The Early Nutrition Programming Project (EARNEST): 5 y of successful multidisciplinary collaborative research[1–5]

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ABSTRACT

Differences in nutritional experiences during sensitive periods in early life, both before and after birth, can program a person's future development, metabolism, and health. A better scientific understanding of early nutrition programming holds enormous potential for implementing preventive strategies to enhance individuals' long-term health, well-being, and performance. This understanding could reduce costs of health care and social services and may enhance the wealth of societies. The Early Nutrition Programming Project (EARNEST) brought together a multidisciplinary team of international scientists and leaders in key areas of the early nutrition programming field from 40 major research centers across 16 European countries. The project had a total budget of 16.5 million Euros and was funded by the European Communities under the Sixth Framework Program for Research and Technical Development and coordinated by the Children's Hospital at Ludwig-Maximilians-University of Munich. The integrated program of work combined experimental studies in humans, prospective observational studies, and mechanistic animal work, including physiologic studies, cell culture models, and molecular biology techniques. The project lasted from April 2005 to October 2010. After the end of the project, the Early Nutrition Academy (http://www.early-nutrition.org) continues to serve as a platform for the exchange of information, scientific collaboration, and training activities in the area of programming. This article highlights some of the scientific results, achievements, and efforts of EARNEST. *Am J Clin Nutr* 2011;94(suppl):1749S–53S.

INTRODUCTION

Evidence has accumulated to show that metabolic events during limited and sensitive time windows of prenatal and postnatal development have marked modulating effects on health in later life, which is a concept often referred to as programming or metabolic programming (1). The term *programming* was first introduced into the scientific literature some 35 y ago by Dörner to describe these phenomena (2). In a visionary article that reviewed a series of clinical and experimental data, Dörner concluded that concentrations of hormones, metabolites, and neurotransmitters during critical early periods of development are capable of preprogramming brain development and functional disturbances up to human adulthood as well as syndromes of reproduction and metabolism. Dörner also proposed an interaction between the genetic material of the individual and environmental influences during early development to determine later function in adult life, which is a concept that has been confirmed by experimental data (1, 3–6). Metabolic programming has been defined as "either the induction, deletion, or impaired development of a permanent somatic structure or the 'setting' of a physiologic system by an early stimulus or insult operating at a 'sensitive' period, resulting in long-term consequences for function" (7).

Retrospective observational studies first published in the 1990s provided important evidence that nutrition during pregnancy and early infancy was able to program lifelong health in humans (8, 9). Results of animal and other experimental studies provided overwhelming evidence for the conclusion that early nutrition influences subsequent risk of cardiovascular disease, gut function, bone health, immunity, longevity learning, and behavior (10). Randomized controlled trials in infants demonstrated a causal relation between nutrition in infancy and later outcomes, including cognitive function and cardiovascular risk factors (11). In addition, the trials raised the possibility that prenatal growth restriction and rapid postnatal catch-up growth lead to adverse outcomes, and accelerated early postnatal growth may be the cause of many adverse programming effects (11). Moreover, the evidence led to the conclusion that early nutritional environment interacts with an individual's genetic disposition to program metabolism and development (ie, nature and nurture interact in programming). It has been appreciated that risk of noncommunicable diseases such as obesity, diabetes, hypertension, and cardiovascular diseases is determined by genetic risk factors and lifestyle in adulthood and by perinatal metabolic programming (**Figure 1**).

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[3] This article does not necessarily reflect the views of the Commission of the European Communities and in no way anticipates the future policy in this area.

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THE EARLY NUTRITION PROGRAMMING PROJECT

The Early Nutrition Programming Project (EARNEST; http://www.metabolic-programming.org), which was funded by the European Commission's (EC's) Directorate-General for Research, is the world's largest research project on nutrition programming. The project gathered and integrated data from a multidisciplinary approach exploring large prospective cohort studies, randomized controlled human trials, and animal studies to examine how early nutrition affects long-term health in adulthood (**Figure 2**). The EARNEST was funded by the EC under the Sixth Framework Program for Research and Technical Development, which contributed 13.4 million Euros toward a total cost of 16.5 million Euros. The project ran from April 2005 to October 2010 and was coordinated by the team of Berthold Koletzko at the Children's Hospital, Ludwig-Maximilians-University, Munich, Germany.

