



THE EARLY NUTRITION PROGRAMMING PROJECT

Project Number: FOOD-CT-2005-007036

Acronym: EARNest

(EARLY Nutrition programming - long term follow up of Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research.)

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EU reviewers rate EARNest project as "very good"

The second annual review of the Early Nutrition Project took place in June and the reviewers gave the project the highest rating of "a good to excellent project", particularly, they said, in regard to its size and complexity. Some of the achievements outlined in the second annual report to the EU are highlighted below.



Theme 1 The follow up examinations of the former study participants are in progress. Efforts have been taken in terms of harmonisation and standardisation of study design, exposures and outcome measures, with the ultimate aim of establishing a common database. The feasibility of this approach was demonstrated by meta-analyses based on individual patient growth data collected in four of the original cohorts followed up within EARNest. Also in this Theme, a study of the effect of supplementing infant formula with a prebiotic mixture of galacto- and long chain fructo-oligosaccharides in infants with a high risk of atopy found that the group fed the supplemented formula had a lower rate of atopy than the unsupplemented group at six months.

Theme 2 Observational studies in theme 2, which comprise all the major longitudinal studies holding information on dietary exposures in pregnancy and early childhood, have been extended. A website has been created which gives an overview of all such cohorts in Europe, and comparisons of early dietary exposure distributions in these cohorts have been initiated. An analysis of maternal diet on the risk of cryptorchidism and on infant psychomotor development has been carried out on data from the Danish cohort. Ongoing genetic triad analyses have continued in the Norwegian cohort. Detailed comparisons between the Danish and Norwegian cohort databases have been undertaken with the overall aim of enabling coordinated analyses based on both data sets.

Theme 3 New findings this year include: administering an antihypertensive drug during the suckling period in rats alleviated some of the adverse programming effects of maternal undernutrition; a high carbohydrate diet during the weaning period in rats showed programming effects but smaller than that during the perinatal period; in sheep, nutrient restriction during the period of fetal brain, heart and kidney development when followed by juvenile obesity had a potentially protective effect against glomerulosclerosis in the kidney and fat accumulation around the heart.

Theme 4 There has been excellent progress in studying consumer perceptions and understanding in this area. The concept of programming by early nutrition is widely acknowledged among scientists and recognized by governmental bodies, but it is not yet reflected in their communications aimed directly at parents or in policy documents for professionals.

Theme 5 The health economic effects of early nutrition were studied using the inclusion of long chain polyunsaturated fatty acids into infant formulas as an example. The corresponding Markov model revealed an increased life expectancy of 1.2 quality years and a lower cost for the health care system.

The report concluded that the project has made good progress during the first two years and there are good reasons to be confident that the further project objectives can be met according to the schedule during the next three years. Furthermore the basis has been laid to establish the "Early Nutrition Academy", which will pursue the aims of the EARNest consortium after the duration of the project.

Early Nutrition Academy

EARNest has committed itself, as part of its implementation plan, to establish an "Early Nutrition (Programming) Academy" (ENA). The aims of the Academy are to:

- foster nutrition research and its standards, in particular as it relates to nutrition in women of childbearing age, infants and children, including basic science, epidemiology and applied nutrition, as well as standards of nutrition practice
- foster nutrition education
- provide training in research skills
- communicate research findings (e.g. by provision of an abstract service)
- foster implementation and dissemination of knowledge
- help shape EU policy
- help transfer knowledge and technology to commercial users
- reach out over and beyond the membership of EARNest



All these goals are essentially the same as EARNest so why establish an additional Early Nutrition Academy? The advantages of the Academy are that it will be able to extend the EARNest activities (e.g. training activities) beyond the EARNest partnership. It will also be able to form a legal entity that can raise funds from sponsors to support and enhance the training and research activities beyond what EARNest can achieve and that will survive beyond the lifetime of EARNest. It will be able to continue to support research collaboration (including the preparation of research applications, e.g. for FP7), training, and scientific communication.

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Report of International Conference in Budapest

The International Conference on "Early nutrition programming and health outcomes in later life: obesity and beyond" attracted over 250 scientists from over 30 countries around the world. European scientists were well represented but there were also many from the US, Australia, Japan, the Middle East and Russia. The conference was a satellite of the European Congress on Obesity and so considered in particular the long term programming effects which might contribute to obesity in later life. Basic scientific research, data from epidemiological studies and clinical trial results were all presented during the programme.

