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Infant Nutrition and Primary Prevention: Current and Future Perspectives

A. Lucas^a, Hugh A. Sampson^b

^aMRC Childhood Nutrition Research Centre, Institute of Child Health, London, UK; and

^bJaffe Food Allergy Institute, Mount Sinai School of Medicine, New York, USA

In the past two decades there has been a major change in focus in the field of nutrition. Previously, the main interest was meeting nutritional needs; now the major emphasis is the impact on health. Indeed, our new understanding of the biological effects of nutrition that influence health has revealed the immense potential for nutrition in primary prevention.

The Concept of Primary Prevention

Primary prevention is generally considered as the prevention of a disease before it occurs, or reduction of its incidence. However, this concept needs to be expanded here since early nutritional interventions are often targeted towards optimizing neurodevelopmental potential. Therefore, the suggested definition of primary prevention for this Workshop is as follows:

To prevent or reduce the risk of disease and prevent impairment of cognitive potential

The means of achieving primary prevention by nutrition is through education, clinical or public health practice or intervention, and through policy, legislation and regulation. However, these strategies are all dependent on the establishment of a solid research base – the focus of this Workshop. Research in primary prevention may and should have a fundamental basis, as considered in several chapters, but ultimately effective prevention strategies depend on formal evidence-based research that establishes the impact of nutrition on health and developmental outcomes.

Impact of Nutrition on Health

Nutrition has the potential to influence health in a broad variety of ways, which may be usefully categorized as in table 1.

Table 1. Impact of nutrition on health

1	Short-term or immediate effects
2	Long-term effects 'Programming' during critical periods Impact of nutrition throughout childhood
3	Diet as a 'vehicle' for factors that impact on health

In the following sections I shall give illustrations in each of these categories, taking for convenience data from my own center's work, simply to illustrate some concepts that underlie the large array of examples that will emerge at this Workshop.

Short-Term or Immediate Effects of Nutrition

Primary prevention may occur *during* a short-term intervention. An important example is the effect of human milk in neonatal intensive care in preventing life-threatening necrotizing enterocolitis (NEC) or neonatal sepsis. For instance, our own study on 926 preterm infants under 1,850g birth weight [1] showed that in exclusively formula-fed infants confirmed NEC occurred in 7.2%; whereas in those partially or totally human milk-fed NEC occurred in only 2.5 and 1.2%, respectively. Above 30 weeks gestation, when other risk factors for NEC are less common, diet emerged as particularly influential, with 1/20 of the rate of NEC in those fed human milk versus formula. Indeed in a national survey of NEC (unpublished) those above 30 weeks fed predominantly human milk who developed NEC had a mortality of 5%, compared to 26% in those predominantly formula-fed. Further work from a randomized trial [2] and observational data also show a major reduction in neonatal sepsis in those fed human milk.

In general, when appraising the 'prevention potential' for a nutritional intervention, there are three key factors to consider: (a) the quality of evidence available; (b) the size of the effect demonstrated, and (c) the feasibility of the intervention.

In the above example, the evidence that breast milk reduces the risk of NEC or sepsis is based on numerous observational studies, some randomized trial data and biological plausibility; the effect size is large, and in terms of feasibility, counseling of mothers of preterm infants to provide at least some expressed breast milk has been effective. Thus, use of breast milk in neonatal care for primary prevention is widely employed.

Long-Term Impact of Nutrition

Nutrition as a 'lifestyle' factor throughout childhood has raised considerable interest in relation to a number of disease processes, particularly obesity and associated non-insulin-dependent diabetes in view of the current epidemic – a major focus of this Workshop. Here, however, I shall consider perhaps the fastest growing area of current nutritional research: 'programming', and its relationship to prevention.

Programming was defined by Lucas [3] as the concept that a stimulus or insult, when applied to a critical or sensitive period in development may have a long-term or life-time effect on the structure or function of the organism.

Background

The concept of 'critical periods' dates back to Spalding's formal description in the 19th century of 'imprinting' in chicks. The first evidence for *nutritional* programming came from the work of McCance [4] in animals in the early 1960s demonstrating in rats the long-term impact of neonatal nutrition on adult size. Since then numerous animal studies including those in primates have shown that in adulthood nutrition may program such outcomes as blood pressure, lipid metabolism, insulin resistance, atherosclerosis, bone health, learning, behavior and even lifespan [3–9].

