Long-Term Health Impact of Early Nutrition: The Power of Programming

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Keywords

Early nutrition · Pregnancy · Infant nutrition · Metabolic programming · Developmental origins of health and disease · Obesity · Adiposity

Abstract

The Power of Programming conference 2016 at Ludwig-Maximilians-Universität Munich brought together about 600 researchers and other stakeholders from around the world who reviewed the recent evidence on the lasting health impact of environment and nutrition during early life, from pre-pregnancy to early childhood. The conference was hosted by the Early Nutrition Project, a multidisciplinary research collaboration funded by the European Commission with collaborating researchers from 35 institutions in 15 countries in Europe, the United States and Australia. The project explores the early origins of obesity, adiposity and associated non-communicable diseases, underlying mechanisms and opportunities for prevention. The project also proactively supports translational application of research findings. In fact, some existing evidence has already been rapidly adopted into policy, regulatory standards and practice. Further, broad dissemination of findings is achieved through the established digital eLearning platform of the Early Nutrition eAcademy, video clip-based learning and

graphically supported messaging to consumers. The project demonstrated powerful effects of early metabolic programming on later health. Compared to other common prevention strategies, modifying risk trajectories in early life can achieve a much larger risk reduction and be more cost-effective. While some effective prevention strategies have been promptly implemented in policy and guidelines, legislation and practice, in other areas, the uptake is limited by a paucity of quality human intervention trials and insufficient evaluation of the feasibility of implementation and econometric impact. This needs to be strengthened by future collaborative research work.

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The Power of Programming Conference 2016

This issue of the Annals of Nutrition and Metabolism presents manuscripts based on presentations at the international conference “The Power of Programming conference 2016” held at Ludwig-Maximilians-Universität Munich, Germany in October 2016. The conference was truly global with attendance by about 600 participants from 49 countries on all 5 continents. Delegates comprised scientists from a variety of disciplines; health care professionals; experts in public health, policy and regulatory af-

fairs; and representatives of commercial companies related to biomedical, dietetic and food products, as well as consumer, patient and parent groups. The conference programme was built around the theme of long-term programming effects of early nutrition and lifestyle before and during pregnancy, in infancy and in early childhood, on later health and disease risk. New information was shared in 97 lectures and 132 poster presentations. While a broad spectrum of long-term health effects was addressed, particular attention was directed to programming effects on later obesity, adiposity (body fatness), and related non-communicable disorders such as insulin resistance, diabetes and other metabolic disorders, cardiovascular diseases such as stroke and ischaemic heart disease, asthma and some forms of cancer. In addition, 6 workshops were held including a “New Investigators Forum,” a workshop on the eLearning platform “Early Nutrition eAcademy” and a workshop with information on the EC-funded project DynaHEALTH. During the discussions, a strong focus was directed to the potential of translational application of research results and wider dissemination to achieve a broad impact of scientific progress, as well as defining future research opportunities. The scientific quality of the conference was rated as good by 47% of delegates and as excellent by 53%.

The Early Nutrition Project

This Power of Programming conference was hosted by the Early Nutrition Project, a multinational, multidisciplinary research collaboration that receives funding from the European Commission’s Framework 7 Programme (<http://www.project-earlynutrition.eu>; FP7-289346-EARLY NUTRITION) and co-funding from the Australian National Health and Medical Research Council for the funding period 2012–2017. With a total budget of 11.1 million Euro and collaborating researchers from 35 institutions in 15 countries in Europe, the United States of America and Australia (Table 1), the Early Nutrition Project coordinated at Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-Universität Munich, is the largest research project worldwide on developmental origins of health [1]. The project objectives are focussed on exploring the early origins of obesity, adiposity and associated non-communicable diseases (NCDs), underlying mechanisms and opportunities for preventive interventions. This focus has been prioritized because of the strong evidence of developmental programming of NCDs as well as their very high and further increasing disease burden [2–6], includ-