The Early Nutrition Programming Research Consortium, which brings together a multidisciplinary team of international scientists and leaders from major research centers across 16 EU countries, aims to address some key issues in the area of early nutrition programming such as the extent of early life programming in contemporary populations, relevant nutritional exposures, sensitive time periods, underlying mechanisms, and effective interventions for the prevention or reduction of adverse programming effects.

The following 3 major lines of research aim to deliver evidence for early nutritional programming: human epidemiologic studies, molecular and animal studies, and randomized controlled trials in mothers and infants (12). Research within EARNEST was clustered in corresponding themes with the aim to strengthen interactions and to enhance research output. Through its integrated approach, the EARNEST aimed to provide evidence that would contribute to the creation of robust and effective public health policy and interventions as well as improved early nutrition to prevent and reverse harmful programming, all of which holding an enormous potential for improving the health of future generations.

FOLLOW-UP OF RANDOMIZED, CONTROLLED, INTERVENTION TRIALS

Theme 1 of the project investigated early nutritional programming of adult disease risk in humans by following up previously well-conducted randomized controlled trials of specific nutrition interventions in pregnancy and infancy and by assessing disease markers in childhood and early adulthood. Nineteen trials were being followed up as part of the EARNEST. Some of these trials investigated dietary supplementation during pregnancy (eg, with fish oil or folate), whereas other trials have compared breastfed infants to infants fed with formulas of different compositions. The age of follow-up of study subjects ranged from 5 y to adulthood. Most of the studied health-outcome markers related to risk of obesity or cardiovascular disease, but markers for the development of the immune system, bone mass, and neurological development were also included. Many of the proposed follow-ups involved the same outcome measures; thus, the identification and standardization of these follow-ups across different studies at an early stage facilitated the pooling of data and meta-analyses, which provide the statistical power necessary to detect meaningful effects of early nutrition on a number of aspects of long-term health.

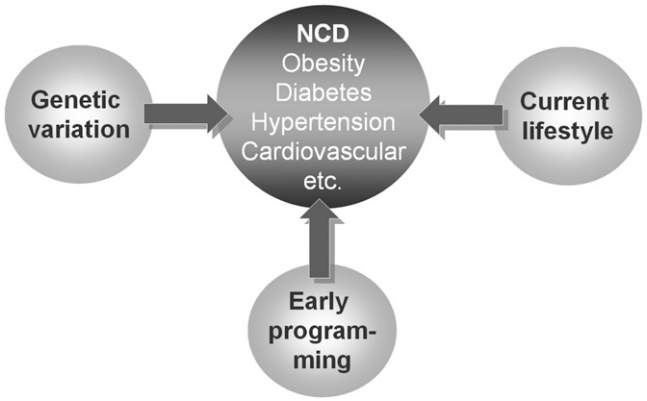

FIGURE 1. The long-term risk of noncommunicable diseases (NCD) is influenced by genetics, current lifestyle, and early programming in the prenatal period.

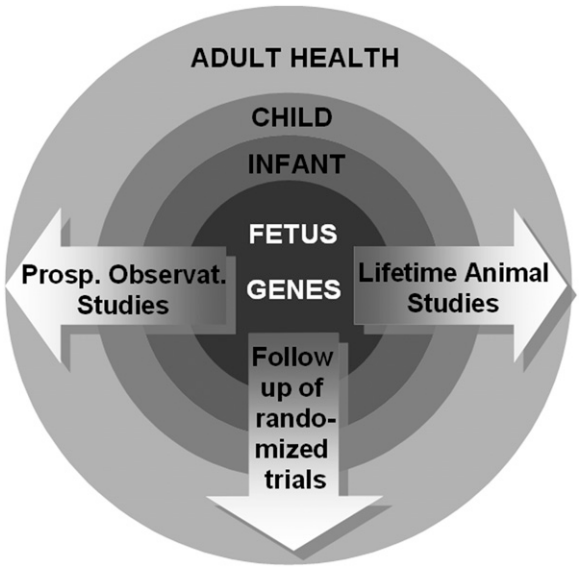

FIGURE 2. Multidisciplinary collaboration in the Early Nutrition Programming Project. Prosp. Observat., prospective observational.

