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REVIEW

How could complementary feeding patterns affect the susceptibility to NCD later in life?

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Abstract *Aims:* The purpose of this paper is to provide a general framework for thinking about pathways and potential mechanisms through which complementary feeding may influence the risk of developing non-communicable diseases (NCDs).
Data synthesis: To provide a context for the lack of clear and consistent evidence relating complementary feeding to NCD risk, methodological challenges faced in trying to develop an evidence base are described. Potential pathways through which complementary feeding may influence obesity-related NCD risk are described and illustrated with examples.
Conclusions: Numerous aspects of complementary feeding, including diet composition as well as patterns of feeding have the potential to influence the early development of obesity, which in turn predicts later obesity and NCD risk. Specific dietary exposures during the period of complementary feeding also have the potential to program future disease risk through pathways that are independent of adiposity. These factors all require consideration when making recommendations for optimal complementary feeding practices aimed at prevention of future NCDs.

Introduction

A substantial literature relates fetal and early infant nutrition to adult non-communicable disease (NCD) outcomes [1,2], and a strong recent focus has been on the role of rapid weight gain in infancy. Rapid early weight gain, typically defined as an increase of >0.67 unit increase in weight-for-age Z-score over a designated interval, has been associated with increased risk of obesity in later childhood and into adulthood [3–7]. However, despite its important role as a determinant of growth, relatively little attention has been paid to the role of complementary feeding in the development of NCDs. Current guidelines for complementary feeding (American Academy of Pediatrics

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[8], ESPGHAN [9] and the World Health Organization [10] tend to focus on timing of introduction of solid foods, feeding frequency, avoidance of allergens, and iron sources, with attention to short term growth and health, but no attention to the longer term consequences. Moreover, aspects of complementary feeding may influence NCD risk through pathways that are independent of growth and body composition. The main purpose of this paper is to provide a general framework for thinking about pathways and potential mechanisms through which complementary feeding may influence NCD risk, which may be useful to inform the development of NCD prevention strategies. First, to provide a context for the lack of clear and consistent evidence of how complementary feeding may relate to NCD risk, some methodological challenges investigators face in trying to study these relationships will be described. Second, potential pathways through which complementary feeding may influence obesity-related NCD risk will be described and illustrated with examples.

Challenges and their implications for causal inference and research needs

Researchers interested in investigating the relation of early feeding to later health and disease outcomes face a number of daunting challenges. The difficulties are reflected in substantial variability in the quantity and quality of evidence supporting the links, and include the following.

1. *Lack of evidence from randomized trials in humans.* Very little information is available from experimental studies in infants during the period of complementary feeding. In some cases, effects of diet in older children have been extrapolated to younger children. Most information on long term associations comes from observational studies that preclude causal inferences. Some insights into potential roles of feeding come from experimental animal studies that establish biological plausibility for hypothesized pathways.
2. Numerous aspects of complementary feeding have the potential to influence short and long term health. These include not only the amount and nutrient composition of foods, but also the age at which foods are introduced, the form (liquid or solid), sensory qualities, and frequency of feeding, and caregiver feeding styles. In the actual practice of infant feeding, these are highly interrelated, so the identification of their separate effects is difficult. In addition, one aspect of feeding can operate through multiple pathways.
3. *Long lag times between exposures and outcomes.* In the absence of longitudinal data throughout childhood and into adulthood, it is difficult to isolate a unique role of early feeding. Moreover, if some specific aspects of early feeding are associated with adult NCD risk, is it because diet *tracks* or because diet *programs* disease risk? Tracking refers to the continuation of a dietary pattern established in infancy, so the ultimate effect on disease risk may represent additive effects from repeated exposure. Tracking may reflect the persistent influences of common underlying social, cultural, and environmental determinants of dietary patterns across the life course. For example, a high salt diet during the complementary feeding period, throughout childhood and into adulthood may be underpinned by a common underlying cultural food pattern, making it difficult to identify a unique and separate effect of the infant diet. Similarly, a common question is whether the association of breastfeeding with reduced risk of obesity reflects a true biological, protective effect of breastfeeding or whether it reflects that mothers who breastfeed also provide a healthier diet throughout childhood. In contrast, *programming* of later disease risk by some aspect of diet would involve persistent anatomic, metabolic, or physiologic changes that influence disease risk directly or alter susceptibility to environmental influences. For example, the hypothesized effect of excess milk protein intake on NCD risk may reflect programming of the insulin-like growth factor-1 (IGF-1) axis [11]. To isolate age-specific effects and differentiate effects of programming versus tracking, experimental protocols are needed to limit exposures to a particular developmental period, a design more easily achieved in animal than in human experimental studies.
4. *The complexity of diet makes it difficult to isolate a role for specific nutrients*, independent of other nutrients or total energy. For example, an isocaloric "low protein" diet may be a high carbohydrate diet, thereby making it difficult to attribute risk to one or the other macronutrient. Food-nutrient or nutrient—nutrient interactions may also mean that one aspect of diet may be exacerbated or mitigated by another.
5. *Food composition changes over time.* The composition of many prepared and processed foods has changed over time. The sodium content of infant formula and prepackaged infant foods has changed over time, with more products containing no added salt or sodium-containing preservatives and the types of fats and oils used in many processed foods have changed. For example, trans-fats have been eliminated from many products. Thus, the diet of today's infants may be quite different from the infant diet of today's adults, limiting our understanding of the biology and the generalizability of results of long term studies.
6. *Retrospective feeding data are subject to bias and lack of specificity.* Unless detailed data are collected prospectively during the period of complementary feeding (or experimentally altered in controlled experiments), misclassification of feeding exposures is likely owing to recall bias.
7. *Heterogeneity in response to diet* or dietary components may reflect genetic or gender differences, or differences or susceptibility programmed by prenatal factors. Unless sources of heterogeneity can be identified, conclusions may be reached about lack of main effects in a heterogeneous population, even when important effects may exist in a subgroup.
8. *Pathways may differ by outcome under study.* The relative importance of pathways operating through and independent of energy balance and body composition may differ by outcome. For example, some cardiometabolic diseases may be more strongly influenced