OBESITY

Breast milk, formula, the microbiome and overweight

Elisabetta Mueller and Martin Blaser

Jessica D. Forbes and colleagues found that infants who received formula early in life were more likely to be overweight at 1 year of age than those exclusively breastfed. Formula feeding was associated with altered intestinal microbiome characteristics at 3 months. These findings link early-life formula feeding and an altered microbiome with subsequent overweight.

Refers to Forbes, J. D. et al. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. *JAMA Pediatr*. https://doi.org/10.1001/jamapediatrics.2018.1161 (2018).

Jessica D. Forbes, Meghan B. Azad and colleagues performed a large, thorough study in Canadian children under 1 year of age that provides evidence that formula feeding increases the risk of subsequent overweight in 1-year-old children[1]. Conversely, the authors provide evidence that breastfeeding is protective against obesity and that the duration of breastfeeding is associated with the amount of protection (a longer duration was associated with increased protection); thus, this study joins a series of prior studies that found similar associations.

> the authors provide evidence that breastfeeding is protective against obesity

The relationship between breastfeeding and protection from subsequent obesity alone is important, as yet another observation linking breastfeeding to improved health in babies, but the study also provides insights into the mechanisms that lead to protection. The authors examined the intestinal microbiome in all of the children in the study at 3 months of age to assess whether links existed between the weight outcomes to the different exposures, the overall communities within the microbiota and the specific microorganisms present. In doing so, they confirmed previous observations and substantially extended our knowledge of the relationship between the microbiome and outcomes in children.

One characteristic of any microbiome is its diversity, which can be measured in several ways. A relatively simple metric is the alpha diversity, which can be a measurement of the overall richness of the collection of taxa that are present in a given sample, or can reflect the evenness of the populations (for example, are all of the taxa present in more or less the same proportions or do some members dominate over others?). High richness and high evenness usually, but not always, go together. Intuitively, we think that a population with high alpha diversity is better, but nature does not always comply with our pre-set beliefs.

In fact, confirming prior studies[2], the authors found that the alpha diversity present in breastfed babies was lower in early life than in the formula-fed infants, who as a group develop overweight to a greater extent as young children. How can we explain this seemingly paradoxical result? In reality, nature is not a democracy — all microorganisms were not created equal. Every species, including us humans, has an evolutionary history, and in fact, we co-evolved over millions of years with particular intestinal microorganisms[3]. As a consequence of co-evolution, some organisms are generally beneficial for us[4], and these organisms dominate the intestine of healthy babies, thus creating a microbiome of apparently low alpha diversity. The dominance of these healthy organisms is at least in part created through the co-evolved micronutrients present in breast milk and by the resistance of these organisms to the antimicrobial compounds present[5].

Thus, in the absence of co-evolved micronutrients and the antimicrobial compounds found in breast milk, as occurs in exclusively formula-fed babies, the population of intestinal microorganisms is shifted to a diversity composition that is higher than of that found in babies who are breastfed. Forbes, Azad and colleagues show that this shift is associated with a change in metabolic development that appears to lead to increased weight gain 9 months later[1]. This work is consistent with model systems in mice, in which perturbation of early-life intestinal microbial populations leads to later-in-life metabolic consequences[6].

More specifically, Forbes, Azad and colleagues found that the formula-fed children who had high intestinal microbiome diversity at 3–4 months of age were more likely to become overweight compared with children who were breastfed. The composition of the microbiome at 3–4 months of age had a stronger association with the weight of a child than the composition of the microbiome at 12 months, which is consistent with an early-life model. Their work re-affirmed the positive effects of 'beneficial' microorganisms, such as the *Bifidobacter* and Proteobacteria species in early life, and conversely those associated with overweight (for example, increased Lachnospiraceae at 3–4 months, equalizing by 12 months). What is clear from the research is that not all commensals are equal and the proportions of microorganisms in a population seem to matter.

We must ask ourselves, how might a shift in the microbial populations early in life lead to increased adiposity later in childhood? Presumably, once the altered pattern of the intestinal microbiome has been set, the tendency to overweight is established, and that tendency could remain for the entirety of an individual's life, which has been demonstrated in studies on over-feeding early in life[7]. The study by Forbes, Azad and colleagues clearly shows that the most important of the observed factors with respect to development of adiposity is formula versus breast milk; the effect sizes dominate over the nature and timing of complementary foods, which indicates where the focus on future studies and interventions to prevent obesity should be.

Credit: Paulo Sousa/EyeEm/Getty

One of the key developmental decisions in early life concerns energy: how much to save and how much to spend. Although the microbiome represents an exciting frontier, we must remember that obesity reflects energy input exceeding energy output. Factors including amount of food ingested and nutrient types absorbed in the intestine are critical elements contributing to the extent of calorie acquisition, ultimately affecting the amount of energy stored in adipose tissues. Forbes, Azad and colleagues suggest that the effects on body weight are, at least in part, due to alterations of the gut microbiome. Whether this is true or represents an association is a testable hypothesis. The most important factor in weight gain is caloric intake, which is difficult to ascertain in breastfed infants. Maternal milk production varies by mother's caloric intake, as high-fat diets lead to lipid-enrichment and therefore increased calorie milk. Food choices that affect diets are determined by the socioeconomic status, as is the choice to breastfeed[8]. The authors of the present study were aware of this and adjusted their data on weight gain by many covariates, including education and maternal body weight.

> "we must remember that obesity reflects energy input exceeding energy output"

We also need to determine how early exposure to exclusively breast milk or formula leads to long-term alterations in metabolism via the mechanisms mentioned above. Bottle feeding is associated with increased milk intake[9]. Basic measurements of energy intake in infants fed either milk or formula might aid in the determination of the effects of the two feeding practices on weight gain, exclusive of the taxa identified in the gut. Long-term follow-up studies on the cohort of infants analysed in this report will be important to better determine the effect of early exposure to breast milk or formula, and possibly to improve feeding practices for obesity prevention. In addition to better calorie dynamics with breastfeeding, the breast-milk-selected microbiome might also affect caloric use, but it was not possible to directly address that in this study.

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https://doi.org/10.1038/s41574-018-0066-5

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Acknowledgements
The authors are supported by U01AI222285, from the National Institutes of Health and the C & D Fund to M.B. The authors thank I. Goldberg for his critical insights.

Competing interests
The authors declare no competing interests.