

# Infant nutrition and lifelong health: current perspectives and future challenges

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Understanding the role and importance of nutrition in early postnatal life, as an influence on lifelong vulnerability to poor health, is an important part of current research. We need to be able to define optimal patterns of infant feeding, not just to support growth and development in infancy, but also as determinants of later health. To date, much of the focus on the long-term effects of infant nutrition has been on milk feeding, to compare breast and formula feeding and to evaluate the effects of exclusivity, timing and duration of feeding different types of milk in infancy; other aspects of infant feeding such as age at introduction of solid foods and type of weaning diet have received less attention, and relatively little is known about their links to later health. Contemporary data are needed to enable us to move beyond explanation of historical infant feeding data in order to understand and predict health outcomes in future generations. Ongoing and new population studies, that include infants from diverse settings, will be key to providing generalizable data that can be used to define optimal feeding practice. There are some methodological challenges ahead, although significant progress has already been made, and further progress is envisaged in the future. In particular, the opportunity to bring together epidemiological studies and new mechanistic insights that will help identify key aspects of infant nutrition and their causal effects offer great promise both in moving this field forward as well as the potential for health benefits for future generations.

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## Introduction

The importance of David Barker's work on nutrition and growth in early life, and their influence on lifelong health, will be rehearsed many times in this themed issue of *J DOHaD*. His contribution to the way early-life experience is now considered as a determinant of long-term physiology and function was immense and has had widespread impact – from influencing the scientific research agenda through to the formulation of health policy.<sup>1–4</sup> However, perhaps the key aspect of this legacy is the value now placed on ensuring that the nutrition of mothers and young children is prioritized, because this is essential not only for their own health but also for that of future generations.<sup>5</sup> This short review, based on a presentation at the Commemorative Meeting in September 2014, addresses the role and importance of nutrition in early postnatal life as an influence on adult health. It considers some recent developments in our understanding, where future research in infant nutrition may be going, as well as some of the methodological challenges that face researchers in the field. Although interest in infant nutrition has increased hugely in recent decades, there is much more to be learnt about optimal patterns of feeding in early life.

## Infant growth

Postnatal growth velocity is greatest in infancy – occurring at a time when the infant is entirely dependent on others to meet its nutrient needs. Infants are vulnerable, and it is well known that inadequate nutrition and restriction of growth at this stage can result in permanent stunting<sup>1</sup> as well as having potential for long-lasting deficits in neurological function.<sup>6</sup> Although growth monitoring has been used routinely for decades, we do not yet have a complete understanding of what is optimal in terms of patterns of early growth. For example, although poor growth in infancy is recognized as a cause for concern, rapid weight gain has been linked to later obesity as well as a number of risk factors for cardiovascular disease.<sup>7–9</sup> The underpinning mechanisms are not understood, although recent studies provide some clues, such that rapid weight gain, particularly in early infancy, has been shown to be associated with lower concentrations of the appetite-regulatory hormones ghrelin and adiponectin in adolescence<sup>10</sup> as well as with differences in the insulin-like growth factor metabolic pathways.<sup>9</sup> To date, there have been few studies of childhood growth in relation to adult health outcomes. Some of the most important insights regarding optimal pathways of growth have therefore come from follow-up studies of men and women born in Helsinki, Finland, between 1934 and 1944.<sup>11,12</sup> Their childhood growth, hospital admission and mortality records can be linked, allowing description of the patterns of growth that characterized the men and women who later developed coronary

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heart disease (CHD) and type 2 diabetes. For example, when compared with other men, those with CHD grew poorly in infancy, had low body weight and were short at 2 years of age – but the period of poor early growth was followed by a period of relatively rapid weight gain in childhood.<sup>12</sup> Deleterious outcomes associated with this pattern of growth have also been described in a study of young Indian adults: impaired glucose tolerance and diabetes in adult life was more common among men and women who were thin in infancy but who had accelerated gains in body mass index after the age of 2 years.<sup>13</sup>