Given the immense potential for disease prevention raised by this work, corresponding studies in humans have been imperative. In 1982 we initiated the first formal intervention trials, based on the pharmaceutical trial model, to test the programming concept in humans [10], first in preterms then full-term infants. From the later 1980–1990s there was also an explosion of retrospective observational studies relating size in early life (as a putative marker of nutrition) to later disease [11].

Programming Effects on Cardiovascular Disease

Breastfeeding is now emerging as important in the primary prevention of cardiovascular disease risk [12]. Numerous observational studies in healthy full-term infants have shown that breastfeeding is associated with a later reduction in insulin resistance, blood pressure, LDL cholesterol and obesity – the latter three, the subject of formal meta-analyses. However to confirm causation, studies on preterm infants have been important since it is possible, in those whose mothers elect not to provide breast milk, to conduct formal randomized outcome trials comparing donated banked breast milk with formula. Moreover, because breast milk intake in preterms can be recorded accurately (since it is fed by nasogastric tube), a 'dose-response relationship' between intake and later outcome can be explored – important, if found, in supporting causation.

Our own such trials on preterm infants provide experimental evidence that human milk feeding in the neonatal period reduces, later in adolescence, blood pressure, LDL cholesterol, insulin resistance and leptin resistance (metabolic tendency to obesity), and the greater the human milk intake the greater the benefit [13–16]. Thus, extensive evidence in term and preterm infants, now including experimental evidence from formal outcome trials, shows that human milk reduces the key features of the metabolic syndrome – the major risk complex for cardiovascular disease.

In a recent review Singhal and Lucas [12] linked these findings into a broader concept – the postnatal growth acceleration hypothesis. This hypothesis is based on extensive evidence from studies in diverse animal species [17] (from butterflies to primates), human observations [18, 19] and now our own experimental interventions on preterm and full-term infants, that rapid growth acceleration (upward centile crossing) in the early postnatal period increases later cardiovascular disease risk. Thus the advantage for breast milk-fed infants could be related to their slower early growth rate [12].

The potential long-term impact of breast milk feeding or other strategies to prevent early growth acceleration is large. In our trials the impact on later blood pressure of either breast milk in preterm infants or using a standard versus nutrient-enriched formula in small-for-gestational age full-term infants [12] was over 3 mm Hg. Yet, the Framingham study noted that just a 2-mm reduction in population diastolic blood pressure would result in around 100,000 less strokes and coronaries in the US each year. The impact of breast milk on later cholesterol – around a 10% reduction – would, in adults, reduce cardiovascular risk by 25% and mortality 13–14% [12].

Programming and the Brain

The programming effect of early nutrition of the brain is equally important in terms of primary prevention. In a randomized trial in preterm infants, use of a standard versus enriched preterm formula (in the early 1980s, when standard formulas were often used) resulted in a major deficit in later IQ, reaching 13 verbal IQ points in males [20]. Those (males and females) fed the standard formula had, at 7–8 years, a 38% incidence of some degree of mental or motor impairment compared to only 15% in the group fed the enriched formula. Our (unpublished) evidence shows that the cognitive effects persist into early adulthood when we have also found differences between randomized groups in the structure of the brain (using MRI scanning with statistical parametric mapping). In term infants, previous studies on the impact of undernutrition on neurodevelopment were observational and confounded by poverty and poor social circumstances. However, the first randomized trials of early nutritional supplementation in developing countries are beginning to demonstrate the long-term cognitive effects of early nutrition [21]. Nevertheless, the effect-size appears greater in those born preterm.

The impact of specific nutrients (e.g. iron, zinc, taurine, long-chain polyunsaturated fatty acids) and of breastfeeding are also receiving much study, and have considerable potential for the prevention of reduced cognitive performance [21].

Balance of Risks

It is of interest, however, that whilst a high plane of early nutrition is important for brain development, a lower plane of nutrition and growth appears to favor cardiovascular health, as discussed above. This apparent conflict requires risk-benefit analysis. In preterm infants, the brain is particularly sensitive to the impact of nutrition. For this reason, a high plane of nutrition and growth takes precedence – hence the rationale for breast milk fortifiers and multi-nutrient-enriched preterm formulas in neonatal care. However, in full-term infants, whilst early nutrition appears to have a major impact on later cardiovascular risk, the impact on the brain appears less than in preterms. Whilst further research is needed, these findings in healthy infants suggest slower early growth, as seen with breastfeeding, would be more optimal.

