Publishable Summary Period 3 – Extended Version

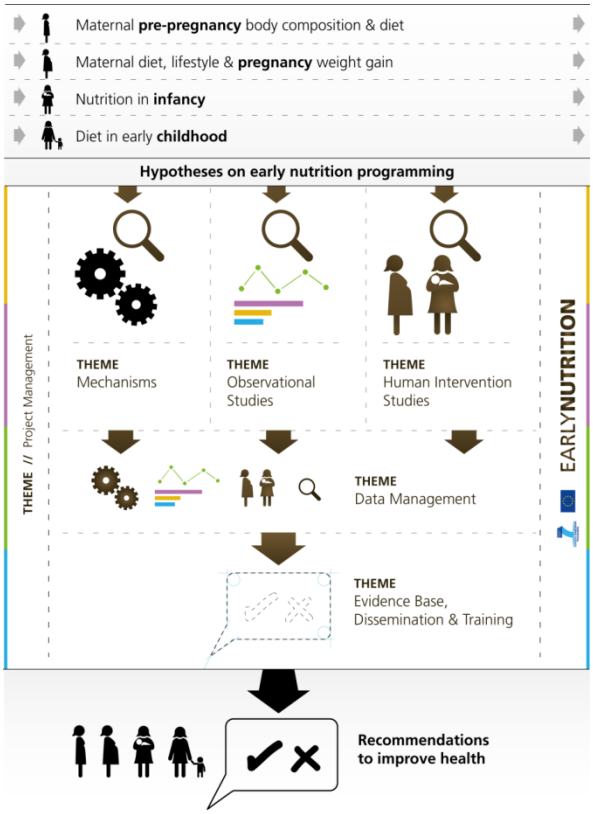
Summary description

Increasing evidence, most recently from the EU FP6 Project EARNEST, but also from many other investigators, demonstrates that early nutrition and lifestyle have long-term effects on later health and the risk of common non-communicable diseases (known as "developmental or metabolic programming"). Because of the increasing public health importance and the trans-generational nature of the problem, obesity and associated disorders are the focus of the project 'EarlyNutrition', running from 2012-2017 with a total budget of 11.12 million Euros, including a contribution by the European Commission of 8.96 Million Euros. This project brings together 36 partners from academia, industry and the SME sector from 12 European countries, the USA and Australia forming a strong multi-disciplinary team of international leaders in the field which achieves balance and complementarity. The EarlyNutrition project explores the three current key hypotheses on likely causes and pathways to prevention of early life origins of obesity (specifically adiposity) and associated disorders. It brings together extraordinary expertise and study populations of 470,000 individuals to investigate:

- *the fuel mediated 'in utero' hypothesis* which suggests that intrauterine exposure to an excess of fuels, most notably glucose, causes permanent changes of the fetus that lead to obesity in postnatal life;
- *the accelerated postnatal weight gain hypothesis* which proposes an association between rapid weight gain in infancy and an increased risk of later obesity and adverse outcomes; and
- *the mismatch hypothesis* which suggests that experiencing a developmental 'mismatch' between a sub-optimal perinatal and an obesogenic childhood environment is related to a particular predisposition to obesity and corresponding co-morbidities.

EarlyNutrition will provide the scientific foundations for evidence based recommendations for optimal early nutrition that incorporate long-term health outcomes, with a focus on obesity and related disorders. Evidence is produced from animal and placental studies (Theme 1), prospective cohort studies (Theme 2), and randomised controlled trials in pregnant women and infants (Theme 3). Theme 4 covers scientific strategic integration, recommendation development and dissemination, including systematic reviews and behaviour change approaches (see Figure 1). Four target groups are studied: women before pregnancy, pregnant women, infants and young children.

Figure 1: Themes and structure of EarlyNutrition



Scientific and technical expertise in placental biology, epigenetics and metabolomics provides understanding at the cellular and molecular level of the relationships between early life nutrition and the risk of later obesity and adiposity. This, in turn will help refine strategies for intervention in early life to prevent obesity. The project's impact comprises definitive evidence on early nutrition effects on health, enhanced EU and global policies, major economic benefits through obesity prevention and value-added nutritional products, and practical recommendations on optimal nutrition in the four target groups. Wide dissemination is achieved through active engagement with stakeholders.

The research programme of EarlyNutrition is centred around six main project objectives:

Objective 1 - to investigate and understand mechanisms for early nutrition programming effects through short term animal studies and studies in placenta (addressed in Theme 1):

Lifetime animal studies which parallel interventions in human pregnancy and early post natal life enable a greater understanding of the relevant mechanisms at the molecular, cellular, organ and whole body level for the development of obesity and related disorders in male and female offspring to be gained. Epigenetic and metabolomic approaches in the project provide a more detailed insight into mechanisms at the cellular and biochemical level, including observed gender differences, and determine opportunities for development of new biomarkers of both exposures and outcomes. Moreover, studies of placental function offer an understanding of the permissive or preventative role of the placenta in the risk of later obesity and of differences according to foetal gender, and address the potential for novel gender specific placental biomarkers to predict childhood obesity and risk of metabolic diseases.