Table 1. Partner institutions participating in the Early Nutrition Project

European academic partners	Country
LMU Muenchen	Germany
Kings College London	UK
Medical University of Graz	Austria
Statens Serum Institute	Denmark
University of Murcia	Spain
University of Nottingham	UK
Norwegian Institute of Public Health	Norway
University College Dublin	Ireland
University Amsterdam	The Netherlands
University Rovira I Virgili	Spain
Leiden University Medical Center	The Netherlands
University of Southampton	UK
Erasmus University Medical Center	The Netherlands
University of Granada	Spain
University of Copenhagen	Denmark
Medical University of Warsaw	Poland
University of Cambridge	UK
University College Cork	Ireland
University Degli Studi di Milano	Italy
The Children’s Memorial Health Institute	Poland
National and Kapodistrian University of Athens	Greece
Centre hospitalier chrétien, Liège	Belgium
Small and medium enterprises	
Medscinet AB	Sweden
ServiceXS BV	The Netherlands
Biolution GmbH	Austria
Industry Partners	
Danone Research BV	The Netherlands
Beneo GmbH	Germany
Abbott Nutrition Research	Spain
Partners in the USA	
University of California	California, USA
Harvard Medical School, Boston	MA, USA
University of Texas Health Sciences Center	Texas, USA
The MetroHealth System, Case Western Reserve University School of Medicine	Cleveland, USA
Partners in Australia	
Telethon Institute for Child Health Research, University of Western Australia	Western Australia, Australia
Murdoch Children’s Research Institute, University of Melbourne	Victoria, Australia
University of Adelaide	Adelaide, Australia

ing high losses of life years and particularly of healthy life years (Figure 1). The World Health Organisation (WHO) concluded that currently, obesity is the 5th leading cause of global deaths and responsible for 44% of the burden of diabetes mellitus, 23% of ischaemic heart disease, and 7–41% of certain cancers [7]. Since the available options for obesity treatment are far less than satisfactory, the priority in combatting the obesity epidemic is on developing and im-

Fig. 1. The high disease burden of different degrees of overweight and obesity is apparent from the loss of life years and of disability adjusted life years (healthy life years) in affected people aged 20–39 years. Drawn from data of [5].

plementing effective and cost-effective prevention strategies. The recently published WHO report on “Ending Childhood Obesity” developed by an international scientific expert group with contributions from 100 WHO member states concluded that particular opportunities for effective prevention of obesity and associated NCDs exist in pregnancy and pre-pregnancy, in infancy and early childhood, and in adolescence, which is considered a pre-pregnancy period in females [7]. This focus of the WHO report reflects the 3 key hypotheses on early life origins of adiposity and associated disorders that the workpackages of the early nutrition consortium are designed to jointly test with different and complementary methodological approaches, that is, the fuel mediated in utero hypothesis, the accelerated postnatal growth hypothesis, and the mismatch of pre- and postnatal growth trajectories hypothesis [3, 4] (Fig. 2). Epidemiological evidence from current prospective cohort studies describes effects and effect sizes of early environmental and nutritional exposures and develops the basis for interventions in pregnancy and early childhood, which are tested in randomized controlled trials. In addition, the project aims at characterizing underlying mechanisms for effects of programming factors acting during periods of developmental plasticity, such as endocrine, metabolic, structural and growth-modulating factors and the regulatory function of the placenta (Fig. 3).

Fig. 2. The workpackages of the Early Nutrition Research Project are designed to jointly test 3 key hypotheses on early life origins of adiposity and associated disorders with different and complementary methodological approaches, that is, the fuel mediated in utero hypothesis, the accelerated postnatal growth hypothesis, and the mismatch of pre- and postnatal growth trajectories hypothesis.

The Early Nutrition Project has contributed to a better understanding of the impact of Early Nutritional Programming on health during childhood and later life. As of May 2017, a total of more than 250 scientific publications arising from the project work have been entered into the database of the project website. Early nutrition has produced better evidence for the impact of lasting ef-

Color version available online

Fig. 3. Nutritional and metabolic factors acting during sensitive time periods of developmental plasticity before and after child-birth modulate cytotogenesis, organogenesis, metabolic and endocrine response, and epigenetic regulation of gene expression, and thereby induce metabolic programming of lifelong health and disease risk.