Diet as a Vehicle for Factors That Impact on Health

The human diet is a complex medium that may act as a vehicle for numerous factors that can influence short and long-term health. These include pathogenic organisms (e.g. HIV in breast milk and *Enterobacter sakazakii* in infant formulas), environmental contaminants (e.g. dioxins, phytoestrogens) and a variety of potentially toxic factors. It is one of the latter, aluminum, I shall cite as an illustrative example here.

Parenteral aluminum has long been known to be neurotoxic. Before its removal from renal dialysis solutions, patients became frankly demented. However, intravenous feeding solutions used in the pediatric population may be significantly contaminated with aluminum, for instance, in calcium gluconate [22]. We tested the hypothesis that in preterm infants, frequently fed intravenously and born at a sensitive stage of brain development and with limited excretory capacity, parenteral aluminum might be especially neurotoxic. A large randomized trial was conducted comparing those fed on regular total parental nutrition (TPN) versus a specially sourced low aluminum TPN including calcium chloride rather than gluconate [22]. At the 18-month follow-up those receiving more than the median number of days of TPN for the cohort (9 days) had a 10-point deficit in the mental development index (MDI) if fed on the standard versus low aluminum solution in the newborn period. Taking the whole cohort, each day of standard TPN solution, as fed in many Western units, was associated with loss of 1 MDI point [22]. This illustrates the importance of achieving high standards of quality control

Table 2. Research issues in primary prevention by nutrition in infancy and childhood

Critical interactions
Timing of the window
Emergence of the effect
Quality of evidence required
Risk-benefit analyses
Mechanism

of feeds for infants in relation to primary prevention. Such control is often best achieved at a legislative or regulatory level.

Research Issues in Primary Prevention

Whilst the potential for primary prevention via nutrition is high, research in this area is complex. I shall consider here an illustrative selection of key research issues listed in table 2.

Critical Interactions

Nutrition may interact with genes, subject characteristics, and environmental factors.

Genetic Factors

Interaction between early diet and family history for later risk of atopy provides an instructive model. Whilst all observational studies comparing breast and formula feeding are confounded by demographic factors, preterm infants provide an opportunity for randomly comparing human milk (from a milk bank) with formula (see above). In the only such randomized outcome trial for atopy [23], those with a family history of atopy who were randomly assigned to formula versus human milk in the neonatal period had over twice the incidence of eczema, nearly three times the incidence of food and drug reactions and a strong trend of more wheezing at 18 months follow-up. Conversely, in those with a negative family history, there was trend in the opposite direction [23]. Indeed, in a further trial of preterm versus term formula where the former group had higher cow's milk protein intake, in those with a negative family history of atopy, infants receiving the greatest cow's milk protein intake had the lowest incidence of atopy 18 months later [23]. Thus, whether later tolerance or sensitization occurred appeared to be genetically determined.

More work is needed to identify *specific* genes that interact with the diet. In young adults we found that early evidence of the atherosclerotic process (reduced flow-mediated endothelial-dependent arterial dilatation) was dose-related to the plasma n-3 fatty acid level (principally related to fish intake). However, this beneficial effect of fish intake on later vascular health was only seen in *glu298asp* heterozygotes (30% of the population) of the *eNOS* gene (influential for vascular health); the *glu298glu* homozygotes were unaffected [24].

These data illustrate that genetic characterization of family history may be needed in some primary prevention studies to identify the optimal target group for intervention.

Subject Characteristics

Not all subgroups within a population are equally affected by diet. In most studies, including our own, on nutrition and later neurodevelopment, males show the major response [20]. This is also seen in the extensive corresponding animal literature [8]. Furthermore, in an unpublished 15- to 18-year follow-up we found that higher verbal IQ after using a nutrient enriched diet (see above) was only seen in appropriate- and not small-for-gestational-age infants.

Thus, again, target subgroups within a population that respond most favorably to the nutritional intervention require identification.

Environmental Interactions

One of the most concerning interactions in the programming area is that between infant diet and our subsequent Western environment – probably our Western diet.

In the 1980s Lewis et al. [7] assigned baboons to breast versus formula feeding during infancy and then placed both groups on a ‘Western-style’ diet, rich in saturated fats, to test whether early nutrition in a Western context could influence later cardiovascular health. In adulthood, the previously breastfed group appeared the disadvantaged one in terms of higher LDL cholesterol, lower HDL, higher cholesterol absorption from the gut and reduced cholesterol excretion. Thus, the previously breastfed baboons appeared to be programmed to ‘conserve’ cholesterol – perhaps an advantage in the ‘wild’ on a natural diet. But on a Western diet, this became disadvantageous, emphasized by the postmortem evidence that throughout the arterial tree, the previously breastfed group had around twice the area of early atherosclerosis compared to the previously formula-fed group [7].

