Breast-feeding as 'personalized nutrition'

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Introduction

Health benefits of breast-feeding have been recognised since antiquity,[1] and yet with every passing decade, our scientific understanding of breast-feeding as a mode of nutrition seems to accelerate rather than reach a 'final plateau'. We already have compelling evidence that it matters, yet we also have much to discover about *how* exactly breast-feeding functions as a biological process, how and why it varies between mother-infant dyads, and what this means for promoting successful breast-feeding to the benefit of mothers and infants. Breastfeeding is arguably the ultimate 'biosocial' trait, simultaneously linking complex physiological processes with multiple components of behaviour in both mother and offspring that are amenable to cultural influences.[2]

Breastfeeding provides nutrition for functions that extend far beyond somatic growth, and has implications for development of the brain, gut and immune function, as well as cellular health.[3] Breast-feeding confers multiple health benefits on the offspring, including protection from infections, increased intelligence, and probable protection against obesity and diabetes, as well as reducing risks of breast cancer and diabetes in the mother.[4]

From an evolutionary perspective, breastfeeding represents 'maternal investment', through which the mother can promote her genetic fitness by increasing the quality of her offspring.[5] On the one hand, maternal fitness is promoted by allocating key nutrients and energy to each offspring, a process honed for success over millions of years of evolution.[6] On the other hand, mothers often allocate resources across multiple offspring, who to some extent are competitors for that investment. While each offspring might benefit from being breastfed

for longer, the mother may wean it earlier, in order to start investing in the next. Thus breastfeeding may also be considered to represent a dynamic 'tug-of-war' between parties with a genetic 'conflict of interest'.[7] **Figure 1** illustrates breast-feeding as the context for two related optimisation games, through which both mother and offspring seek to maximise their own genetic fitness.[8] Importantly, the phenotypic characteristics of both mothers and offspring, and their behavioural and physiological interactions, influence the outcomes of these connected optimization games.[7]

Insert Figure 1 near here

Within both biomedical and evolutionary frameworks, a consolidating theme has been that of breastfeeding as 'personalised nutrition'. Poor maternal nutritional status may constrain the delivery of both macronutrients and micronutrients to the offspring,[9] while maternal body composition is associated with the concentrations of hormones in breast-milk such as leptin that may influence early programming of infant appetite.[10] Breast-feeding also exposes the infant to food flavours resulting from the maternal diet.[11] These experiences may then shape later food preferences and acceptance of the solid foods available to the family and culture during the process of weaning.[11]

Breast-feeding also enables mothers to transfer immunity to the infant, whose own immune function is immature at the time of birth. First, breast-milk contains large quantities of secretory IgA antibodies, which are representative of the mother's own history of infections.[3] Second, breast-milk, and particularly colostrum, contains leukocytes (macrophages and neutrophils) that can destroy microbial pathogens by phagocytosis.[3]

Third, breast-milk contains antimicrobial factors such as lysozyme and lactoferrin.[3] Intriguingly, the quantity of leukocytes in breast-milk increases not only if the mother has an infection, but also if the offspring has an infection,[12] supporting the concept of dynamic interaction between these parties illustrated in Figure 1.

Finally, breast-milk also contains microRNAs and stem cells, which may exert tissue-specific effects on gene expression relating to immune and developmental functions in the offspring.[12, 13] However, studies are only beginning to produce evidence for differential methylation of offspring DNA through breast-feeding.[4, 14]

Collectively, these elements of 'personalisation' highlight how breast-feeding functions as an early protective niche, during which the offspring can adapt to ecological stresses under the mediating influence of maternal phenotype', a scenario known to ecologists as the 'safe harbour' hypothesis.[15] During pregnancy, and to some extent during lactation, mammalian offspring do not experience ecological stresses directly, but are rather exposed to the magnitude of 'maternal capital', ie diverse aspects of phenotype which reflect the mother's relationship with her physical and social environment (**Figure 2**).[16] It is within this overall protective niche that the maternal-offspring dynamic interactions described in Figure 1 play out.