Table 2. Subscapular skinfold thickness in infants aged 6 months is reduced by an antenatal lifestyle intervention in obese pregnant women to improve maternal diet (glycemic load and saturated fat intake) and physical activity (UPBEAT trial, 342 intervention, 356 control). Modified from [12]

Skinfolds	Z-score (95% CI)	<i>p</i> value
Triceps	−0.14 (−0.38 to 0.10)	ns
Subscapular	−0.26 (−0.49 to −0.02)	<0.001

ns, not significant.

fects of Early Nutrition Programming on health, well-being and performance, and the risk of obesity and associated disorders. The project has provided further clarification of the causative maternal/offspring exposures, effect sizes, key processes and mechanisms regulating programming, and on key concepts related to programming, such as the roles of accelerated foetal and/or infant growth and mismatch in the programming of obesity susceptibility. Joint evaluation of studies has been performed [8] and joint databases have been established that will facilitate further data sharing and combined individual patient data analyses. Standardization and harmonization of methodological approaches to describe key exposures and outcomes, and harmonized methodologies, for example, for assessing outcomes, sample collection and handling, analytical approaches, data management and evaluation, will improve and enhance future intervention studies and facilitate collaboration for meta-analyses and comparison of results from different studies.

Translational Application of Research Results into Practice

A key goal of the Early Nutrition Project followed from its conception was to support the transfer of indicative research findings into translational application. Here we describe just 2 examples that had a marked impact on improving practice.

Three randomized clinical trials exploring the possible impact of lifestyle modification in pregnancy on health outcomes were included in the Early Nutrition Project. The Limit trial enrolled 2,212 overweight women with a singleton pregnancy who were randomized to standard care, or to a comprehensive dietary and lifestyle intervention delivered by research staff who focussed on limiting the dietary intake of sugar and saturated fat, and on enhancing physical activity. In the intervention group, there was a non-significant trend for a lower adjusted relative risk for large for gestational age infants (0.90, 95% CI 0.77–1.07; $p = 0.24$), and a significant reduction in the number of infants born with a high birth weight of above 4,000 g, which is a secondary endpoint (relative risk 0.82, 95% CI 0.68–0.99; $p = 0.04$) [9]. Since birthweight >4 kg predicts a doubled later obesity risk [10], this finding may be of considerable clinical relevance. The UPBEAT trial recruited 1,555 obese pregnant women and randomized them to standard care of a behavioural intervention with eight health trainer-led sessions focussing on diet and physical activity. The intervention reduced gestational weight gain but did not affect the primary outcomes, i.e. gestational diabetes in mothers and large for gestational age birth infants [11]. However, in infants followed up at the age of 6 months, subscapular skinfold thickness was found to be reduced in the intervention group, suggesting an effect of the pregnancy intervention on later infant adiposity [12] (Table 2). It appears that interventions in pregnancy alone may not be sufficient to achieve an optimal benefit, but rather programmes that need to be initiated across the early life stages from pre-pregnancy to early childhood should be explored. Also, investment in exploration of the metabolic and other predictors of fetal growth and associated health outcomes appears worthwhile to inform future focussed interventions [13].

Considerable preventive opportunity also exists with postnatal interventions. A large observational study in Germany reported that breastfeeding is associated with a sizeable risk reduction of obesity at early school age [14]. This finding was replicated in many other observational studies [15–18], which have strengthened efforts to promote, protect and support breastfeeding. We hypothe-

Fig. 4. The dietary intakes of infants fed conventional infant formulae at the age of 3 and 6 months, expressed as percentages of intakes of breastfed infants, are slightly higher for energy [21] but markedly higher for protein [24].