Plenary sessions on a number of the broader questions in the field of early nutrition programming allowed the wider issues to be debated and explored. These proved lively and stimulating. **Professor George Davey-Smith** discussed the challenges facing epidemiological studies of the effects of early life on later disease. He discussed the problem of how to fully take into account confounding effects and set out various ways this could be improved. He also drew attention to the potential offered by Mendelian randomisation for investigating relationships between genetic variants which are not confounded by other factors and outcomes. **Professor David Leon** offered a "life course" critique of the early nutrition programming hypothesis which asked why focus on fetal life only, how behavioural risk factors later in life were taken into account and how a more holistic perspective would enable a better understanding of disease risk over a lifetime. **Professor Alan Lucas** gave a challenging and thought-provoking talk on where the evidence on the benefits of breastfeeding stood. He argued that changes in lifestyle over millennia meant that breast milk should not just be assumed to be the ideal milk for babies now but that promotion of breastfeeding should be based on sound evidence of benefit.



The parallel symposia provided a wealth of informative and interesting talks and discussions. An excellent presentation by **Professor John Mathers** on epigenetics and their contribution to fetal programming explained this new and exciting area of science to those unfamiliar with it. Epigenetic markings are permanent marks on the gene which alter their expression and lead to different functions. They connect environmental exposure with gene expression and function.

Other symposia on "Early nutrition and later cardiovascular risk", "Programming of obesity and metabolic disease" and "Causes of adult obesity - origins in early life" explored the role of early nutrition programming on later obesity risk in great depth.

Professor Philip Smith closed the conference by outlining the priorities for obesity research for the National Institutes of Health in the US. Early nutrition programming and the role of epigenetics in the development of disease susceptibility were among these.

The conference took place in the stunning art nouveau Palace Hotel in the centre of Budapest where the reception and dining areas of the hotel had retained the original 1911 art nouveau styling with decorative stained glass windows and lights. The gala dinner, cruising down the Danube provided another opportunity to appreciate the fine architecture that Budapest has to offer.

Multi-media interest in CHOP and EARNEST

The first results from the CHOP project coincided with the end of the consultation period in the UK on current infant growth charts, currently based on old data from formula-fed babies. This is a topic under consideration in many countries across the globe following the publication in 2006 of the WHO's revised growth charts.

With this timely news background, media interest in the CHOP message on low protein infant feed matching the more desirable and slower growth rate of breast-fed babies exploded. 'Current infant growth charts may have contributed to rapid increase in obesity' became the cry!

The international New Scientist journal devoted a two page spread to the topic 'Babies overfed to meet flawed ideal' - with quotes from Professor Bert Koletzko, Professor Peter Aggett and Professor Lucilla Poston and coverage followed across the UK national press. The story aroused the BBC's interest but was pipped at the post by new research on salt - the BBC will cover when the new UK growth charts are published!

Scientific, healthcare and consumer websites picked up on the story as have a number of health and medical titles with more coverage due over the next few months.

Dr Agnes Horvath, appointed the new Hungarian Minister for Health that same day, addressed the EARNEST Conference, pledging her commitment to addressing the rapidly rising rates of childhood obesity in Hungary and the country's comparatively low life expectancy. Local Hungarian media and European papers covered her attendance and interest in EARNEST the Early Nutrition Programming Project and the results from CHOP.



Professor Bert Koletzko, Co-ordinator of the EARNEST and CHOP Projects with Dr Agnes Horvath, Hungarian Minister for Health at the EARNEST pre-Congress Satellite meeting, Budapest, April 2007

First results of CHOP trial presented at Budapest

The first results of the EU Childhood Obesity Programme were presented by Project Co-ordinator Professor Berthold Koletzko at the EARNEST International Conference in Budapest. They indicate that low protein content infant formulas bring metabolic and endocrine benefits, as well as body growth rates close to those of breastfed babies. The further follow-up of the children as part of EARNEST will indicate whether these changes are associated with lower childhood obesity at a later age.