Objective 2 - to investigate early nutrition programming effects through studies of prospective human cohorts followed up in childhood, adolescence and adulthood (addressed in Theme 2):
Observational analyses from well characterised contemporary cohorts of pregnant women and their offspring examine the hypotheses underlying programming through examination of pre- and postnatal growth velocities, together with determination of the influences of gestational glucose tolerance and of maternal overweight and obesity. In addition the role of maternal factors potentially affecting later adiposity, such as pre-pregnancy nutrition and weight, pregnancy diet, stress, lifestyle, physical activity and metabolism, gestational weight gain, genetic variation and ethnicity are determined. Data from observational cohorts define the contributions of postnatal breast milk composition and infant complementary feeding, gender, environment, physical activity and geographic background in relation to later adiposity and associated disorders. Moreover, the roles of gender, ethnicity and disadvantaged backgrounds in relation to early nutrition programming are addressed as well.

Objective 3 - to provide an improved evidence base for recommendations on optimal Early Nutrition utilising human intervention studies with particular focus on the later health of the offspring (addressed in Theme 3):
Follow up studies in childhood of intervention trials in pregnancy and in the first months of life, and new randomized controlled trials test the hypothesis that modification of maternal and infant diet (breast- and formula feeding, complementary feeding) and of lifestyle such as maternal physical activity behaviours can reduce childhood adiposity. In addition, the optimal strategy for delivery of these interventions and their acceptability are determined and the hypothesis that novel approaches to improving infant formula composition can reduce later adiposity risk is tested.

Objective 4 - to develop recommendations for Target Groups through systematic collation of evidence from Themes 1-3 and the literature, and to define improved methods of achieving implementation among consumers and health professionals (addressed in Theme 4):
Strategic integration of findings from Themes 1 to 3, systematic reviews of evidence relating to early nutrition of pre-pregnant women, pregnant women, infants and children and studies among consumers allow evidence based recommendations on optimised nutrition before and during pregnancy, and during the breastfeeding period and the early life of infants with special reference to later health development of offspring to be formulated. Furthermore, behaviour change approaches to enhance implementation of recommendations among consumers and health professionals are characterised and dissemination to relevant stakeholders is achieved.

Objective 5 - to create and manage databases (addressed in Theme 5):
Comprehensive, well managed and integrated databases enhance scientific quality and make data and samples available for broader scientific exploitation.

Objective 6 - to manage the project by strategic integration. To provide training opportunities for participants and other relevant stakeholders in topics relevant to the project (addressed in Theme 6 / 4):
The project's management policy improves the project output, facilitates multidisciplinary exchange and collaboration, fosters new collaboration and enhances dissemination and exploitation of project outcomes. The project's training policy improves training of new researchers and future innovators and leaders in the field and covers all aspects of training from scientific to communication. Training measures are divided into internal training to harmonise methodology and external training to enhance Spreading of Excellence.

Description of the work performed after the fourth year of the project

Within Theme 1, several experimental Workpackages examine the mechanisms behind the programming of obesity and related disorders.

The hypothesis that maternal obesity alters human/animal placental mRNA expression was not proven, but placental lipid metabolism in lipid droplets was modified. Technical issues delayed placental fatty acid transfer studies, and the approach to modelling placental fatty acid transfer in lean and obese women has been refined. Completed dietary/exercise intervention studies in obese pregnant rodents showed proof of principle that interventions can reduce obesity and some related disorders. Metabolomic profiling of pregnant womens' blood samples led to the first characterisation of metabolite profiles in pregnancy and identification of obesity-related metabolic 'signatures', potential targets to prevent programming of obesity. Novel sex differences in the metabolome and time needed for re-analyses led to some delays. Technical delays hampered one epigenetic study, but many hundreds of samples have been processed to better address the molecular mechanisms which may underlie developmental programming of obesity, with some emerging and very interesting preliminary data.

Theme 2 is investigating mechanisms for early nutrition programming through our prospective human cohorts followed-up in childhood, adolescence and adulthood.