Later, Barker [11] noted that whilst breastfeeding was associated with lower rates of ischemic heart disease overall, if prolonged beyond a year in more vulnerable males, it was associated with increased ischemic heart disease. More recently we showed in 400 20- to 30-year-olds that, beyond 3–4 months of breastfeeding (not exclusive), increasing duration was associated

with progressive worsening of vascular distensibility 20–30 years later [25]. This is now supported by a further Scandinavian study also showing that vascular health in 10-year-old children was worse in those who were breastfed longer.

These studies [7, 11, 25] collectively raise the hypothesis that breastfeeding, if sufficiently prolonged, is an adverse risk factor for cardiovascular disease when followed by a Western diet. Thus, breastfeeding overall is beneficial for vascular health – but the optimal duration in the West is unknown. Of course, the data impugn our Western diet rather than breastfeeding and prolonged breastfeeding is not in any way challenged in developing countries. There are also other outcome benefits for breastfeeding. Nevertheless, in a Western context, research in this area is now critical.

Taking these interactions collectively, the research implication is that:

The impact on health of a nutrition intervention may be highly influenced by genes, subject characteristics and by current and future environment.

Timing of the Window

Defining the optimal window for nutrition intervention is a key research issue. For cardiovascular programming the period beyond birth (whether term or preterm) appears to be a particularly sensitive one [12]. Conversely, for the brain, gestation appears important so that term infants may be less sensitive (not insensitive) than those born preterm.

With regard to cardiovascular disease, a key research question has been whether prevention is best achieved by prenatal or postnatal intervention. Whilst there is extensive evidence that fetal environment may influence outcome, when birth weight is taken as a measure of fetal growth, its relationship with later cardiovascular risk factors (blood pressure, insulin resistance and LDL cholesterol) is small; whereas the impact of postnatal nutrition based on both experimental and observational studies, is large [12]. Fetal growth manipulation is also difficult to achieve whereas postnatal nutrition can be modified practically. More work is needed, but the postnatal period is emerging as an important one in terms of prevention potential for cardiovascular disease. Thus:

The efficacy of a prevention strategy may be highly influenced by its timing.

Emergence of the Effect

Lewis et al. [9] showed in baboons that overfeeding in infancy resulted only in a temporary increase in body weight which then remained normal throughout

'childhood'. However, those overfed in infancy became progressively obese in adulthood; an excellent example of programming, in which a 'memory' had been retained of the early intervention, yet outcome effects were not expressed until adulthood.

Examples of late-emerging effects are found in humans. In our own trial (cited above) preterm infants randomly assigned to human milk or formula in the neonatal period, showed no difference in blood pressure at 7–8 years, but a major reduction in blood pressure was seen in those fed human milk by 13–16 years [14]. A more disturbing example was found in our randomized trial of a formula with and without long-chain polyunsaturated fatty acids (LCPUFA). In all, 460 full-term subjects were studied including a reference group. Follow-up at 18 months showed no differences in developmental scores between groups [26]; but at 4–6 years, the group given LCPUFA had a significant 6-point reduction in IQ (unpublished). Our other LCPUFA trials show that outcome is dependent on source (see Chapter X), and other sources of LCPUFA have not had this adverse effect. Nevertheless taking these late-emerging programmed effects collectively a clear research message emerges:

Long-term follow-up is essential in intervention trials of early nutrition to ensure detection of late emerging effects, which may have implications for safety as well as efficacy.

Quality of Evidence Required in Studies on Prevention

Many health practices in nutrition are defended only by observational data, which are often confounded (for instance differences in breast- and formula-fed infants). It is difficult therefore to use such data to prove causation and hence underpin health practices.

An example of the difficulty in establishing causation from observational data comes from the observed relationship between birth weight and later insulin resistance, interpreted as fetal programming [15]. However, in our own randomized trial demonstrating experimentally the influence of postnatal diet on later insulin resistance in adolescence, we were able to do an instructive secondary analysis. Birth weight, postnatal growth and, of course, postnatal nutrition were each found to be significantly related to later insulin resistance. However, when all three were placed as independent variables in the same regression model, only postnatal growth remained significantly related to insulin resistance [15]. This suggested that postnatal growth explained the effect of postnatal nutrition, but also the *birth weight* effect. If so, birth weight may be more a proxy for *future* growth (postnatal catch-up, which occurs more at lower birth weight), rather than *fetal* growth, as previously assumed.

