Long-term effects of early nutrition on later health

Reporting

Project Information

EARLYNUTRITION
Grant agreement ID: 289346

Funded under
Specific Programme "Cooperation": Food, Agriculture and Biotechnology

Total cost
€ 11 597 678,02

EU contribution
€ 8 962 771,00

Coordinated by
LUDWIG-MAXIMILIANS-UNIVERSITAET MUENCHEN
Germany

Start date
1 February 2012

End date
31 October 2017

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RESULTS PACK

1 June 2018

FOOD 2030: Innovative EU research ensures food system is future-ready
Executive Summary:
The project ‘EarlyNutrition’ has collated convincing evidence demonstrating that early nutrition and lifestyle before and during pregnancy, during the breastfeeding period, and during infancy and early childhood have important long-term effects on later health and the risk of common non-communicable diseases. We focused on developmental or metabolic programming of obesity and associated disorders because of the increasing public health importance and the trans-generational nature of the problem. In a close interdisciplinary collaboration of 36 partners from academia, industry and the SME sector from 12 European countries, the USA and Australia, the EarlyNutrition project explored three key hypotheses on likely causes and pathways to prevention of early life origins of obesity (specifically adiposity i.e. increased body fat content) and associated disorders. It brought 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 provided strong 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 has been produced from animal and placental studies, prospective cohort studies, and randomised controlled trials in pregnant women and infants. Mechanistic studies provided novel insights into placental nutrient transfer from the mother to the unborn child, epigenetic and metabolic regulation, and identified novel biomarkers for risk phenotypes. Intervention trials showed safety and feasibility of prenatal modification of diet and lifestyle, with the potential to modify pregnancy weight gain and some offspring outcomes, and the results indicate directions for future preventive strategies. We found considerable benefits of breastfeeding among obese women for both mother and child. Infant formula feeding with less protein contents than previously used has a very marked benefit of reducing child obesity up to school age, with a greater effect size than any other currently known prevention strategy. We showed a refined, novel approach with less protein and modified protein quality of infants to be feasible and safe. Replacing sugar by a less glycaemic carbohydrate in formula for older infants is safe and acceptable. We found important sex differences in several experimental and clinical studies which seem relevant for the design of preventive strategies. Barriers to the implementation and take up of dietary and physical activity recommendations were identified and addressed. A major impact for training, qualification and international interlinkage of young researchers was achieved. Based on extensive systematic reviews of available evidence, EarlyNutrition developed practical recommendations for preventive lifestyle and dietary choices focussing on our four target groups of women before pregnancy, pregnant women, infants and young children. Project outputs were widely disseminated across Europe and the world, effectively supported by a barrier free distance learning platform for professionals that we established that helped to
engage widely with civil society. Our results have already had high impact on guidelines of international bodies and the World Health Organisation, and regulatory standards of the European Union and the global Codex Alimentarius, and on commercial application, and on guiding research approaches. The results of the EarlyNutrition studies will most certainly contribute to the promotion of health and the prevention of obesity and associated disorders.

Project Context and Objectives:
Increasing evidence demonstrates that early nutrition and lifestyle have important 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 were the focus of the project ‘EarlyNutrition’ which has been 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 brought 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 explored three key hypotheses on likely causes and pathways to prevention of early life origins of obesity (specifically adiposity i.e. increased body fat content) and associated disorders. It brought 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 provided strong 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 covered scientific strategic integration, recommendation development and dissemination, including systematic reviews and behaviour change approaches. Four target groups were studied: women before pregnancy, pregnant women, infants and young children.

Scientific and technical expertise in placental biology, epigenetics and metabolomics provided 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 helped to 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 has been achieved through active engagement with multiple stakeholders.

The research programme of EarlyNutrition has been 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 postnatal 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 were 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 have been 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 tested 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 have been determined and novel approaches to improving infant formula composition that can reduce later adiposity risk have been developed and 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 have allowed to develop 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 have been characterised and dissemination to relevant stakeholders has been achieved.