We have compiled the world's largest meta-analysis (39 studies) of gestational weight gain, body composition and smoking in relation to offspring adiposity/co-morbidities. A new publication demonstrated that a greater number of modifiable early life risk factors associates with large differences in childhood adiposity/obesity risk, with major policy implications. Long term follow-up found no relation between long-chain omega-3 fatty acid intake in pregnancy and adolescent adiposity or early type-2 diabetes. Analyses of growth velocities have shown independent influences on childhood adiposity of high velocities of both prenatal and early infancy soft tissue accretion, but also novel evidence for interaction between faltering of fetal growth and an obesogenic childhood environment. Nutritional analysis of breast milk composition in 597 samples from women in 5 European countries, has shown many new findings, including correlations between pre-pregnancy weight and milk insulin/IGF-II levels.

Theme 3 combines 6 randomized clinical trials or follow up studies, respectively, investigating pre or postnatal interventions.

The follow-up studies are progressing. In the CHOP study (WP12) examination of the subjects at age 11 years has already been completed, with a higher follow-up rate than anticipated. Childhood follow-up from the three maternal prenatal intervention studies is either complete (LIMIT) or ongoing (ROLO, UPBEAT)(WP11) and the first meta-analysis of infants is underway. The AMELIE trial (WP14) had already been completed. During the current period data have been evaluated and a manuscript has been submitted and accepted for publication. In the NIGO study (WP11) a markedly unequal recruitment rate in the two study centres prompted us to change the study sites, which is currently implemented and expected to improve and speed-up recruitment considerably. After the delayed start the PROTEUS study (WP13) has progressed very well and has successfully recruited subjects. Current estimate is that the inclusion has reached the target number of subjects summer 2016, while the intervention period will add another 6 months from the time of last inclusion.The data safety and monitoring board found no indications that the study formula is not safe.

In summary there was impressive progress in Theme 3. Considering the enormous amount of data generated and the delays in two of the intervention studies Theme 3 would greatly benefit from an extension of the project duration by 6 months.

Theme 4 involves a number of tasks including collating information on current and developing new recommendations on optimised nutrition for women prior to pregnancy, pregnant women and infants and children, which take into account the effects of early nutrition on later health.

Successful progress has been seen. The review of current guidelines has been completed. The first draft of the recommendations for all four target groups has been prepared. Additionally, the analyses of the various datasets will be described and a synthesis will be made to provide a summary of similarities and differences between the main influences on diet, dietary behaviours and physical activity across EU countries.

Strong dissemination has been achieved on all deliverables and publications. Every opportunity has been used to spread the combined expertise within the consortium to other members of the consortium and to external individuals. Practical workshops have been organized and the e-learning platform ENeA is continuing to grow. (www.early-nutrition.org/ENeA).

Theme 5 comprises the data management infrastructure for clinical trials and biobanking for various studies in project EarlyNutrition through a dedicated Workpackage (WP20).
All databases had been developed and deployed in the first half of the project, except one because of delay in finalizing the study protocol. In the current reporting period, the last database was deployed. All databases have been successfully used to collect data of these studies.

Expected final results and potential impact

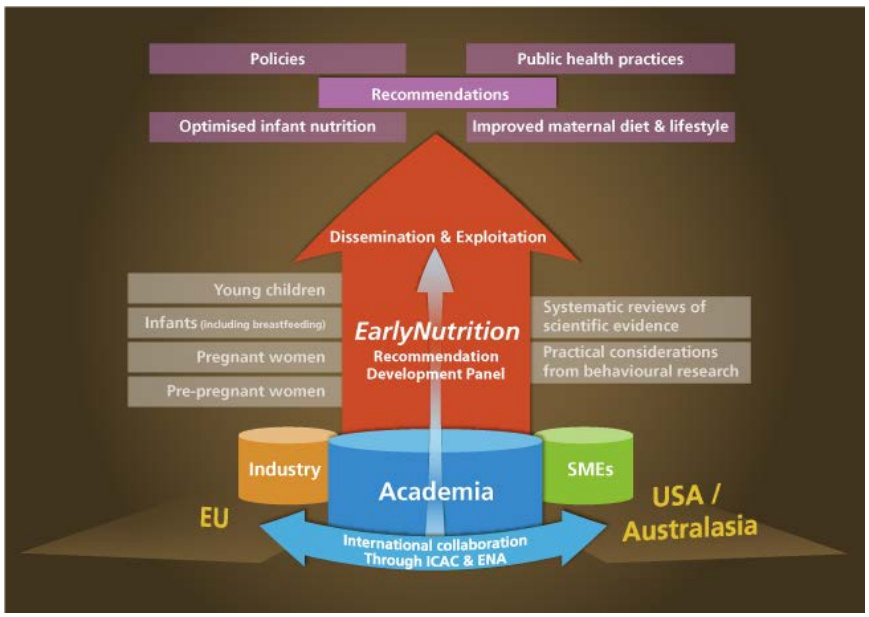
Project EarlyNutrition will lead to a better understanding of the impact of early nutritional programming on health during childhood, adolescence and adults in specific subgroups of the population. Furthermore, research in the project will help to identify the nutritional needs of women of childbearing age in Europe. The results should lead to recommendations on optimized nutrition before and during pregnancy, during the breast feeding period and during the early life of infants, with special reference to later health development of offspring. Most current recommendations for pregnant women, particularly obese women, and for young children do not take into account the long-term health consequences of nutrition. EarlyNutrition will systematically review the evidence, draw conclusions and formulate recommendations on optimized nutrition before and during pregnancy, during the breastfeeding period and childhood with special reference to later health development of offspring. Barriers to change will be explored in research investigating driving forces of consumer preferences and behaviour to ensure the suitability and user-friendliness of the recommendations.