Insert Figure 2 near here

So far, however, variability in breast-feeding has generally been conceptualised in relatively narrow terms, referring to the direct biological characteristics of mother and offspring. It has

recently become clear that many of the genes that act most influentially on human metabolism derive not from our own species, rather from those of our microbiomes. On this basis, we must reconsider how breast-feeding links maternal and offspring biologies, and how it may promote health.

Present research activities

Until recently, the microbiome was considered primarily in terms of pathogens, but there is growing recognition that it represents an ecological system incorporating beneficial commensals and symbionts that play critical roles in immune and metabolic health.[17] Exactly how the microbiome contributes to human metabolism is still rapidly unfolding. At a broader level, a striking finding is that the transplantation of gut microbiota from adult male to immature female mice resulted in elevated testosterone in the females,[18] suggesting that even a biological trait as fundamental as gender may in part be contingent on the activity of the microbiome.

The human gut contains diverse microbes that play a key role in homeostasis under the selective pressures generated both by host diet and appetite, and by competition from other species.[19] On the one hand, the microbiome shapes the capture of energy from the diet, while on the other, the resulting metabolites shape numerous signalling systems that impact appetite, inflammation and immune function, and various organs and tissues including the brain.[19] Collectively, the microbiome contributes millions of genes to human metabolism, and variability in the underlying mix of species translates directly into variable metabolic

effects. A wide range of forms of malnutrition have been associated with a perturbed gut microbiome, known as dysbiosis.

One crucial mother-offspring transfer of microbiota occurs at the time of delivery, but breast-feeding also plays a key role in the establishment of the gut microbiome, promoting both the colonization and the maturation of the infant gut.[17] The bacteria present in breast-milk vary in association with the stage of lactation, gestational age at delivery, and maternal nutritional status.[20, 21] Through these influences, the infant microbiome undergoes a process of maturation, during which its changing composition assists the shift from digesting breast-milk itself to digesting solid foods.[22] This process of maturation continues through the period of complementary feeding, and only reaches a composition similar to that of adults by around 3 years of age.[23]

Formula-feeding, and the early introduction of solid foods, have long been understood to impact body composition in the short term, and may potentially impact long-term obesity risk.[24, 25] These associations may be mediated by their disruptive effects on the colonization and maturation of the infant microbiome, which may in turn propagate long-term metabolic effects.[10]

Researchers in the 19th-century had already learned that human milk contained carbohydrates other than lactose, subsequently termed human milk oligosaccharides (HMOs). These molecules contain lactose but are more complex and occur in multiple different forms, and while evident in the milk of other species they are especially varied in humans.[26] HMOs were soon recognised to provide metabolic substrates that promoted

healthy development of the infant intestinal microbiome, but more recent research has shown that they also prevent pathogen attachment on mucosal surfaces, lower the risk of infections, and provide important nutrients for brain development. Moreover, they may also protect against mastitis in the mother.[26]

If breast-feeding promotes growth and immune function, why do some breast-fed infants nevertheless become severely malnourished? A study in Malawi demonstrated that HMO variability may play a key role. Compared to the breast-milk of mothers whose infants demonstrated severe growth retardation, that of healthy mothers contained greater sialylated oligosaccharide concentrations.[27] The researchers transplanted the microbiome of a growth-retarded infant into germ-free mice and piglets. By feeding these animals dietary ingredients similar to those in a typical Malawian human diet, whilst also randomizing some of the animals to receive sialylated bovine milk oligosaccharides, they showed that the oligosaccharides increased lean tissue accretion in the growth-stunted animals.[27] This study thus demonstrated a causal growth-promoting role of HMOs, mediated by their effects on the microbiome.

However, the role of the microbiome in breast-feeding may be much broader, and might for example contribute to infant appetite, and hence drive variability in infant vocalisation and suckling.

Need of future research

Such work on the microbiome is just one component of recent work emphasising biological variability within breast-feeding. Historically, breast-feeding has been promoted largely as a single entity, on the grounds that it generically represents the optimum form of infant nutrition. Substantial effort has been made to generate an evidence base demonstrating its health benefits, and to establish how its promotion can be maximised. The introduction of baby-friendly hospitals to maximise the initiation of breast-feeding, and efforts to provide mothers with the time, resources and social support to continue breast-feed through infancy have all been crucial.