Results from the EU Childhood Obesity Project: implications for growth charts and protein content of infant formulae

The European Childhood Obesity Project is a multicenter study that tested the hypothesis that higher protein intakes with infant formula led to more accelerated weight gains in the first 2 y of life, higher long-term risk of obesity, and other adverse outcomes (early protein hypothesis). Some 1138 healthy, formula-fed infants in 5 European countries were randomly assigned to receive cow-milk–based infant and follow-on formula with lower (1.8 and 2.2 g protein/100 kcal) or higher (2.9 and 4.4 g protein/100 kcal) protein contents for the first year. For comparison, 619 exclusively breastfed children were also followed. Weights and lengths of infants were determined at inclusion and at 3, 6, 12, and 24 mo of age. The primary endpoints were the length and weight at 24 mo of age, expressed as the length and weight-for-length z scores that were based on the 2006 World Health Organization (WHO) growth standards. Six hundred thirty-six children in the lower-protein (n = 313) and higher-protein (n = 323) formula groups and 298 children in the breastfed group

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were followed until 24 mo. Findings showed that lengths were not different between randomly assigned groups at any time. At 24 mo, the weight-for length *z* score of infants in the lower-protein formula group was 0.20 (95% CI: 0.06, 0.34) lower than that of the higher-protein group and did not differ from that of the breastfed reference group (13).

These results have led a number of infant-formula companies to enhance their efforts to modify the composition of their formulas and reduce their protein content to more closely match the growth pattern of breastfed babies. The protein content of infant formulas used to be as high as 4 g/100 kcal in the 1970s and was reduced to ≈3 g/100 kcal in the 1980s when concerns about the adequacy of intake of cow-milk protein were attenuated. In view of concerns about excessive intakes, the protein content of formulas has continued to fall. The minimum protein content stipulated in the European Infant and Follow-on Formula Directive of 1991 was 2.25 g/100 kcal, which has been reduced to 1.8 g/100 kcal in the 2006 Directive. Similarly, the WHO recommendations on safe amounts of protein intake for infants ≤12 mo of age have been reduced by as much as ≈20% compared with previous recommendations from 1985 (14).

Nutrients in early diet, fish oil, and prebiotics: intervention studies examining various health outcomes

Another study within theme 1 was the 16-y follow-up of children born to mothers in Denmark who had been randomly assigned to receive a fish-oil supplement or placebo during the last trimester of pregnancy. Findings showed a significantly lower risk of asthma in children who received fish oil than in children randomly assigned to receive olive oil (15). Supplementation of an infant formula with a mixture of prebiotic oligosaccharides in infants was explored in a controlled trial, and the investigators reported a significantly lower occurrence of atopic dermatitis and infections in the prebiotic group ≤2 y of age (16, 17). Another study followed up infants randomly assigned to receive different protein hydrolysate formulas ≤10 y of age and found that feeding with a hydrolyzed formula in infancy was positively associated with a higher acceptance of an extensively hydrolyzed casein formula at school age after adjustment for sex and study center (18).

An additional study within theme 1 followed up infants born preterm or at term that had been randomly assigned to receive formulas intended to modify bone mineralization. The infant dietary randomization group did not affect the peak bone mass or turnover at the age of 20 y. However, early feeding of human milk resulted in a higher bone mass in early adulthood, which appeared to reflect the effects of nonnutritive factors in breast milk. These findings may have implications for later osteoporosis risk and require additional investigation (19).

PROSPECTIVE, EPIDEMIOLOGIC STUDIES IN LARGE COHORTS

Theme 2 comprised most of the major European longitudinal studies that provided information on dietary exposures in pregnancy and early childhood (http://www.birthcohorts.net). Early dietary exposure in these cohorts was compared and similarities and disparities in intakes of major protein sources during pregnancy have been identified. Moreover, comparative dietary analyses during pregnancy across Europe are underway, and preliminary blood pressure and body composition datasets are available for exploratory analyses. A data analysis from the Danish National Birth Cohort detected a relation between maternal fish intake and the improvement of psychomotor development in offspring in the first 18 mo of life (such as the ability to climb stairs or to orientate a book) (20). As a matter of interest, this relation was independent of observed beneficial effects of breastfeeding.

