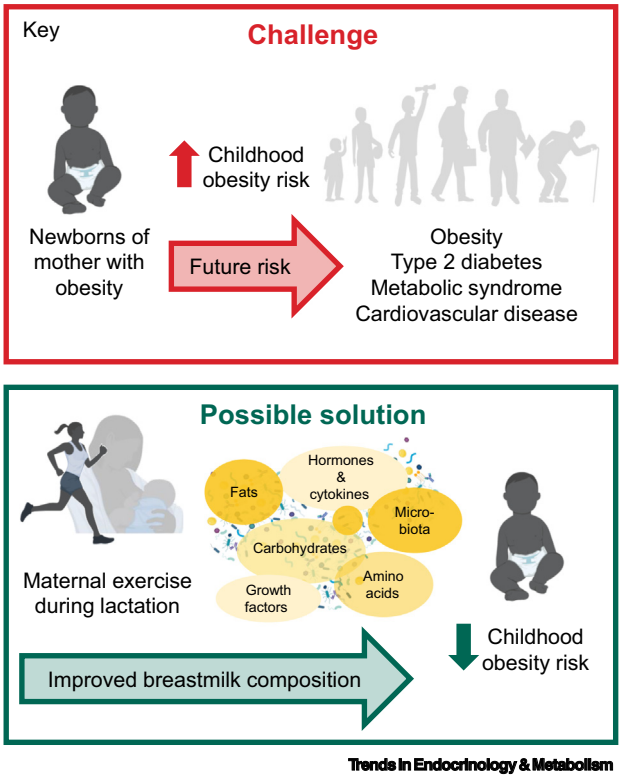

Figure 2. Parts of the figure were created with BioRender.com

Even if genetics partly accounts for the risk of **common polygenic obesity** in both childhood and adulthood, the proportion of variation in BMI currently explained by sequence variations in genetic loci is only ~1–2% in children [27] and ~6% in adults [28]. A large portion of the heritability of obesity thus remains unexplained. Epigenetic modifications are a key mechanism underlying this 'missing heritability' for obesity [29]. Early infant nutrition, and especially breastmilk, is thought to be a crucial factor influencing life-long health via epigenetic programming [30,31]. The period from conception to 2 years of age, known as 'the first 1000 days', is the most critical period for pathophysiological disorders leading to obesity in childhood and later life (Figure 3) [32]. Data from human cohorts have shown that faster weight gain in early infancy is associated with a greater risk of subsequent obesity [33,34], with rapid weight gain in the first 3 months of life associated with a higher body fat percentage and a higher degree of central obesity in childhood [35] and later in life [36].

During early postnatal life, the role of breastfeeding is a recognized factor in discussions of the nutritional background of childhood and later-life obesity. Breastfeeding has well-established nutritional and immunological advantages [37]. Breastfed children have a 13% lower likelihood of becoming overweight or obese compared with bottle-fed children [38], but these observational data may be confounded by unadjusted or non-measured factors.