Fig. 5. The Early Protein Hypothesis stipulates that a high infant protein supply in excess of metabolic requirements increases the plasma and tissue concentrations of insulinogenic amino acids, the growth mediators insulin and IGF-1, leads to enhanced infant weight gain and body fat deposition and to increased long-term risk of obesity. Modified after [19, 20].

sized that the protective effect of breastfeeding might be due at least in part to a lasting programming effect of the much higher protein supply to infants fed conventional infant formula, as compared to breastfed infants, “The Early Protein Hypothesis” [19, 20]. Formula-fed infants have a slightly higher energy intake (by 15–18%) than those breastfed (Fig. 4) [21], which is related to a higher energy cost for growth (lower energetic efficiency) in formula-fed infants [22, 23]. In contrast to the relatively small difference in energy intake, conventional formula feeding provides 55–80% more crude protein intake, calculated on the basis of total nitrogen intake [24]. The difference in true protein supply is even greater, given that about a quarter of human milk nitrogen content is comprised of non-protein nitrogen compounds, and a significant portion of bio-functional human milk proteins resists intestinal digestion and is excreted in stools in the intact form. We considered that this marked difference in protein supply might be responsible for the programming effect of infant feeding choices on later obesity (The Early Protein Hypothesis; Fig. 5) [19, 20]. We assumed that a high protein supply at infancy that exceeds the metabolic requirements would increase plasma and tissue con-

centrations of insulinogenic amino acids, the growth mediators insulin and IGF-1, and induce a higher infant weight gain and body fat deposition as well as an increased long-term risk of obesity [25]. The Early Protein Hypothesis was confirmed in a large clinical trial performed in 5 European countries, which enrolled 1,678 healthy infants born at term with a birthweight appropriate for gestational age. Infants were either fully breastfed for a minimum duration of 3 months by parental choice, or if parents chose to formula feed, they were randomized double blind at a median age of 2 weeks to feeding with conventional formula with a high protein content, or an isoenergetic intervention formula with a reduced protein content; both formulae were provided for the duration of the first year of life [26]. The lower protein supply led to a marked reduction of plasma concentrations of essential amino acids and of the secretion of insulin and IGF-1 [27–29] and to a normalization of the body mass index at the age of 2 years, as compared to the breastfed reference group [26]. Among the more than 60% of initially enrolled children in whom data on body mass index could be obtained at the age of 6 years, the obesity prevalence was 3.6% in previously breastfed children, 10.5% in chil-

Fig. 6. The Early Protein Hypothesis was confirmed in a large trial that enrolled 1,678 healthy infants born at term who were fully breastfed for a minimum duration of 3 months or were randomized double blind to feeding for the first year of life with conventional formula with a high protein content, or were fed an isoenergetic intervention formula with reduced protein contents that were more similar to levels in human milk. At the age of 6 years, the prevalence of obesity was markedly reduced in children previously fed a lower protein formula to a level more similar to the breastfed reference group. Drawn from data of [30].

dren fed conventional infant formula, but only 5.2%, and thus less than half, in children previously randomized to reduced protein formula [30] (Fig. 6). The adjusted relative obesity risk at early school age was increased 2.6-fold by higher vs. lower protein supply in infancy (95% CI 1.33–5.10, $p = 0.005$).

These results strengthen the conclusion that the observed risk reduction for later obesity associated with breastfeeding reflects a causal effect related to the relatively low protein content of human milk. Therefore, breastfeeding should be effectively promoted, protected and supported to attenuate the later obesity risk, in addition to its numerous other benefits [31], which has now been broadly adopted in obesity prevention policies [7]. It has also become widely and rapidly accepted that infant formula used for those infants that are not or not fully breastfed should provide lower protein contents than previously used, with levels more similar to human milk contents [31]. It is very encouraging that our results have rapidly been adopted and the composition of many infant formulae marketed in Europe and globally has been

