Nutritional Programming and Later Life

The role of macronutrient quality during the first 1,000 days

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Key messages

- Between conception and the conclusion of the first two years of life, growth is faster than during any other period in life including puberty.
- Nutritional requirements in early life are relatively high, but the relative (macro)nutrient contribution and the dietary supply both change.
- Nutritional interventions during the first 1,000 days of life provide a window for "primordial disease prevention" – preventing disease in later life by reducing developmental risk factors.
- The quality of growth and metabolic development can be positively impacted by dietary protein quantity and quality as well as dietary fat quality, securing a foundation for later health.

Primordial disease prevention

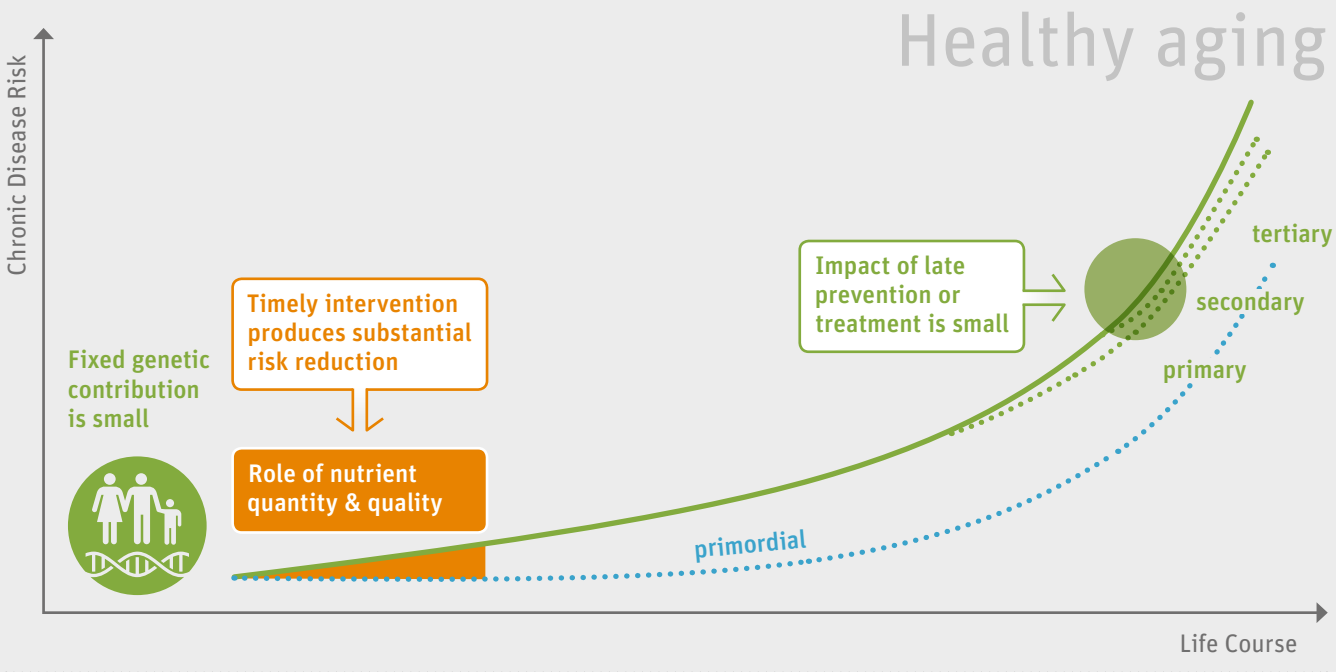
Worldwide, changing lifestyles and an increase in life expectancy have led to an increased number of people suffering from chronic noncommunicable diseases (NCDs).[1,2] Clearly, unhealthy diets and sedentary lifestyles contribute to obesity risk throughout life, but growing evidence indicates that the vulnerability to NCDs is largely set during the first 1,000 days, the period from conception until 2 years of age. Interventions during this period may induce only subtle changes in the developmental path, but, from a life-course perspective, have great potential to reduce later chronic disease risk compared to late interventions.[3] Interventions in early life thus provide a window for "primordial disease prevention" – an opportunity to prevent later life disease by reducing developmental risk factors. As an industry player active in the field of early life nutritional solutions and education, Danone's scientific interest is to better understand the role and contribution of the diet to later health and disease risk, and to translate these insights into our products and educational work.

