Commentary

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# Infant feeding and obesity risk in the child

## ABSTRACT

Early nutrition in infancy may influence later child health outcomes including overweight through 'programming'. Systematic reviews suggest that breastfeeding is associated with a modest reduction in the risk of later overweight and obesity. This commentary explores some of these mechanisms behind this association. Generally breastfed infants are leaner than artificially (formula)-fed infants and behavioural and hormonal mechanisms may explain this difference. The theory is that a high nutrient diet in infancy adversely programs the principal components of the metabolic syndrome in the child (body mass index, blood pressure and blood lipids) by promoting growth acceleration, whereas slower growth benefits later cardiovascular disease and its risk factors. Artificial-feeding stimulates a higher postnatal growth velocity with the adiposity rebound occurring earlier in those children who have greater fatness later, whereas breastfeeding has been shown to promote slower growth. The adverse long-term effects of early growth acceleration emerge as fundamental in later overweight and obesity. The higher protein content of artificial baby milk compared to the lower protein content in breastmilk is responsible for the increased growth rate and adiposity during the influential period of infancy of formula-fed infants. Breastfeeding, on the other hand, has a protective effect on child overweight and obesity by inducing lower plasma insulin levels, thereby decreasing fat storage and preventing excessive early adipocyte development. Plausible biological mechanisms underlying the protective effect of breastfeeding against obesity are based on the unique composition of human milk and the metabolic and physiological responses to human milk.

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## INTRODUCTION

Systematic reviews examining infant feeding and obesity risk have been conducted (Arenz et al 2004; Harder et al 2005; Owen et al 2005) and the extensive literature highlights the conflicting existing evidence on this topic. Because obesity is multifactorial, disentangling the breastfeeding effect is difficult and requires control of confounding variables for which information may not always be available or complete. Socioeconomic, psychological, behavioural, ethnic and cultural influences additionally affect the emergence of childhood obesity such as food preferences, food availability, physical activity and sedentary behaviour (Schonfeld-Warden & Warden 1997). Nevertheless, a recent systematic review showed that artificial-feeding affected fat mass later in life and that compared with breastfeeding, artificial-feeding was associated with altered body composition in infancy and later life (Gale et al 2012). But what are the mechanisms behind the associations of formula-feeding and later obesity risk observed in epidemiological studies (Bartok & Ventura 2009)? In this commentary, some of these mechanisms will be explained.

### *Behavioural*

Generally breastfed infants are leaner than artificially-fed infants (Dewey et al 1993; Poskitt & Cole 1978) and behavioural and hormonal mechanisms may explain this difference (Aynsley-Green & Bloom 1980; Axelsson, Ivarsson & Raiha 1989; Heinig et al 1993; Ketelsegers et al 1996; Metges 2001). Bottle-feeding may promote more parental control and less self-regulation than breastfeeding. Focus groups of low-income mothers participating in a nutrition program revealed that most mothers believed a heavy infant was a healthy infant and supplemented

the diets of their infants to alleviate fears that their child was not eating enough (Baughcum et al 1998). Thus while artificially-fed infants may be governed by judgment of the feeding parent, breastfed infants have more discretion over their milk consumption than artificially-fed infants. It is argued that regulation of intake differs between breast- and bottle-fed babies and that breastfeeding enables the infant to develop the capacity to self-regulate as opposed to responding to the judgment exercised by the parent or carer in the case of artificial-feeding (Dewey et al 1993). Maternal feeding styles that are less controlling and more responsive to infant cues of hunger and satiety may allow infants greater self-regulation of energy intake (Lederman, Akabas & Moore 2004). A breastfed infant self-regulates his/her energy intake based on energy requirements (Dewey & Lönnerdal 1986) and ceases feeding in response to internal cues which may be lost with the reduced self-control during bottle-feeding. One study showed that infants who were fed from the bottle early in infancy were more likely to finish a bottle in late infancy compared to those breastfed in early infancy (Li, Fein & Grummer-Strawn 2010). It was also shown that the type of milk (formula or expressed breastmilk) had no influence on whether the bottle was finished, demonstrating that it may be the physical act of suckling rather than the composition of the milk that was important. Hence, formula-fed infants may be more likely to have larger meals, further apart, consuming up to 20–30% higher volume than breastfed infants (Sievers et al 2002). However, a recent trial found a role of free glutamate in infant intake regulation calling into question the claim that formula-feeding impairs infants' abilities to self-regulate energy intake (Ventura, Beauchamp & Mennella 2012).

The smell, taste and composition of breastmilk vary from morning to night and from day to day, between breastfeeds and even during a breastfeed depending on maternal diet and whether the milk is fore- or hindmilk. Maternal milk exposes infants to a variety of flavours that influence their food choices and dietary habits later in life (Mennella, Jagnow & Beauchamp 2001). The varying fat content during a breastfeed may signal to the infant that their meal is coming to an end (Li et al 2010) or more recently it was suggested that different levels of hormones in hindmilk, towards the end of a feed, may signal satiety in the infant, resulting in cessation of feeding (Karatas et al 2011).