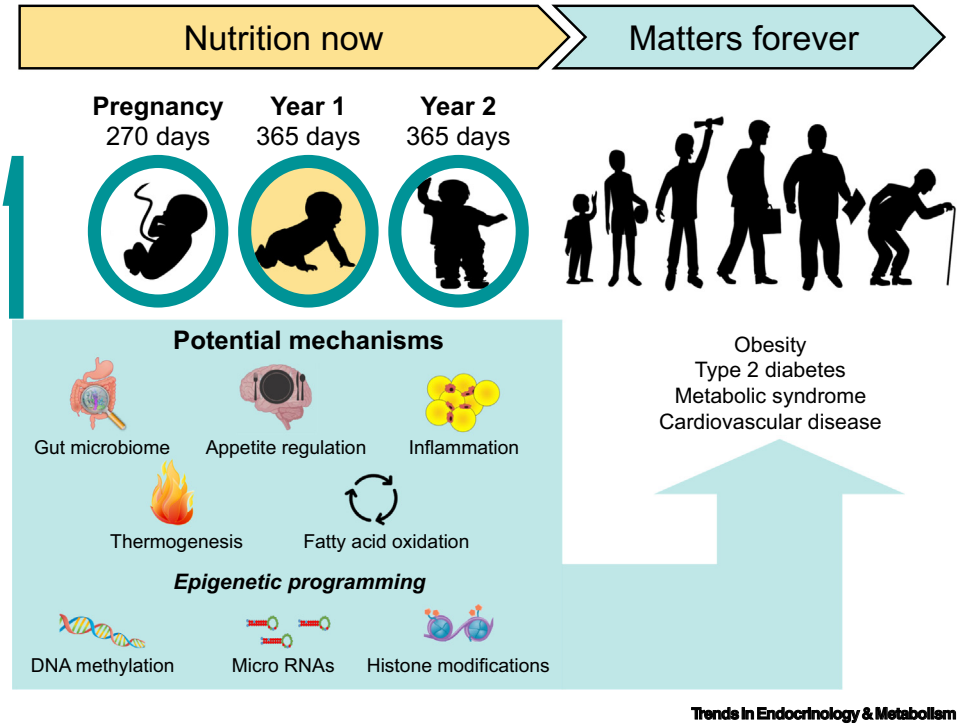

Figure 3. The first 1000 days include pregnancy and the first 2 years of life. Epigenetic DNA imprinting is particularly active during this period. Nutrition during this period, both via the placenta *in utero* and through breastmilk, formula milk, and solid food after birth, plays a key role in epigenetic DNA imprinting, thus affecting individual susceptibility to the subsequent development of obesity and other noncommunicable diseases. Parts of the figure were created with BioRender.com.

Maternal metabolism, exercise, and lactational programming of obesity

Human breastmilk contains diverse substances with potential mechanistic roles in metabolic health during early childhood, including macronutrients, micronutrients, metabolic hormones, adipokines, **miRNAs**, and inflammatory markers [39–41]. Our premise is that breastmilk is nutritionally optimal for infants, including for those born to women with overweight/obesity. However, recent evidence suggests differences in breastmilk composition between mothers with high and low BMI [19,42–48]. Maternal obesity is associated with changes in the breastmilk metabolome reminiscent of the metabolic signature in the plasma of individuals with obesity and type 2 diabetes, with high concentrations of several acylcarnitines involved in branched-chain amino-acid metabolism [19]. For a subset of the metabolites differing between women with obesity and normal-weight women, these differences are correlated with infant weight and fat percentage [19,42]. Maternal obesity is also associated with changes in the concentrations of **human milk oligosaccharides (HMOs)**, which are associated with growth during the first 5 years of life [45–48]. Furthermore, Isganaitis and colleagues showed that breastmilk adenine was positively correlated with both maternal BMI and infant weight at 1 month, whereas the metabolite 5-methylthioadenosine correlated with both maternal BMI and infant body fat percentage [19]. Another study showed that the three metabolites mannose, lyxitol, and shikimic acid, all which were increased in breastmilk from women with obesity, could predict higher infant adiposity over the first 6 months of life [42]. Collectively, these findings suggest that breastmilk components play a role in the mother-to-child transmission of obesity. This concept is supported by several studies in mice. For example, offspring born to lean dams and cross-fostered by obese dams have a profoundly dysmetabolic phenotype [49]. In humans, a study of infants born to mothers with type 2 diabetes who were fed either their own mothers' milk or banked human milk from non-diabetic

donors showed that the consumption of milk from the mothers with diabetes was associated with higher body weight at 2 years [50]. Maternal metabolic homeostasis during the lactation period may therefore influence the infant's risk of childhood obesity.