> "Growing evidence indicates that the vulnerability to NCDs is largely set during the first 1,000 days"

Growth during the first 1,000 days

Growth during the first 1,000 days is faster than during any other period in life, including puberty.[4] Between birth and 3 years of age, body size doubles and body weight increases fivefold. Consequently, relative nutritional requirements are high, but the actual nutrient needs as well as the dietary supply change considerably. While initially the health and nutrition status of the mother play a pivotal role, after the introduction of solids the increasing contribution of complementary foods and the development of healthy eating and drinking habits may become more important dietary factors. The nutritional environment provides the energy and building blocks for growth, as well as the signals that steer the interplay between metabolic organs and influence their set points and response repertoire.[5] Failure to provide the right nutrients may result in permanent alterations in organ size and functionality that cannot be changed thereafter.[6] Fat stores in the body, for instance, start to develop during the final trimester of pregnancy and grow exponentially during the first year of life, leading to a peak in adiposity around

FIGURE 1: Early life provides a unique opportunity for later disease prevention



Modified from Gluckman PD, Journal of Developmental Origins of Health and Disease 2010:1(01);6-18. Adapted with permission.

6 to 9 months after birth. Although adipose tissue stores continue to grow throughout childhood and adolescence, they show a stable cell number in adulthood.[6] Obese adults, however, have more adipose tissue cells compared to lean individuals.[7] Cell numbers are already doubled around 2 years of age in children on an obesogenic development path, indicating that development of adipose tissue stores in early life strongly determines later storage capacity.

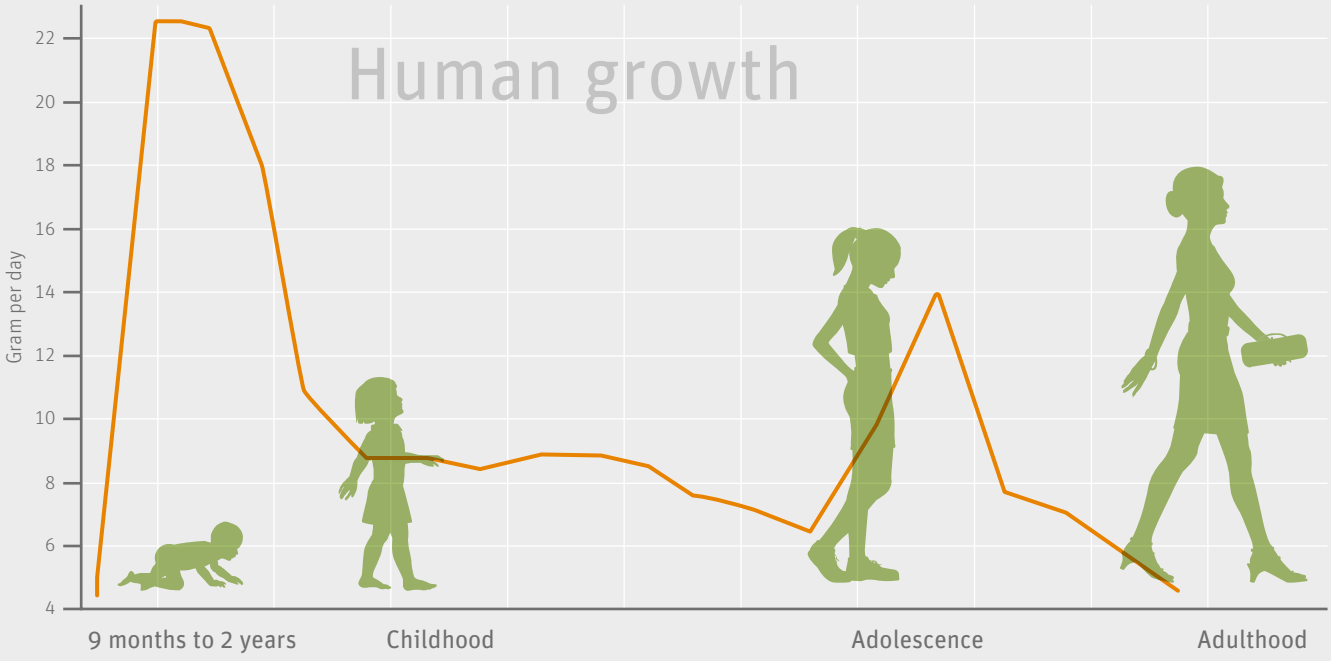
Changing nutrient requirements

The change in nutrient requirements from pre- to postnatal life up to the age of 3 to 4 years hints at the relevance of (micro)nutrient density and (macro)nutrient balance. We often talk about nutrition in terms of "evidence-based medicine": we expect that the addition of a "good" nutrient will result in a desired effect. However, we eat foods, not nutrients, and most food sources provide multiple nutrients. These nutrients do not act in isolation and may interact with each other. Also, the addition of one nutrient will automatically change properties of the others. In addition to the amount and balance between nutrients, nutrient quality is also relevant. For instance, two sources of dietary fat may deliver the same quantity but, based on differences in fatty acid (FA) composition, a different quality. These differences may be meaningful, especially when organs are still growing and maturing, as is further explained below.