Results from detailed comparisons between the Danish (Danish National Birth Cohort) and Norwegian [MoBa (den norske Mor & barn-undersøkelsen)] cohort databases and statistical power calculation have shown that for several scientific questions that relate to rare outcomes, coordinated or pooled analyses were justified. Thus, protocols on coordinated analyses regarding the effect of maternal diet on malformations and childhood cancer have been established.

Joint publications on parallel studies between Denmark and Norway on "the possible protective effect of Mediterranean diet on preterm risk" (21) and "the effect of physical activity in pregnancy and risk of pre-eclampsia" (22) have delivered evidence that it is possible to undertake even complicated joint analyses on the basis of both datasets.

MECHANISMS OF EARLY LIFE PROGRAMMING: MOLECULAR AND CELL STUDIES USING ANIMAL MODELS

Specific questions in relation to metabolic programming have been addressed in theme 3 by using well-defined dietary interventions during specified prenatal or postnatal periods.

In an article entitled "Postnatal catch-up growth after fetal protein restriction programs proliferation of rat preadipocytes," EARNEST-funded authors reported that fetal protein restriction, followed by catch-up growth, increased perigonadal fat mass and programmed a higher capacity for preadipocytes to proliferate (23). Another publication reported that, at 9 mo of age, male offspring who had experienced forced catch-up growth after fetal protein restriction featured an increased relative fat mass, hyperglycemia, and hypercholesterolemia. Significant alterations in gene expression that play a role in the differentiation and function of adipose tissue involved in lipid metabolism were also shown (24).

Studies that addressed the long-term outcomes of exposure to maternal nutrient restriction at different stages of gestation with regard to the adverse responses after exposure to an obesogenic environment led to the conclusion that clinically relevant adaptations, such as primary markers of the metabolic syndrome, were only seen if a nutritional challenge in utero was followed by a period of accelerated postnatal growth early in the postnatal period and/or if the offspring became obese (25).

The EARNEST group at King's College London (London, United Kingdom) investigated whether maternal obesity during pregnancy could program an increased susceptibility to obesity in offspring and, thus, lead to what has been called "an intergenerational cycle of obesity" (26). Findings of the study that investigated the effects of maternal obesity in mice revealed that the offspring of obese mothers ate more at the age of 4–6 wk than did the offspring of the nonobese control group although fed the same diet (26). At the age of 3 mo, the offspring of obese mothers were fatter and showed lower levels of physical activity and increased levels of insulin and endothelial dysfunction. Moreover, by 6 mo, offspring of obese mothers had increased glucose

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concentrations and blood pressure. Thus, maternal obesity resulted in adult offspring adiposity as well as metabolic and cardiovascular dysfunction in the developing mice.

EARNEST researchers in Cambridge, United Kingdom, have looked at the effects of early nutrition programming on breast cancer risk (27). Women with both low and high birth weight have been shown to be more likely to develop breast cancer. It was suggested that the poor growth of mammary tissue and subsequent compensatory growth increased the later susceptibility to breast cancer. The investigators gave rats an isocaloric low protein diet during pregnancy and lactation (27). Results showed that offspring of the low-protein dams initially grew poorer with a compensatory growth after 4 wk. The offspring were also more likely to develop early mammary tumors at the age of 4 mo. During compensatory growth, increased expressions of insulin-like growth factor I , insulin, and estrogen receptors were detected.

INTERDISCIPLINARY APPROACHES WITHIN EARNEST AND RELATED EC-FUNDED PROJECTS

The promotion of interactions between different lines of research was one of the wider aims to benefit from synergies within the EARNEST consortium. For instance, data from studies in mice suggested that maternal iron deficiency resulted in increased blood pressure in the offspring (28). Iron deficiency during human pregnancy is common, even in developed societies. Whether the effect also occurs in women was tested in the Avon Longitudinal Study of Parents and Children cohort study, but the results did not concur with observations in animal studies (29). On the basis of measures available, low iron in mothers resulted in decreased, not increased, blood pressure in the offspring. There are several possible explanations for the disparity, but the results were particularly important because they pointed to the need to test hypotheses that arise from mechanistic studies in human cohorts.