As a reflection of the potential dangers of formulating practice recommendations on the basis of observational data, retrospective studies had

Table 3. Levels of mechanistic research on prevention

Genomics, omics and cell biology
Physiology
Structure
Behavior
Anthropology
Evolution

suggested promotion of postnatal growth would be advantageous for later cardiovascular disease risk [27]; yet experimental studies in both animals and humans have now shown the opposite, as discussed above. In conclusion:

Wherever possible, experimental studies form a more secure basis for proof of causation and for underpinning practice than observational ones.

Risk-Benefit Analyses

The evidence that more rapid growth favors the brain yet slower growth favors later cardiovascular health indicates the need for risk-benefit analyses in the formulation of health practices, as discussed above. A more general message emerges from this, namely that:

It may not be safe to devise nutrition policies solely on the basis of the outcome of interest to the investigator. A broader range of outcomes may be needed to define an optimal intervention strategy.

Research into Mechanism

Whilst not the focus of this introductory paper, I shall consider here a few illustrative aspects of mechanistic research. An understanding of mechanism is not a prerequisite for developing effective prevention practices though clearly should be a goal for future development of the field. Such research needs to be a number of levels, as listed in table 3.

Substantial research at a basic biological level is now directed at the descriptive biology and fundamental mechanisms involved in programming and the health impact of early nutrition.

Within the genetic sphere, one area of focus has been the genetic propensity to respond to the nutritional stimulus – that is, nutrient–gene interactions (as discussed above). However, of greater fundamental interest is the converse phenomenon – the impact of nutrition on genetic expression. Lucas [10] proposed that the ‘memory’ of the original nutritional programming

event must be stored in some way to be transmitted through cell generations and expressed later in life. The proposed mechanisms include adaptive changes in gene expression, clonal selection and differential proliferation of cell types within tissues [10]. An understanding of such processes is not only of importance to nutritional programming but to the broader issue of how events in general during early critical periods could have long-term effects.

At a physiological level one key issue is the study of ‘coupling mechanisms’ that link early nutrition to ‘receptors’ in sensitive tissues and initiate the physiological changes that will have future health significance. Hormones are likely coupling agents. Factors such as insulin, IgF-1, leptin and gut hormones are known to be influenced or programmed by early nutrition and have plausible effects that could influence health outcomes. Thus, leptin programmed by neonatal nutrition has been shown to influence vascular function [16, 28]. The significantly higher insulin release after a feed in formula-versus breastfed infants in the first week of life is a plausible factor in the later difference in cardiovascular disease risk between these groups [29].

As an example of the importance of exploring mechanism at a *structural* level, our studies showing that neonatal nutrition has long-term impact on a part of the brain co-localized with numeracy skills (unpublished) has led to substantial research showing the impact of early nutrition and specific nutrients, such as taurine, on numeracy [30].

Mechanistic research relating to behavior and social anthropology will be of importance in the understanding of our modern epidemic of obesity. And evolutionary modeling across species has generated fundamental biological hypotheses that underpin human research relevant to health – for instance the postnatal growth acceleration hypothesis [17]. In summary:

Multilevel mechanistic research is needed to provide a sound underpinning for future prevention strategies.

Overview

Thirty years ago it could not have been conceived how immense the potential would become for primary prevention through infant and child nutrition. This chapter only provides illustrative examples of broad areas considered at this Workshop including the programming of obesity, cardiovascular disease, neurodevelopment, bone health, immunity, atopy and cancer.

Research in this area is complex, with many pitfalls, as illustrated in this introduction. Nevertheless, given the major potential to reduce the burden of human disease, substantial worldwide research investment is a high priority.

Perhaps the most important conceptual development from a health perspective is the recognition that nutrition can no longer be seen simply in terms of meeting nutrient needs, but rather, it should be viewed as a

therapeutic intervention that influences health and development. Once this conceptual leap is made, it becomes clear, as in other areas of therapeutics, that nutrition practice cannot be based, as it often has been, on theory, politics or uncontrolled observations. Formal evidence-based research is now required to provide a sound basis for primary prevention by early nutrition.

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