Although further evidence is needed to define the pathways of growth in prenatal and postnatal life that are associated with lifelong health in contemporary populations, significant progress has been made in establishing infant growth standards in the past decade. New growth data were published by the World Health Organisation,<sup>14</sup> using longitudinal standardized measurements of healthy infants who were living in six different countries. The populations were diverse, but infants across all centres were raised in supportive environments: they were healthy, exclusively or predominantly breastfed for at least 4 months and were born to mothers who did not smoke. A key message from this study is that for such infants the patterns of early growth are similar, across a range of ethnicity and cultural backgrounds.<sup>14</sup> The pattern of growth described is seen as a better representation of how infants *should* grow, compared with the growth reference used in the past.<sup>1</sup>

### Type of milk feeding in infancy

To date, the focus of most studies regarding infant nutrition has been on milk feeding, in order to compare breast and formula feeding, and to evaluate the effects of exclusivity, timing and duration of feeding different types of milk in infancy. Breast milk composition is known to be very variable, differing in nutrient content within feeds, across the period of lactation, as well as between women.<sup>15,16</sup> More recently, an important development has been the wider recognition of the complexity of the composition of breast milk, particularly in terms of its content of a diverse range of bioactive components, which include anti-microbial and anti-inflammatory factors, enzymes, hormones and growth factors.<sup>17–20</sup> These bioactive components affect the infant's immune status, with short-term protective effects in relation to infection, as well as facilitating immune development and maturation.<sup>20</sup> These effects have led to description of breast milk as a 'communication vehicle' between the mother's immune system and the infant.<sup>20</sup> The consequences of not breastfeeding have been extensively documented, with lower rates of gastrointestinal and respiratory infections found in breastfed infants (when compared with other infants), both in developed and developing settings.<sup>21</sup> Importantly, promotion, protection and support of breastfeeding has been identified as one of the interventions with the greatest potential to prevent mortality in young children in countries that have a high burden of maternal and child undernutrition.<sup>22</sup>

The greater appreciation of the influence of early experience on long-term health has focused new attention on permanent, programmed effects of breastfeeding on lifelong physiology and function. There is now considerable evidence from historical cohorts that links greater exclusivity and longer duration of breastfeeding to lower blood pressure and serum cholesterol in adult life, better cognitive development and to a lower risk of becoming overweight and developing type 2 diabetes.<sup>1,2,15</sup> These effects are thought to be primarily due to compositional differences when comparing breast and formula milk, including a lower protein content as well as an array of bioactive constituents in breast milk. Although the underlying mechanisms are not fully understood,<sup>23,24</sup> there is now evidence that epigenetic changes occur in early postnatal life.<sup>23</sup> A range of bioactive constituents in breast milk have been shown to induce changes in DNA methylation<sup>23</sup> and it is possible that lack of exposure to these constituents in formula-fed infants could lead to differences in the regulation of epigenetic processes, gene transcription and/or protein synthesis, when compared with breastfed infants, with long-term consequences for health.<sup>23</sup> Bioactive constituents in breast milk also influence the establishment of the gut microbiota in infancy, and there is emerging evidence that this may be a pathway that links variation in early feeding patterns to later obesity and cardiometabolic risk.<sup>23,25</sup> The emerging-omics sciences, new detailed characterizations of the microbiome, together with continuing epigenetic analyses are really exciting developments in this area, and will be essential for our understanding of the causal links between exposure to breast milk and later health outcomes.<sup>23</sup> This will be key to our ability to gauge the potential for future strategies to promote, protect and support breastfeeding, not only to prevent infections in infancy but also to promote lifelong health.