For the scientific community, EarlyNutrition will produce better evidence for the impact of lasting effects of "Early Nutrition Programming" on health, well-being and performance, with a focus on obesity and associated disorders. It will provide further clarification of the causative maternal/offspring exposures, effect sizes, key processes and mechanisms regulating programming, will confirm or refute key concepts related to programming, such as the roles of accelerated foetal and/or infant growth and "mismatch" in the programming of obesity susceptibility, and will define new interventions to reverse the obesity epidemic. It will contribute towards a better understanding of the impact of early nutritional programming on health during infancy, childhood, adolescence and in pregnant women. It will provide further evidence towards identifying the nutritional needs of women in Europe before and during pregnancy, based on a better understanding of the long-term consequences in their offspring. A “database toolkit” and standardized approaches to describe key exposures (including dietary patterns) and outcomes, and harmonized methodologies e.g. for assessing outcomes, sample collection and handling, analytical approaches, data management and evaluation, will improve and enhance future intervention studies and facilitate collaboration as well as comparison of results from different studies and meta-analyses of results.

The wider societal implications of project EarlyNutrition are to strengthen the evidence for effective ways of reducing the susceptibility to obesity and its associated disorders, which could lead to future generations with a reduced propensity to gain excessive amounts of weight. The policy recommendations arising out of the project will therefore contribute to the primary prevention of obesity and its associated disorders, metabolic syndrome, diabetes, cardiovascular disease, asthma and certain cancers. This will help to reverse the increasing rates of obesity seen across all European countries. Figure 2 (below) summarizes how the expected results

(with recommendations for the four Target Groups) will be directed towards the 'lead' users (academia, industry and SMEs) and how the relevance of the results will impact upon policies, public health practices, and optimised maternal diet and lifestyle and infant nutrition.

Figure 2: Integration of project components leading to outcomes



More information about the project is available on www.project-earlynutrition.eu .

The project consortium consists of 29 partners from academia, three partners from industry and three partners from the small and medium enterprise (SME) sector:

- Ludwig-Maximilians-Universität München (LMU Muenchen, Germany) -
- King's College LONDON (KCL, UK) -
- Medical University of Graz (MUG, Austria) -
- Statens Serum Institute (SSI, Denmark) -
- University of Murcia (UMU, Spain) -
- University of Nottingham (UNOTT, UK) -
- Norwegian Institute of Public Health (NIPH, Norway) -
- University College Dublin, National University of Ireland, Dublin (NUID UCD, Ireland) -
- University Amsterdam (VUmc, Netherlands) -
- University Rovira I Virgili (URV, Spain) -
- Leiden University Medical Center (LUMC, Netherlands) -
- University of Southhampton (Southampton, UK) -
- Erasmus University Medical Center (ErasmusMC, Netherlands) -
- University of Granada (UGR, Spain) -
- University of Copenhagen (UCPH, Denmark) -
- Medical University of Warsaw (MUW, Poland) -
- The chancellor, Masters and Scholars of the University of Cambridge (UCAM, UK) -
- University College Cork, National University of Ireland, Cork (UCC, Ireland) -
- University Degli Studi di Milano (UMIL, Italy) -
- The Children´s Memorial Health Institute (IPCZD, Poland) -
- National and Kapodistrian University of Athens (NKUA, Greece) -
- Medscinet UK LTD (MedSciNet, UK) -
- ServiceXS BV (ServiceXS, Netherlands) -
- Biolution GmbH (BIOL, Austria) -

- Danone Research BV (DNR, Netherlands) -
- Beneo GmbH (BENEO, Germany) -
- Abbott (ABT, Spain) -
- The Regents of the University of California (UCI, United States) -
- Harvard Pilgrim Health Care Inc Corp (HPHC, United States) -
- The University of Texas System (UTHSC, United States) -
- Case Western Reserve University Corporation (CWRU, United States) -
- Telethon Institute for Child Health Research at the University of Western Australia (UWA, Australia) -
- Murdoch Children's Research Institute (MCRI, Australia) -
- The University of Adelaide (UA, Australia) –
- Centre Hospitalier Chretien ASBL (CHC, Belgium)