### *Critical window for 'programming'*

Early nutrition in infancy may influence later health outcomes including overweight through 'programming' (Lucas 2000). Developmental programming postulates long-term detrimental effects on adult health due to nutritional imprinting during critical developmental periods. Nutrition in infancy has been investigated as a method of intervention to reduce health problems later in life and studies of breastfeeding have shown protective effects against the components of metabolic syndrome that continue into adulthood and reduce the likelihood of developing metabolic disease in later life. However, there was no evidence that increasing consumption of formula/cows' milk in early infancy was associated with insulin resistance in young adulthood in one longitudinal study (Williams et al 2012). Indeed, a crucial period during postnatal growth relating to obesity risk has been hypothesised. However, the timing of this period remains uncertain, with some suggesting the crucial period to be in the first few weeks of life (Singhal & Lanigan 2007) while others have suggested that up to 2 years may have an effect (Toschke et al 2004). Regardless of this discrepancy, breastfeeding is a key factor in influencing infant health during this period. The first few days of life appear to be the critical window in the development of obesity later in childhood and adolescence (Stettler, Stallings et al 2005). Mechanisms during this critical window of exposure include structural changes that never recover, such as decreased beta-cell mass, accelerated cellular ageing, telomere shortening with cell division and oxidative damage, and epigenetic programming changes from transcription to translation of protein (Druet & Ong 2008).

### *Growth*

Substantial evidence over 40 years indicates that early nutrition and growth affect long-term cardiovascular health. The theory is that a high nutrient diet in infancy adversely programs the principal components of the metabolic syndrome by promoting growth acceleration (upward percentile crossing) (Singhal & Lucas 2004), whereas slower growth reduces the risk of later cardiovascular disease and its risk factors. These same researchers showed that early growth acceleration programmed the abnormal vascular biology associated with early atherosclerosis, whereas slower growth was beneficial. Other researchers showed that infants who were at the highest end of the distribution of weight or body mass index (BMI) or who grew rapidly during infancy were at increased risk of subsequent obesity (Baird et al 2005; Singhal et al 2004). The pattern of early growth contributes to later obesity. Artificially-fed babies have a higher postnatal growth velocity with the adiposity rebound occurring earlier in those who have greater fatness later (Chivers et al 2010). The type of infant feeding also impacts on adipokines later in life. Adipokines affect insulin sensitivity and contribute to a chronic sub-inflammatory state that may play a central role in type 2 diabetes, cardiovascular disease, obesity and fatty liver disease (Antuna-Puente et al 2008; Kadowaki et al 2006).

The theory of reverse causation in relation to growth suggests that infants who have lower growth

trajectories and therefore lower energy requirements, are satisfied with breastfeeding for longer. Children 'programmed' to be larger require higher energy intake and demand more food, resulting in a mother supplementing with formula or solid food earlier (Kramer et al 2002).

### *Growth acceleration hypothesis (early weight gain)*

The adverse long-term effects of early growth acceleration emerge as fundamental in later overweight and obesity (Metcalfe & Monaghan 2001). Childhood growth acceleration (erroneously called catch-up growth) is associated with later insulin resistance, obesity (Ong et al 2000) and cardiovascular disease (Eriksson et al 1999), dyslipidaemia, raised insulin concentration and increased insulin growth factor 1 (IGF-1) (Forsen et al 2000). Growth acceleration is highest in early infancy suggesting that this period may be critical. Furthermore, early programming of the hypothalamic-pituitary-adrenal (HPA) axis could directly affect later cardiovascular disease (CVD) and type 2 diabetes (T2D). The *growth acceleration hypothesis* suggests that rapid early weight gain, rather than the specific mechanisms that cause it, may program for later obesity, as well as the other aspects of metabolic syndrome, including high cholesterol, high blood pressure and insulin resistance (Singhal & Lanigan 2007). This hypothesis is strengthened by the results of studies of early infant growth showing that upward-percentile crossing, for weight and length in infancy, leads to an increase in obesity risk later in life (Baird et al 2005; Oddy et al 2006). Indeed, in many studies breastfeeding results in faster weight gain compared to formula-feeding in the first few months but breastfed infants have lower weights later in infancy (Gillman 2010; Lucas et al 1994). This evidence supports the link between a longer duration of breastfeeding and a decreased risk of obesity and hence metabolic syndrome later in life.