"These first results of the EU Childhood Obesity Programme emphasise the importance of promotion of and support for breastfeeding, together with the development of the right composition of infant formula, and support for the choice of appropriate complementary food" summarised Professor Koletzko. *"They contribute to the growing body of scientific evidence that early nutrition can exert important long term 'programming' effects on early development and later health,"* he added.

The clinical trial

About 990 infants were included in the study and were followed-up until the age of two years. About 335 children were randomised to a formula with low protein and 350 children to formulas with a high protein. In parallel, some 305 breastfed children were followed. The intervention phase with the different infant formulas took 12 months and the children were followed up until they were two years old.

Randomisation between groups was successful, as the lower and higher protein groups did not differ in terms of socioeconomic status (percentages of foreigners and single mothers, persons in household, educational level, number of siblings), smoking habits and parental anthropometry. Also, there were no differences in gestational age, birth weight, birth length and head circumference at birth between the two formula groups. Compared to the formula fed groups, parents in the reference group of breastfed children were found to be of higher education and with lower smoking frequency. The analyses of the infants diets found no differences in the energy intakes of the two groups but the expected differences in protein and fat intakes during the first year of life.

Anthropometry results

The primary hypothesis of the study was that one possible causal factor for the difference in long-term obesity risk between breast and formula fed infants is the much lower protein content of breast milk compared to infant formula.

i) Comparison of low and high protein groups

The two measures relating weight to length, i.e. weight-for-length and body mass index (BMI) showed significant differences between the groups with the infants fed the high protein diet having significantly greater values at 12 and 24 months.

ii) Comparison with the breast feeding reference group

The infants fed the low protein formula showed growth patterns over the 24 months which were more similar to the breast fed infants. Expressed as BMI, there was no significant difference between the averages of the low protein formula group and the breast fed group at 24 months.

Results from biochemical and endocrine analyses

A further hypothesis to be tested was that a protein intake in excess of metabolic needs, especially of branched chain amino acids, would increase the secretion of insulin and insulin-like growth factor 1 (IGF-1), possibly leading to enhanced growth during the first two years of life which might predispose to a higher obesity risk in later life. IGF-1 stimulates the development of adipocytes and is associated with increased obesity.

The high protein formula fed infants showed significantly higher plasma concentrations of IGF-1, as well as lower plasma concentrations of insulin-like growth factor binding protein 2 (IGF-BP2). The urinary excretion of C-peptide (adjusted for urinary creatinine concentration to correct for differences in fluid excretion), tended to be higher in infants with higher protein intakes at 3 months of age and was significantly higher at 6 months, which also indicates a greater degree of insulin secretion. The low protein formula fed infants tended to have values more similar to those of the breast fed infants.

The results of the biochemical analyses support the hypothesis that higher protein intakes are associated with increased insulin secretion and stimulation of the IGF-1 axis.



Amani, one of the CHOP participants, aged 3½ years



Young Investigators Forum

The science of early nutrition or metabolic programming is still at a very young stage and therefore makes, as Professor Koletzko pointed out at the International Conference, a very promising career choice for young investigators. EARNEST, and now also the Early Nutrition Academy, is keen to promote the training and development of young scientists in this area as an important means of progressing research in early nutrition programming. To this end, a Young Investigators Forum was held at the International Conference to recognise the achievements of young scientists. Researchers under 35 were invited to submit abstracts of their presentations and 5 winning presentations were chosen. The winners were given their travel and accommodation costs to the conference.

The winners of the Young Investigators Forum were from left to right: Thor Halldorsson from Statens Serum Institute, Denmark; Chantal Dirix from Maastricht University, Netherlands; Pierre Nivot from University of Leuven, Belgium; Tamas Marosvolgyi from University of Pecs, Hungary and also Sirinuch Chomtho from Institute of Child Health, UK.

PeriLip recommends omega-3 supplements during pregnancy

Many members of EARNEST were also members of the Perinatal Lipid Nutrition Group (PeriLip) which recently published its recommendations on the intake of DHA during pregnancy. They recommended that pregnant women should take a daily supplement of 200mg docosahexaenoic acid (DHA). The supplement would increase the likelihood of a healthy birth and boost child development. The committee, composed of more than 50 nutritional experts said it had found that women who included DHA in their diet had healthier pregnancies, that their children had healthier birth weights and that they were less likely to give birth prematurely.