In contrast to maternal obesity, maternal exercise may modify both the nutrients and non-nutrient bioactive agents in breastmilk. Breastmilk is rich in lipids, including 'lipokines', a crucial class of lipids that act as signaling molecules and influence systemic metabolism.[51,52] Some lipokines have been detected in human milk. A breastmilk-specific lipid group, the alkylglycerols, may delay the transformation of the infant's beige adipose tissue (which is more metabolically active) to lipid-storing white adipose tissue [53]. It remains unknown whether alkylglycerol abundance is influenced by maternal exercise. Another lipokine, 12,13-dihydroxy-9*Z*-octadecenoic acid (12,13-diHOME), regulates brown adipose tissue fuel uptake and thermogenesis [54]. This lipokine was recently discovered in human milk and its abundance is inversely correlated with infant adiposity [55], again suggesting that differences in breastmilk composition may be functionally related to early-life obesity risk. 12,13-diHOME increases fatty acid uptake in skeletal muscle and its plasma concentrations increase acutely after exercise [2,56]. However, others have reported no sustained increase in circulating 12,13-diHOME after daily exercise training [3], suggesting that these effects are transient. 12,13-diHOME concentrations in breastmilk increase acutely after exercise in most women [55], but whether such an effect plays a causal role in limiting early rapid weight gain in the offspring remains to be determined. Furthermore, the relative abundance of short-chain fatty acids in human breastmilk may affect weight gain and adiposity during infancy, with negative associations between the levels of short-chain fatty acids (butyrate, formic acid, and acetate) in breastmilk and infant adiposity between the ages of 3 and 12 months [57]. The abundance of several circulating lipid metabolites changes acutely after exercise, in the opposite direction to changes observed in cardiometabolic diseases [2].

Exercise training has been shown to increase the abundance in mouse milk of 3′sialyllactose (3′SL), an HMO crucial in mediating improvements to metabolic health in mouse offspring [12]. The same study also showed that levels of this HMO in human breastmilk 2 months postpartum were weakly but significantly correlated with the mean number of steps taken per day during pregnancy. In rodent studies, maternal exercise in 3′SL-deficient (3′SL$^{-/-}$) mice had no exercise-induced improvements in metabolic health, while cross-fostering offspring from trained 3′SL$^{-/-}$ to trained wild-type dams partially restored the benefits of maternal exercise on metabolic health. Supplementation with 3′SL during the nursing period also improved the metabolic and cardiovascular health of adult offspring. While the mechanisms by which maternal exercise changes the composition of milk and how 3′SL improves offspring metabolism are unknown, the effects of maternal exercise on breastmilk is an area ripe for investigation and an important topic to ultimately be translated to humans.

Epigenetic and inflammatory factors in breastmilk that can alter infant metabolism

Breastmilk can regulate infant metabolism through a variety of mechanisms including growth factors, immune factors, microbiota, appetite hormones, and miRNAs [58,59]. It is one of the richest sources of miRNA among the body fluids, and miRNAs packaged in extracellular vesicles in breastmilk are bioavailable to breastfeeding infants [60]. These small noncoding RNAs bind to regions of mRNAs, modulating protein production typically by degrading or repressing the translation of the targeted RNA [59]. There is translational evidence for a role of breastmilk miRNA in the epigenetic programming of offspring [58]. miRNAs, particularly those in extracellular vesicles, have been identified as the most critical bioactive factors in human breastmilk in the modification of postnatal epigenetic regulation [59], but little is known about the effect of human breastmilk

miRNAs on infant body composition. Two studies have reported associations of selected breastmilk miRNAs with maternal BMI and infant body composition [43,44]. However, these studies investigated two completely different sets of miRNAs by targeted approaches, and the evidence concerning the effect of breastmilk miRNAs on infant body composition remains inconclusive. A recent systematic review reported associations between the circulating levels of some miRNAs and childhood obesity, the evidence being the strongest for miR-122, miR-222, and miR-423 [61]. Both miR-222 and miR-423 are detected in breastmilk and miR-222 levels are higher in the breastmilk of mothers with obesity than in breastmilk from normal-weight women [43].