> "During infancy, human milk is the gold standard for the feeding of any young infant"

During infancy, human milk is the gold standard for the feeding of any young infant. The current WHO recommendations advise 6 months of exclusive breastfeeding followed by continued breastfeeding up to the age of 2 years combined with appropriate complementary food introduction.[8] As a manufacturer of infant and toddler foods, we actively support breastfeeding, for instance via our global parental policy that supports breastfeeding in the workplace.[9] Especially for the first years of life, there is a need for a human milk alternative for those infants who are not, or are no longer, breastfed to ensure suitable nutrition. Consequently, the composition of human milk has been an important topic of research over the past decades.[10,11] While recognizing the gap in composition and functionality between commercial infant milk formula and human milk, it is the responsibility of manufacturers to continuously strive to improve what they can offer as a suitable alternative when breastfeeding is not possible. Any alternative suitable for young infants should be safe and nutritionally adequate as proven in clinical studies with infants. Although some major steps in formula development have been made over the

FIGURE 2: The speed in growth from conception up to adulthood illustrates the uniqueness of the first 1,000 days and comes with particular age-specific nutritional requirements



See this article for specific examples.

past decades, there is still room for improvement, as illustrated by the examples of research on protein and lipid quality below.

Protein levels

Protein levels in infant formula today are still higher compared to human milk, mainly driven by differences in protein quality. It has been hypothesized that differences in protein intake may, at least in part, explain the observed protective effects of breastfeeding compared to formula feeding on later life obesity.[12] However, simply lowering the amount of protein without addressing protein quality may increase formula intake.[13] A series of elegant studies using an amino acid oxidation method provided new insights into the essential amino acid (EAA) requirements for growth in young infants.[14,15] These results enabled us to develop a new concept with improved protein quality by providing a modified EAA mixture to ensure adequate growth allowing for lower protein levels. Studies in young piglets addressed some of the basic safety and tolerance questions[16,17] and supported the initiation of a clinical study to test the concept in infants to assess growth and body composition development in a public-private partnership with the support of an EU grant.[18,19] Studies such as these will help gain insights and support further development of product concepts in which we optimize protein quality (and quantity) in line with child growth needs.

The relevance of lipids in milk

As mentioned earlier, the addition or lowering of one nutrient will automatically change the contribution of all others. Indeed, the "high protein hypothesis" as a driver for differences in growth between formula- and human milk–fed infants may also be explained by the fact that high protein intake is associated with low fat intake, of which the latter is suggested to have greater impact.[20] During the first 6 months of life, when milk is the sole source of nutrition, 40%–50% of the energy intake is provided by fat. Dietary fats not only provide the energy for growth and ensure adequate absorption of the fat-soluble vitamins, but also supply the essential FAs omega-6 linoleic acid (LA) and omega-3 α-linolenic acid (ALA), precursors for the long chain polyunsaturated fatty acids ARA and DHA. Qualitative differences in the supply of fatty acids like DHA and ARA may be of interest, as these can directly affect the development of the brain but also of adipose tissue, metabolic function, and the immune system.[5,21,22]

Lipid quality

Over the past decades, agricultural changes driven by governmental policies have led to profound changes in the intakes of LA, and consequently in the balance between omega-6 and omega-3, leading to shifts in LA and DHA content in human