Particular attention has been focused on possible programmed effects of differences in types and patterns of milk feeding on regulation of energy balance in later life<sup>2,26,27</sup> and in the possibility that breastfeeding promotion could be used as part of efforts to prevent obesity. Alongside consideration of compositional differences and molecular mechanisms, there may be other differences between breastfed and formula-fed infants that are also important in this respect. One possible explanation is that breastfed infants are able to control the amount of milk they consume, learning effective self-regulation of energy intake, which remains with them in later life. Consistent with this possibility is the finding of a recent study in which early introduction of solid foods was associated with greater odds of later obesity in formula-fed infants but not breastfed infants, suggesting that breastfed infants were able to reduce their milk consumption when given solid foods.<sup>28</sup> It is also possible that the mode of feeding is important, as compared with breastfed infants, those who are bottle fed are relatively more passive in the feeding process, and also may be encouraged to empty the bottle at each feed – both of these factors might undermine the infant's ability to regulate its milk consumption.<sup>29</sup>

### The weaning process

In comparison with evidence on milk feeding, the process of weaning – that is, the gradual transition from a milk-based diet to a diet based on solid foods – is not well described. The age at introduction of solid foods and the type of first solid food are often documented, but the assessment of food and nutrient intake during weaning is less common. This could reflect the challenge of assessing intake in very young children; however, additionally, as dietary patterns and intakes are changing rapidly in late infancy, it may be difficult to determine the timing and key exposures that need to be characterized. At present, there is, therefore, limited evidence to enable an understanding of the possible long-term effects of variation in weaning practice on adult health outcomes,<sup>4</sup> although younger cohorts established in recent decades will start to provide these data in the near future.

### Age at introduction of solid foods

The recommended age at which solid foods should be introduced has changed over time<sup>30</sup> and continues to be widely debated.<sup>31,32</sup> Energy requirements in infancy are considered to have been overestimated in the past,<sup>33</sup> and no deficits in growth have been demonstrated among infants who are exclusively breastfed for 6 months in developing or developed settings.<sup>34</sup> This is the basis of the current recommendation to start solid feeding at this age. Both early and late introduction of solid foods have been linked to poorer health outcomes in individual studies,<sup>35–37</sup> although so far the evidence is incomplete and/or inconsistent. For example, early age of introduction of solid foods has been associated with obesity risk,<sup>38</sup> but this is not consistent with findings of recent systematic reviews.<sup>39,40</sup> A significant limitation at present is that there are limited data on health outcomes in adulthood. Birth cohorts established in the last two decades, in which detailed infant-feeding data have been collected prospectively, which can be linked to detailed phenotypic data, will therefore provide valuable information about possible links to long-term health in the future.

### Weaning practice and diet quality in infancy

Relatively little is known about the long-term health effects resulting from qualitative differences in the weaning diet.<sup>4,15</sup> What is known is that even within populations there may be huge variations in feeding practice in infancy, including differences in the solid foods fed, the rate of transition from milk to solid foods, the degree of dietary diversity, portion sizes and balance of family and commercial infant foods.<sup>41–46</sup> These differences have significant implications for nutrient intake in late infancy and potentially could be important influences on growth and development at this stage. This is work in progress, however, as dietary patterns and diet quality in infancy have been characterized in a number of birth cohorts, enabling qualitative differences in the weaning diet to be evaluated in relation to health outcomes in childhood and

adolescence.<sup>28,41–46</sup> Data on adult health outcomes are clearly needed, but, additionally, an essential component of future work will be to develop the evidence base substantially to include infants from diverse backgrounds, beyond developed settings, for whom feeding patterns may be very different.