Beyond the EARNEST consortium, interactions between EC-funded projects were established. Part of the aims of theme 3 was to use the skills available in the Nutrigenomics Network of Excellence. Scientists from the EARNEST collaborated with the Nutrigenomics Network of Excellence bioinformaticists, who helped the scientists to analyze DNA arrays, interpret the results, and develop additional ideas and hypotheses. This was a novel and very effective interaction that resulted in several publications (29–33).

CONSUMER RESEARCH AND ECONOMIC-IMPACT STUDIES

Studies that aimed to investigate understanding of consumers in the field of early life programming concluded that the concept of early nutrition programming was widely recognized by scientist and governmental bodies; however, there was a lack of representation in respective documents and activities targeted to parents to communicate on early nutrition and for policy documents for professionals (34, 35). There were also marked intercountry differences in infant feeding intentions, health-related behaviors of mothers, and views of mothers about the relative importance of infant diet on later health (36). Almost all mothers polled (95%) considered the way they fed their infants important for the health of their infants in their first year of life. However, when mothers were asked about specific long-term health conditions such as obesity, high blood pressure, and cancer, they tended to think early diet was less important, which suggested that the mothers were not as clear about how early diet might affect later health. From the identified gaps in the understanding of new mothers in different countries of the importance of early diet, guidance on what sort of advice should be given in each country can be developed.

With the use of the example of the lowering effect on later blood pressure induced by the intake of long-chain polyunsaturated fatty acids in the first months of life, the potential of major health economic benefits of nutritional programming by early nutrition was shown by Straub et al (37) in this current volume.

TRANSLATIONAL APPLICATION: DEMONSTRATION STUDIES WITHIN EARNEST

Demonstration studies examine the short- and long-term health benefits of adding a novel prebiotic mix to infant formula or of recombinant human milk lipase to preterm infant formula. Prebiotics are nondigestible food ingredients that aim at the selective stimulation of the growth or activity of a limited number of beneficial bacteria (bifidobacteria and lactobacilli) that reside in the colon, thereby positively affecting the host health. Evidence is growing that prebiotics have the potential to modulate the developing immune system. Within the EARNEST, a long-term study is being performed to determine the effect of inulin-type fructans on the incidence of infections and immune markers in infants.

The addition of recombinant bile salt stimulated lipase (BSSL) to formula for preterm infants has the potential to enhance fat absorption and growth. BSSL activity has been shown in fresh human breast milk but is absent from current pasteurized human-milk formulas. A clinical trial to evaluate the effects of BSSL on fat absorption in preterm babies is being conducted to test the safety and efficacy of the intervention.

EARNEST GOES PUBLIC: DISSEMINATION BEYOND SCIENTIFIC PUBLICATIONS

The international conference "The Power of Programming: Developmental Origins of Health and Disease" was held in May 2010 in Munich, Germany (http://www.metabolic-programming.org/munich2010) and was cosponsored by the EARNEST, the Early Nutrition Academy, and the Developmental Origins of Health and Disease Society. The conference was hosted by the Ludwig-Maximilians-University of Munich and attracted >600 scientists from 51 countries on all 5 continents. More than 200 presentations were held in 22 scientific sessions and 4 poster exhibitions that presented results of 5 y of top-level research. The conference provided an environment for scientists, clinicians, and other health professionals and representatives of industry and policy makers at which state-of-the-art information was exchanged and future perspectives were discussed with regard to the advancement of the field and its relevance for policy making to promote health in future generations. The conference had clearly identified that, although enormous scientific progress on early nutrition programming has been achieved, more detailed and specific research needs to be done to unravel the specific effects of different environmental exposures that could affect the development of the fetus in the womb and the young infant. Associations seen in observational studies are not always confirmed in randomized trials, and careful analysis is required to pinpoint

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the active constituents. Teasing out the specific effects of all of these different potential influences requires new ways of doing research. With consideration of the tremendous implications for public health, it will remain an ongoing challenge to the multidisciplinary research community to find a way to capitalize on the beneficial effects of early nutrition programming and reverse its adverse effects for the benefit of future generations.

Beyond the lifetime of the EARNEST, the Early Nutrition Academy will continue to show its inherent potential to support the wider objectives of promoting research and scientific exchange in the broad field of early nutrition programming.

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