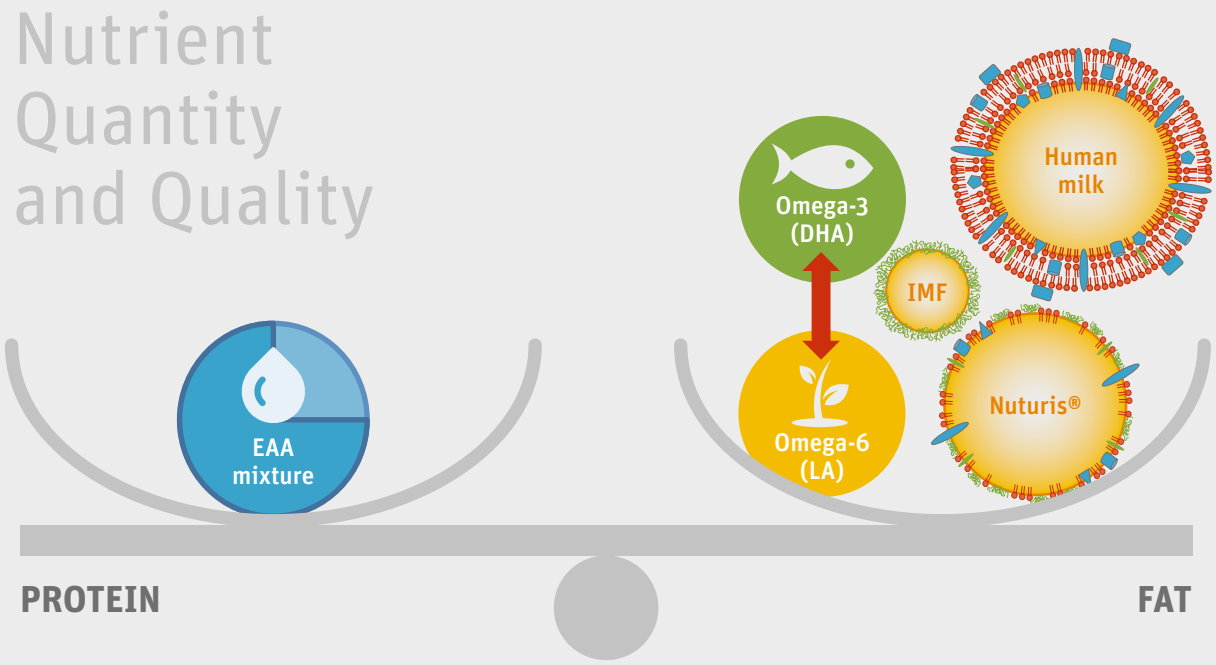
milk.[23,24] Proof-of-principle experiments in a mouse model for neonatal nutritional programming showed that relatively modest changes in the postnatal diet restoring the balance and contribution of omega-3 and omega-6 FAs can reduce fat mass accretion during a later challenge with a Western-style diet.[25,26] Not only differences in FA composition, but also the physical structure of nutrients may contribute to their use and metabolic fate in the body. Inspired by human milk, a formula concept containing large, phospholipid-coated lipid droplets (Nuturis®) was developed mimicking a matrix feature normally only present in raw, unprocessed milk.[27] Using a similar testing paradigm as described above, we showed that the altered dietary lipid structure also effectively reduced the development of excess adiposity when mice were challenged with a Western-style diet.[28,29] This Nuturis® concept is currently being tested in a clinical setting.[30,31]

"Obesity among pregnant women is becoming one of the most important women's health issues"