changed accordingly, with a reduction of protein contents. Also, these data have led to changes in regulatory guidance in the European Union with a general acceptance of a minimum protein content of 1.8 g/100 kcal in infant formula, without the requirement for additional clinical evaluation, and a reduction of the permitted maximum protein content in follow-on formula [32], as well as a proposed reduction of the minimum protein content in follow-on formula to 1.8 g/100 kcal [33]. Also, the revision of the global standard for follow-on formula developed by the Codex Committee on Nutrition and Foods for Special Dietary Uses of the Codex Alimentarius is moving towards lowering the values for protein content [34]. In conclusion, it is very encouraging that the conclusive evidence for programming effects of infant protein supply provided by the European Union funded collaborative research has been rather rapidly adopted into policies, regulatory standards, and infant feeding practices, and hence contributes effectively to the primary prevention of obesity and its associated disorders across populations.

Further Dissemination

The Early Nutrition Project and its participating partners have effectively disseminated the project results. Project results are shared with the scientific community through publications, presentations at scientific meetings, and international workshops and congresses organized by the project. Other stakeholders have been specifically addressed with targeted communication. Evidence-based recommendations on optimized practice of nutrition before and during pregnancy, during the breast feeding period and the early life of infants, have been developed based on the project results and on systematic reviews of available evidence [35–42], in close collaboration with a broad group of stakeholders (prepared for publication). These recommendations are of considerable importance because most of the current guidance for pregnant women, particularly obese women, and for young children does not take into account the long-term programming consequences of early nutrition. We have translated these recommendations into simple messages provided through an attractive graphical format, which are shared with the broad public and specific consumer target groups to facilitate outreach (Fig. 7, 8). Project results and recommendations are also shared globally through the digital eLearning platform Early Nutrition eAcademy (www.early-nutrition.org/enea; Table 3). The CME accredited, interactive courses with self-assessments and case-based

Fig. 7. Public communication of the Early Nutrition Project Graphical on the importance of approaching a normal body weight prior to conception. Copyright: Ludwig-Maximilians Universität München for the Early Nutrition Project.

Fig. 8. Public communication of the Early Nutrition Project on the modest increase of energy needs of pregnant women. Copyright: Ludwig-Maximilians Universität München for the Early Nutrition Project.

trainings are available free of charge. Many of the early nutrition partners and other global leaders in the field contribute in the Scientific Committee, as authors and reviewers. As of May 2017, more than 6,500 health care professionals from 154 countries worldwide participated in the online courses. The top 10 countries with the largest numbers of users include Germany, Mexico, the United Kingdom, Colombia, Spain, Israel, the Netherlands, Slovenia, the United States of America, and Croatia. Of interest, 22% of users are accessing the eLearning courses using mobile devices. Moreover, a video clip-based Massive Open Online Course on “Nutrition and Lifestyle in Pregnancy” has been developed, which is also accessible free of charge (www.early-nutrition.org/MOOC).

Table 3. Online courses related to Early Nutrition Programming offered by the Early Nutrition eAcademy (www.early-nutrition.org/enea; May 2017)

Core modules	
	Nutrition/lifestyle in pregnancy
	Breastfeeding
	Infant formula feeding
	Complementary feeding
Focus modules	
	Nutritional care of preterms
	Early nutrition in low-resource settings
	Nutrition and epigenetics
	LC-PUFAs in pregnancy, lactation and infancy
	Early micronutrient supply

Conclusions

Powerful effects of metabolic programming in early life stages on the later risk of obesity, adiposity and associated NCDs have been demonstrated. Compared to common prevention strategies applied at school age or later, modifying risk trajectories very early in life can achieve a much larger risk reduction and be more cost-effective. While some effective prevention strategies have been promptly implemented in policy and guidelines, legislation, and practice, in other areas, the uptake of further early life prevention strategies into policy and practice is limited by a paucity of quality human intervention trials and insufficient evaluation of the feasibility of implementation and econometric impact, which clearly needs to be strengthened by future collaborative research work.

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Disclosure Statement

The authors declare no conflicts of interest in relation to the content of this manuscript.

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