It is something of a paradox, given the unique importance of this mode of nutrition, that much of the research on which policy is based remains observational. Those mothers electing, or enabled, to breast-feed are not necessarily identical in terms of their background characteristics to those who do not breast-feed. This makes it difficult to partition biological differences between these groups to social factors, the behavioural act of breast-feeding, or the composition of breast-milk itself. Formal randomisation between breast- and formula-feeding is clearly unethical, but recognising the variability *within* beast-feeding offers new opportunities for health-promoting experimental work.

By focusing on the 'personalized' nature of breast-feeding, the characteristics of individual mothers and offspring are drawn to the forefront of scientific enquiry. Likewise, by considering breast-feeding to be a responsive process, it becomes reasonable to expect that interventions targeting one or other party might change the *experience* of breast-feeding, potentially altering its health impacts for both mothers and offspring. The notion that we

could not only promote breast-feeding *per se*, but also promote '*better*' breast-feeding, represents a major new avenue in nutritional research.

I will very briefly mention two broad strands of research that are already emerging in this context, though they are by no means the only examples. The first relates to maternal behaviour. For example, post-partum anxiety among mothers is common, in particular among first-time mothers, and this anxiety may reduce the likelihood of mothers initiating breast-feeding, or maintaining exclusive breast-feeding. Randomized trials are starting to show that this effect can be countered by forms of relaxation therapy.[28]

The second strand relates to the microbiome. The Malawian study described above suggested that a narrow maternal dietary range impacted the maternal microbiome, thereby steering the infant microbiome towards an unhealthy profile. This suggests that changes in the maternal diet might benefit offspring development. A related issue is the potential for maternal antibiotics transmitted by breast-milk to impact the infant microbiome. Though research is still in its early stages, studies have already linked pregnancy exposure to antibiotics with greater child BMI at 2 years.[29] Collectively, this work suggests that targeting the microbiome may be a valuable new way to maximise the health benefits of breast-feeding.

In summary, we need to reconceptualise breast-feeding as not only a form of personalized nutrition, but also as a dynamic process between mothers and offspring that offers opportunities to improve maternal and child health through interventions on diverse relevant traits. Such efforts must not intrude on maternal autonomy, or negate the interests

of women in their own right. Rather, the opportunity is to target various environmental constraints that may detract from the quality of breast-feeding. If we consider maternal phenotype as a 'safe harbour' for the offspring in early life,[15] then we must also acknowledge that the mother may herself be exposed to external stresses or threats, including poor diet, infection and psychosocial stress.[16] If the mother has type 2 diabetes, then she can still breast-feed successfully, but may need additional support to do so. Improved understanding of the physiological, psychological and cultural variability associated with breast-feeding will help meet these aims.

Conflict of interest statement

The author declares no conflict of interest.

Legends for illustration

Figure 1. Schematic diagram illustrating a two 'allocation games' played across generations, whereby each of the mother and the offspring optimize their inclusive fitness. In the first game, the mother optimizes her allocation of parental investment (PI) across competing offspring (O1–O4). In the second game, which is sensitive to the first game, each offspring optimizes its allocation of that investment between competing functions, such as homeostatic maintenance (M), growth (G), immune function (I) and energy stores (E). In post-natal life, breast-feeding is the primary context in which these two games are played. Adapted with permission from reference 8.

Figure 2. Components of maternal phenotype, including dietary intake, that contribute to the 'personalized' element of breast-feeding. While many maternal traits provide protection against external stresses and threats (the 'safe harbour'), maternal infection or metabolic disease such as type 2 diabetes represent the incorporation of stresses within the protective shell.