### Limitations of existing evidence and gaps in our understanding

Most of the epidemiological evidence that relates infant nutrition to long-term health is observational and much of it is from historical cohorts. As infant-feeding practice was very different in the past,<sup>30,47</sup> this has implications for the generalizability of these findings. It is also important to recognize that, although there is substantial evidence of links between infant nutrition and later health, there are some differences and inconsistencies in findings across studies.<sup>4</sup> As there are fewer opportunities to use experimental approaches – for example, to randomize infants to different types of milk feeding, the limitations of observational data may have contributed to inconsistencies in the evidence, and will remain an issue for researchers in this field. Some of the particular challenges in understanding these data deserve mention. First, the composition of breast milk substitutes has changed over time and even in contemporary populations may often differ between studies. Interpreting apparent differences in health outcomes that are thought to be causally related to differences in exposure to breast milk therefore needs a cautious approach as it may capture two aspects of exposure – both effects of exposure to breast milk and also a lack of exposure to the breast milk substitutes being used. Formula milks continue to evolve in their composition, and the differences in composition, when compared with breast milk, require careful evaluation. A second challenge is methodological: patterns of milk feeding are often complex, differing in duration, exclusivity, brand, timing and balance of different milks consumed,<sup>48</sup> requiring detailed prospective data to allow accurate classification of infants according to differences in exposure. Variation in the methods of description and the way these complex data are captured often differ across studies, limiting opportunities to synthesize findings from different populations. A third issue is that weaning practice, including the timing of introduction to solid foods and type of weaning diet, may be linked to the pattern of milk feeding in early infancy. For example, infants who are breastfed are often introduced to solid foods later than infants who are formula fed, and – in many developed settings – have weaning diets that are qualitatively different,<sup>41,49</sup> making it difficult to identify true causal effects of the different aspects of feeding practice. Although it is common to examine patterns of milk feeding independently of variations in the weaning diet, to understand the links between infant nutrition and later health, their separate and combined effects need to be considered. A final challenge, particularly for researchers in developed settings, is that there may be strong social gradients in feeding practice in infancy.<sup>15</sup> Although this is particularly marked for

breastfeeding duration and exclusivity, it also relates to differences in weaning practice.<sup>41,49</sup> As these gradients will also influence other family characteristics, such as patterns of diet and physical activity, differences in infant-feeding practice may be markers of these differences in later lifestyle, and the possibility of residual confounding is always a consideration. Knowledge of the effects of social background on infant-feeding decisions within populations is therefore important for the interpretation of causal links to long-term health.

### Looking forward

Much has been achieved in recent decades to advance the understanding of the importance of differences in infant-feeding practice, not just as an influence on growth and development in infancy, but also their effects on long-term physiology and function. However, there are gaps in the evidence and new, contemporary data are needed to enable us to move beyond explanation of historical data from the past to understand and predict health outcomes in future generations. To deliver on this ambition, there are some particular issues and challenges that future studies will need to address.

Central to developing a more complete evidence base will be the detailed characterization of infant feeding in new and ongoing prospective cohort studies to provide high-quality data from populations in a diverse range of settings. Ideally, the development and use of standardized protocols to assess infant diet, would enable comparable data to be collected across studies,<sup>50</sup> with clear advantages for data synthesis in future meta-analyses, as well as opportunity to bring data together from populations where patterns of confounding influences differ.<sup>51,52</sup> Unfortunately, for some of the reasons already discussed, the standardization of data capture methods and use of common methodology, may be quite challenging at present – for example, to define the ages and/or stages when diet should be assessed, the duration and timing of different aspects of infant feeding, as well as understanding the key dietary exposures that require characterization. However, important insights that will enable progress are likely to come from working closely with mechanistic investigators. New developments in the analysis of breast milk, together with better understanding of the mechanisms that underpin programmed changes in physiology and function,<sup>23</sup> will provide a much clearer understanding of the key dietary exposures that need to be assessed in infancy. This will inform the design of assessment methods to enable the characterization of dietary intake, and hopefully provide opportunity for a move towards common methodologies that can be used across settings in the future. In parallel with such developments, it will be essential to determine whether there are aspects of infant feeding that could be assessed very simply that would provide useful information on the key dietary exposures. This would have the potential for inclusion in routine data collections, and would add hugely to the value and generalizability of the evidence base going forward.

### Conclusion

David Barker's work challenged the long-held belief that non-communicable diseases are explained by adult lifestyle. Much of his distinguished career was devoted to pursuing the idea that differences in nutrition in early life permanently affect physiology and function, determining lifelong vulnerability to poor health. Understanding the role and importance of nutrition in early postnatal life as an influence on such vulnerability is an important part of current research, to enable the definition of optimal feeding patterns in early life, not just to support growth and development in infancy, but also as a long-term determinant of health. Although there are some methodological challenges ahead, significant progress has already been made, and further progress is envisaged in the future. In particular, the opportunity to bring together epidemiological studies and new mechanistic insights that will help identify key aspects of infant nutrition and their causal effects offer great promise both in moving this field forward as well as the potential for health benefits for future generations.

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### Conflicts of Interest

None.

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