DHA, which can be found in fatty fish such as salmon and mackerel, has been linked to brain and eye development. "Based on the systematic reviews of the available evidence, this EU-supported group of international experts unanimously concluded that women should have a regular supply of DHA during pregnancy and the breastfeeding period, as it is of great importance for the child's health," said Professor Berthold Koletzko.

The committee found however that the diets of western mothers tended to be low in foods that would provide the necessary dose. The experts believe that this could be explained by limited levels of awareness of the role of omega fatty acids in infant development.

SOME RECENT PUBLICATIONS BY EARNEST MEMBERS

Krauss-Etschmann S, Shadid R, Campoy C, Hoster E, Demmelmair H, Jimenez M, Gil A, Rivero M, Veszpremi B, Decsi T, Koletzko BV; Nutrition and Health Lifestyle (NUHEAL) Study Group. Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. *Am J Clin Nutr*. 2007 May;85(5):1392-400.

Symonds ME, Stephenson T, Gardner DS, Budge H. Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. *Reprod Fertil Dev*. 2007;19(1):53-63. Review.

Bille C, Olsen J, Vach W, Knudsen VK, Olsen SF, Rasmussen K, Murray JC, Andersen AM, Christensen K. Oral clefts and life style factors--a case-cohort study based on prospective Danish data. *Eur J Epidemiol*. 2007;22(3):173-81.

Taylor PD, Poston L. Developmental programming of obesity in mammals. *Exp Physiol*. 2007 Mar;92(2):287-98. Review.

Symonds ME. Integration of physiological and molecular mechanisms of the developmental origins of adult disease: new concepts and insights. *Proc Nutr Soc*. 2007 Aug;66(3):442-450.

Halldorsson TI, Meltzer HM, Thorsdottir I, Knudsen V, Olsen SF. Is High Consumption of Fatty Fish during Pregnancy a Risk Factor for Fetal Growth Retardation? A Study of 44,824 Danish Pregnant Women. *Am J Epidemiol*. 2007 Jul 13;

Koletzko B, Cetin I, Brenna JT; for the Perinatal Lipid Intake Working Group. Dietary fat intakes for pregnant and lactating women. *Brit J Nutr* 2007;98:253-9

Geppert J, Demmelmair H, Hornstra G, Koletzko B. Co-supplementation of healthy women with fish oil and evening primrose oil increases plasma docosahexaenoic acid, gamma-linolenic acid and dihomo-gamma-linolenic acid levels without reducing arachidonic acid concentrations. *Br J Nutr*. 2007 Aug 3;1-10

ESPGHAN Committee on Nutrition, Aggett PJ, Agostoni C, Axelsson I, De Curtis M, Goulet O, Hernell O, Koletzko B, Lafeber HN, Michaelsen KF, Puntis JW, Rigo J, Shamir R, Szajewska H, Turck D, Weaver LT. Feeding preterm infants after hospital discharge: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2006 May;42(5):596-603.

RELEVANT MEETINGS

2007

5th International Congress on Developmental Origins of Health and Disease
Perth, Australia. 6-9th November 2007 - www.dohad2007.org

2008

Child Health Foundation/ENA Workshop
Transition from milk to food. Obergurgl, Austria. 2-6th March 2008

3rd Scandinavian Pediatric Obesity Conference
Malmö, Sweden. 6th 7th March, 2008 - www.childhoodobesity.net

Early Development and Obesity: Food Preferences, Diet and Appetite Regulation
Liverpool, UK. 28th March 2008 - www.aso.org.uk

16th European Congress on Obesity
Geneva, Switzerland. 14-17th May 2007 - www.iaso.org

DOHaD Society Workshop: Nutritional Models of Developmental Origins of Health and Disease
Nottingham, UK. 4th July, 2008

3rd World Congress on Pediatric Gastroenterology, Hepatology and Nutrition
Iguassu Falls, Brazil. 16-20th August 2008 - www.wcpghan2008.com

For more details about the project and to read previous newsletters, please go to

www.metabolic-programming.org

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