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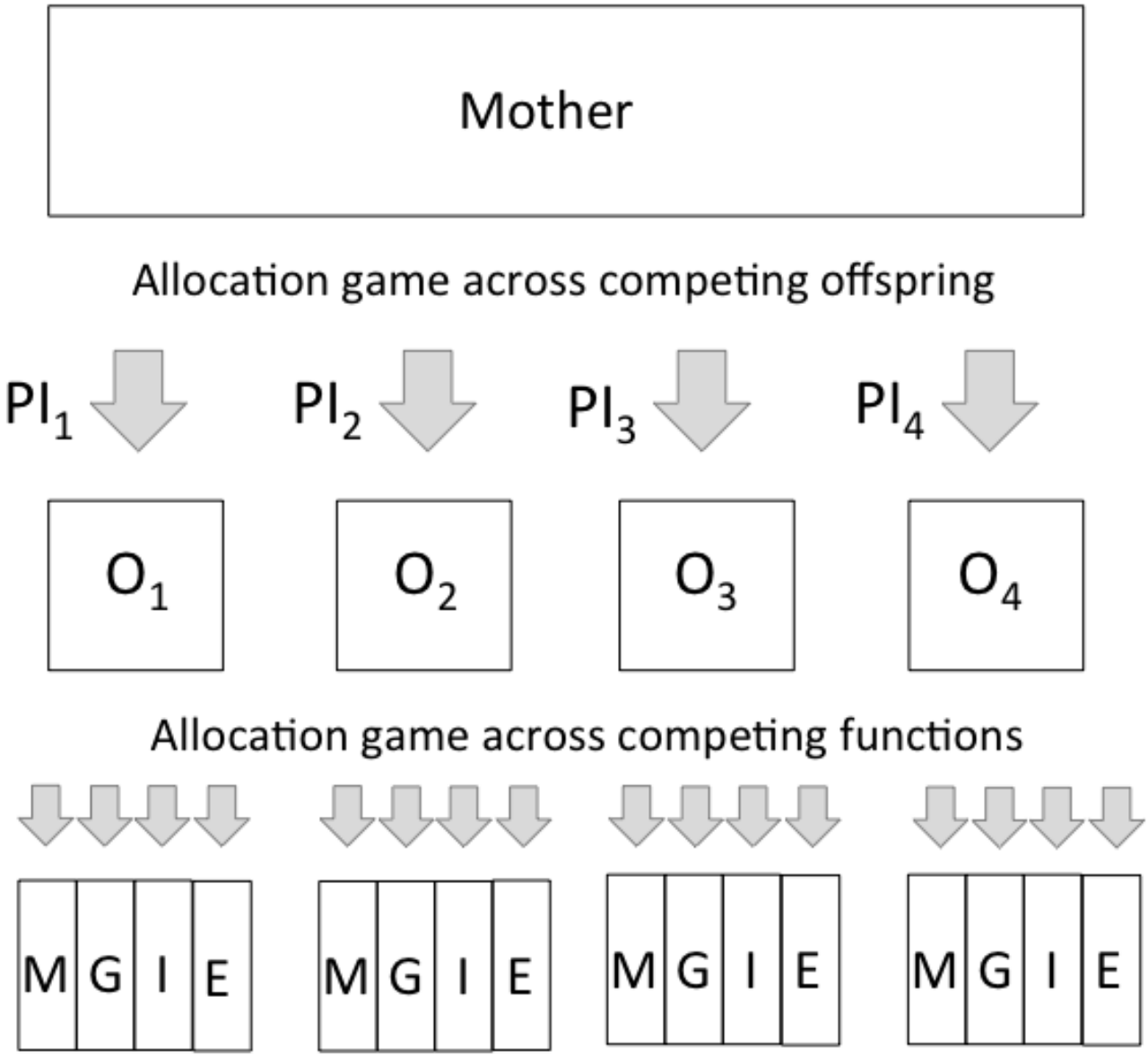
Mother
Allocation game across competing offspring
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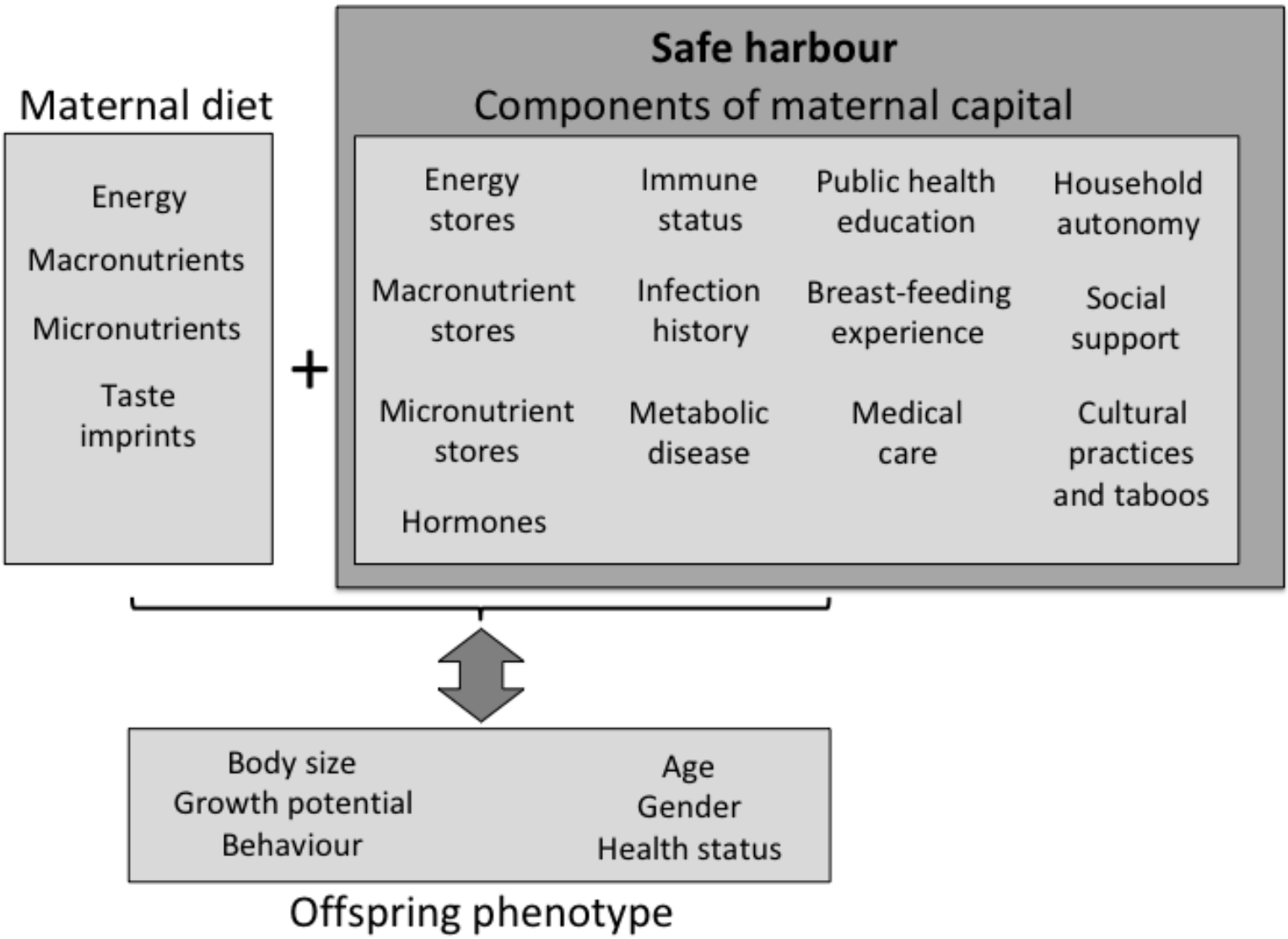
Maternal diet
Energy
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Safe harbour
Components of maternal capital
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Immune status
Public health education
Household autonomy
Macronutrient stores
Infection history
Breast-feeding experience
Social support
Micronutrient stores
Metabolic disease
Medical care
Cultural practices and taboos
Hormones
Body size
Growth potential
Behaviour
Age
Gender
Health status
Offspring phenotype