Potential benefits of nutritional concepts

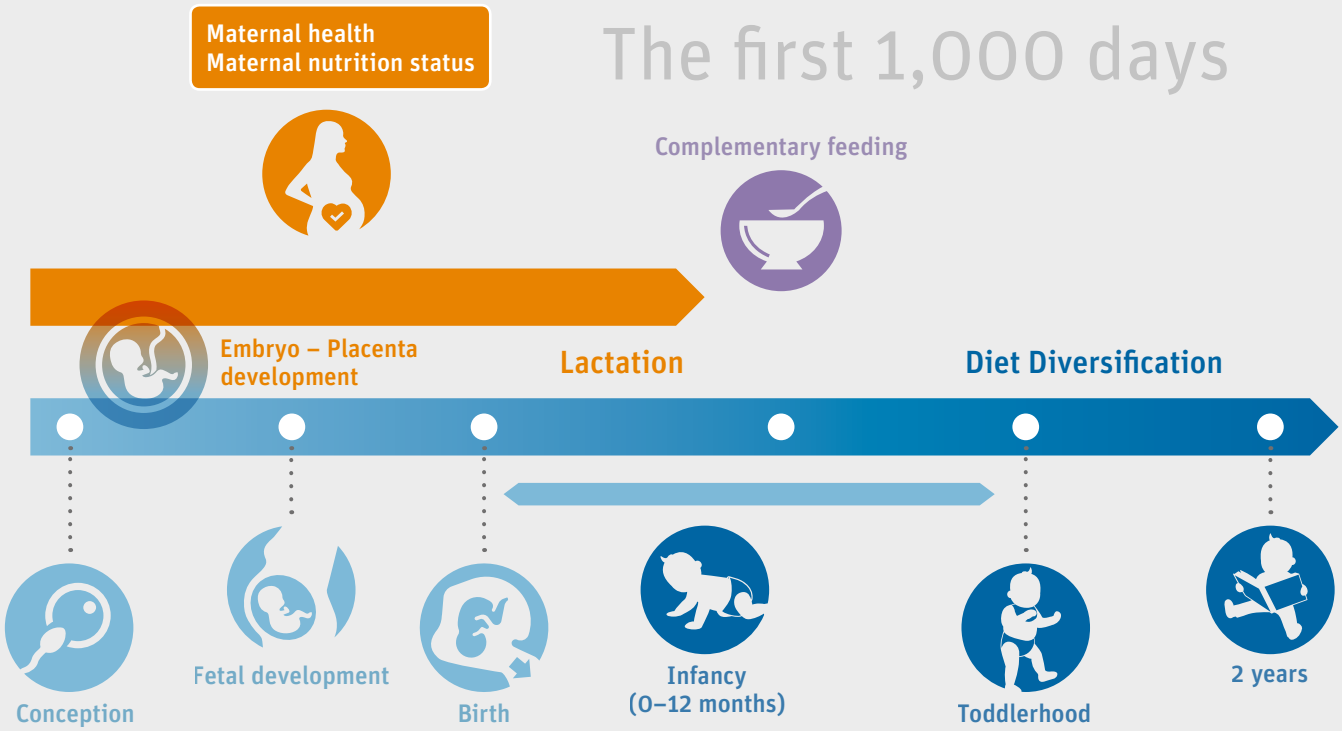
Examples like those on protein and lipid quality discussed above highlight some of the research that is currently delivering initial results on growth adequacy in clinical settings. Further research is ongoing, also illustrating the fact that it may take many years of research and product development before such innovations may be available on the market. For healthy term-born infants, such improvements in nutrient quality may only have a modest effect that is difficult to measure. Many children, however, already experience challenging conditions in the womb that may impact their fetal and postnatal growth, and for these children – for instance, offspring of obese women – the benefits of such nutritional concepts might be more meaningful. Obesity among pregnant women is becoming one of the most important women's health issues.[2,32] Maternal obesity is associated with higher birth weight and more body fat, partly related to the heightened risk of gestational diabetes mellitus (GDM), and representing a risk factor for unbalanced or faster growth and obesity later in life.[32,33] GDM is currently one of the most common medical complications in pregnancy affecting one in every seven births globally.[34] Both mothers and their offspring are at increased risk of short- and longer-term complications, such as development of type 2 diabetes.[35,36] Al-

FIGURE 3: An optimal balance between the amount of protein and fat as well as specific aspects of protein and lipid quality in the diet in early life are important



Examples of research on nutrient quality are, for instance, the mixture of essential amino acids provided by the protein blend, the balance between omega-6 and omega-3 fatty acids in the diet, and the physical structure of dietary lipids (see text for further details).

FIGURE 4: The first 1,000 days provide a unique window of opportunity to nutritionally support the quality of growth in the infant and the metabolic health of both mother and infant, with the potential to reduce the risk of NCDs later in life



though the currently available evidence favors actions directed at controlling prepregnancy weight and preventing obesity and GDM, adequate dietary guidance before and during pregnancy, especially in the case of GDM diagnosis, but also after birth for the offspring, is crucial.[32,37]

The importance of adequate dietary data

To develop meaningful innovations, it is crucial to improve understanding of the health and nutritional reality of the relevant target populations. To this end, we use a standardized approach, consisting of literature reviews in a range of health care–related databases as well as gray literature obtained from international and national organizations and websites of ministries of health and NGOs.[38] The information gathered is subsequently compared to available nutritional recommendations providing reference values.[38] These reviews are repeated at regular intervals to update available insights and guide further research and product development. In the case of crucial knowledge gaps – for instance, in understanding the nutrient intakes of pregnant and lactating women in Indonesia – studies are performed to gather further information.[39,40] Nutritional survey data indeed confirm that the diets of many pregnant and lactating women are often nutritionally unbalanced and do not meet local nutritional guidelines and recommendations.[41,42]

Conclusion

In summary, the window of opportunity to nutritionally support the quality of child growth and metabolic health extends from preconception into pregnancy and continues throughout the postnatal period. The scientific evidence to date supports the notion that optimal nutrition in early life contributes to health and has the potential to decrease the risk of NCDs. Thus, a focus on improving dietary habits and approaches to support more balanced and adequate nutritional intakes tailored to the changing needs of the mother and her developing child during the first 1,000 days is likely to have significant public health benefits. As Hippocrates already stated around 400 BC, "The greatest medicine of all is to teach people how not to need it."

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