### *Protein*

Growth velocity may be a relevant influence in the causal pathway of obesity as suggested for foetal programming of metabolic disease (Lucas 1998; Lucas 2000) and associations between protein intake and growth velocity and weight gain have been reported (Axelsson et al 1989; Fomon et al 1995). Infants 1 week of age who were fed formula with a higher protein-to-energy ratio showed a tendency for higher body weight gains than those fed formula with a lower ratio (Fomon et al 1995) and infants fed formula with a higher protein-to-energy ratio compared with the breastfed group had a higher BMI (Fomon et al 1999). The biological mechanism that may potentiate an association between early life dietary protein intake and obesity may be linked to glucose metabolism (Metges 2001). Formula-fed infants with high protein intakes may have a higher insulin secretion and high hepatic glucose output (Lucas et al 1981; Axelsson et al 1989) because IGF-1 is regulated by dietary protein intake (Ketelslegers et al 1996) and both insulin and IGF-1 are required for pre-adipocyte differentiation and adipogenesis induction. Alternatively, reduced amino acid concentrations induce IGF-1 expression participating in down-regulation of growth (Fafournoux, Bruhat & Jousse 2000). These metabolic changes in formula-fed compared to breastfed infants may have effects on circulating amino acid concentrations through protein-related alterations of energy expenditure, influences on hormones, growth factors and adipose tissue metabolism in response to perturbations of amino acid homeostasis brought about by gene expression regulation from formula-feeding (Metges 2001).

### *Early protein hypothesis*

The *early protein hypothesis* proposes that the higher protein content of formula — up to 70% higher than breastmilk (Heinig et al 1993) — is responsible for an increased growth rate and adiposity during the influential period of infancy (Koletzko et al 2009). The elevated protein of formula stimulates the release of insulin and IGF-1, both of which may enhance growth in 1–2-year-olds (Karlberg et al 1994; Iniguez et al 2006). Raised insulin levels have been observed in formula-fed infants as early as 6 days after birth (Lucas et al 1981), and may cause increased fat deposition and early development of adipocytes (von Kries et al 1999). Raised insulin levels may also program higher long-term insulin concentrations which could contribute to later obesity (Singhal & Lanigan 2007). The reduction of human growth hormone secretion in infants with high protein levels may play a role in obesity by reducing the breakdown of fat by lipolysis (Koletzko et al 2009). Breastfeeding, on the other hand, has a protective effect on obesity by inducing lower plasma insulin levels, thereby decreasing fat storage and preventing early adipocyte development (Lamb et al 2010).

A recent study that compared the BMI of infants fed high-protein formula versus low-protein formula was supportive of the early protein hypothesis, showing a higher BMI at 2 years in the high-protein group, and BMI values closer to that of breastfed infants in the low-protein group (Grote et al 2010). A further explanation may be that plasma insulin levels are higher in formula-fed infants compared to breastfed infants (Lucas et al 1980; Wallensteen et al 1991; Lonnerdal & Havel 2000) which may be due to the higher protein content of formula that in turn influences levels of circulating amino acids (Wallensteen et al 1991; Sherriff & Hartmann 2000). While this difference could well explain higher levels of fat deposition in formula-fed infants, it would be expected to have a far greater effect on adipocyte size rather than adipocyte number

at this stage of life (Rolland-Cachera 1998) and thus the effect may be transient.

### *Bioactive compounds in milk*

Breastmilk has a unique and varied composition when compared to the constant composition of infant formula. Breastmilk has higher fat content and lower protein content, as well as bioactive factors absent in formula (Savino et al 2009). In regards to risk of later obesity, the most important differences between breastmilk and infant formula appear to be related to the lower protein content and the presence of hormones and growth factors in breastmilk (Savino et al 2009). Plausible biological mechanisms underlying the protective effect of breastfeeding against obesity are based on the unique composition of human milk and the metabolic and physiological responses to human milk (Hamosh 2001; Lustig 2001). Breastfed infants may absorb less energy per volume than formula-fed infants as well as receiving modifying growth factors that may inhibit adipocyte differentiation (Garofalo & Goldman 1998; Hamosh 2001).

## CONCLUSION

Obesity may be the main mediator in metabolic syndrome and further disease, and nutrition during early infancy has an impact on the development of later obesity. Metabolic syndrome is associated with a two-fold increased risk of developing cardiovascular disease and a five-fold risk of developing diabetes mellitus type 2 (Eckel, Grundy & Zimmet 2005). The mechanisms by which metabolic risk factors contribute to these diseases are complex and not completely understood. As with other programming effects, that of early diet and growth on later cardiovascular health may amplify with age. Therefore the early postnatal period is a particularly important time for the risk of development of obesity, metabolic syndrome and further health problems such as CVD and type 2 diabetes, that may potentially be addressed through the promotion of breastfeeding.

### *To summarise our current knowledge:*

- Overweight infants are more likely to become overweight children, adolescents and adults.
- Breastfeeding to 6 months of age reduces the rate of overweight and obesity.
- Given the other known risks of artificial feeding, increasing the prevalence of exclusive breastfeeding to 6 months would be a worthwhile public health measure.
- A possible adverse effect of artificial feeding on postnatal weight gain and infant health remains of contemporary public health significance.

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