The past decade has seen an exponential increase in evidence for a role of **gut microbiota dysbiosis** in host obesity, in both adults and children. Specifically, childhood obesity is associated with high levels of bacteria from the phylum Firmicutes and low levels of bacteria from the phylum Bacteroidetes [62]. HMOs have attracted particular attention as breastmilk bioactive compounds with effects on the infant gut microbiome, growth, and health [45–48,63–66]. Infants cannot digest HMOs, but these compounds are metabolized by some of the nursing child's intestinal bacteria. Breastmilk concentrations of certain HMOs have been associated with growth rate in early infancy [45–48], but few data are available concerning the potential mechanisms by which these compounds modulate infant growth. HMOs have been identified as candidate breastmilk compounds linking maternal obesity to infant fat accretion and thus involved in maternal-obesity-related postnatal nutritional programming [45–48]. The first 1000 days of life are central for the constitution of the gut microbiota and provide a unique opportunity to modify this process via breastmilk. If maternal exercise can alter the composition of HMOs in breastmilk, mothers may impact their infants' early gut microbiota via exercise training.

Chronic low-grade inflammation, with high circulating concentrations of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), contributes to metabolic disorders including insulin resistance and obesity. Regular exercise suppresses TNF-α-induced insulin resistance, providing a partial explanation for the protection against chronic diseases afforded by exercise [67]. There is some evidence for an anti-inflammatory effect of exercise during pregnancy on the first breastmilk produced after delivery (colostrum) [68], but the effect of maternal exercise during lactation on breastmilk inflammatory markers has been little studied. Only one previous study has investigated the relationship between exercise in lactating women and cytokines in breastmilk: an observational study reporting associations between exercise level and proinflammatory cytokine levels in breastmilk [69]. However, these correlational data provide no information about causality and no evidence for effects on the infants.

Concluding remarks and future perspectives

Current research clearly demonstrates the beneficial effects of breastmilk on the health of the infant and into adulthood. Recent studies in both rodents and humans have highlighted the beneficial effects of exercise on breastmilk composition and identified some of the mechanisms that confer improved metabolic health on the offspring. There are many critical areas for future investigation and further studies are needed before we can comprehensively define the central mechanisms that regulate the beneficial effects of maternal exercise on breastmilk composition (see Outstanding questions). For example, taking into consideration exercise-induced changes to epigenetic states like DNA methylation, histone modification, and noncoding RNAs that are altered in models of obesity could be critical in defining the effects of exercise. The identification of factors mediating the beneficial effects of exercise on offspring metabolism is essential for translation to humans, and given the constant rise in global obesity this will become increasingly more important. The identification of exercise-regulated components in breastmilk with importance for

Outstanding questions

Is maternal exercise an effective tool to combat the effects of maternal obesity on offspring metabolic health?

How may maternal exercise affect concentrations of HMOs and alkylglycerols in breastmilk?

What is the role of breastmilk components in the mother-to-child transmission of obesity?

Do miRNAs in breastmilk affect infant body composition?

By what mechanisms do HMOs modulate infant growth?

What are the acute effects of different types of exercise on breastmilk composition?

How do different types of exercise training chronically alter breastmilk composition?

How do exercise-induced changes in breastmilk composition affect infant growth and metabolism?

Do findings of increased an abundance of 3′SL in mouse milk after exercise training translate to humans? If so, what are the implications for infant growth and metabolism?

the prevention of childhood obesity could potentially lead to their enrichment in formula milk. One HMO (2′fucosyllactose) is already available in some commercial infant formulas and has been reported to have promising health benefits in infants [70]. Another possibility is donated breastmilk from exercised mothers. Exercise is sometimes not an option during pregnancy and the potential for benefits to the infant induced by maternal exercise after it is born is a future avenue for research.

Author contributions

Both authors contributed to the literature search, figures, data interpretation, and writing.

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Declaration of interests

The authors declare no competing interests.

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