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

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 has markedly improves the project output, facilitated multidisciplinary exchange and collaboration, fostered numerous new collaborations and has enhanced wide dissemination.
and exploitation of project outcomes. The project's training policy has effectively improved training of new researchers and future innovators and leaders in the field and has covered all aspects of training from scientific to communication knowledge and practical skills. Training measures were divided into internal training to harmonise methodology and external training to enhance Spreading of Excellence.

**Project Results:**

**Main S&T results / exploitable foreground**

The investigation of underlying mechanisms for early nutrition programming effects through short term animal studies and studies in placenta (Theme 1) have provided major novel findings and important insights that lay the ground for future application in human studies, including:

- Advances in understanding of placental lipid transfer: a new computer model of lipid transfer proposing an intracellular lipid pool; first characterisation of composition of placenta lipid droplets which may represent a metabolic pool; modification of the lipid droplet composition by a maternal lifestyle intervention and specific upregulation of placenta DHA transfer associated with obesity.
- Placental expression of transporter genes and others of relevance to obesity and inflammatory pathways are not modified by maternal obesity, and do not relate to measures of infant adiposity.
- Exercise rescued the placental hypoxic phenotype in parallel to normalizing maternal insulin levels and insulin sensitivity. Future intervention studies in pregnancy may have greater effect if the focus is placed more on increasing exercise levels rather than on healthy eating.
- The novel approach to integrate data from the in vivo and in vitro studies into a generalizable computer model of transplacental fatty acid transfer was an iterative process that involved multiple disciplines. These ranged from Biochemistry, Cell Biology, Physiology, Engineering to Mathematics and can be used as showcase for the power of multidisciplinarity.
- Animal models from three different laboratories showed that dietary and physical activity interventions in pregnancies complicated by obesity and poor diet can strongly influence the offspring phenotype, improving metabolic function, but with a lesser effect on cardiovascular function.
- Important gender and species differences were observed which are highly relevant for the design and interpretation of further cohort and intervention studies.
- A novel protein reduced infant formula with an improved amino acid composition was developed and tested in animals. Of importance, lower amino acid oxidation levels were observed with the improved amino acid profile. These results very much support the further development and evaluation of a respective, refined formula for babies which could lead to a quantum leap in progress in the approaches to infant feeding. The results are expected to be exploited by the commercial sector in developing commercially viable products with targeted modification of amino acid composition of infant formula aiming at optimizing metabolism, growth and long-term health. IPR protection has been achieved.
- Lack of effect of early life interventions on the metabolome in later life contradicts the hypothesis of a prolonged effect of early life exposures on metabolism.
- Creation of a large database of comparable and standardized metabolomics measurements in infants, children and adults is a new major resource that can be applied by other researchers and commercial users.
- Novel metabolic markers of risk phenotypes were identified, including specific sphingomyelins that were not detected before because of methodological limitations of commercially available approaches. These results have considerable potential for further application and exploitation.
- Preliminary evidence points to altered neonatal methylation status in association with a maternal
intervention in obese pregnant women, which is but a potentially important observation.

A number of the results achieved in Theme 1 appear not to have a direct commercial value, but the respective foreground will be exploited by scientists in this field, promoting science in several aspects, and have been shared through publication in scientific journals, presentations to various target groups and EarlyNutrition workshops.

Both commercial and academic will likely exploit the development and results of animal models demonstrating that adverse consequences of maternal obesity on the offspring are reversible by maternal diet and physical activity. The observation that these interventions were effective should stimulate the development of interventions with similar magnitude of effect on maternal fat mass and insulin sensitivity in obese pregnant women. All future trials should consider the potential sex specific effects that was detected.

The lack of a persistent effect of early life interventions on the later metabolome has marked impact amongst researchers in this field. The established database provides a unique resource for data sharing with academic and commercial parties. Demonstration of new specific markers of metabolic phenotypes has commercial potential for indexing the susceptibility of an individual to adverse consequences of obesity, diabetes, and metabolic disease, following validation in other cohorts.

The identification of novel metabolic markers of risk phenotypes, including specific sphingomyelins that were not detected before because of methodological limitations of commercially available approaches, has considerable potential for further application and exploitation which is being pursued.

Further analysis of the neonatal epigenetic DNA methylome in relation to later infant and childhood adiposity is warranted; the observation of an association with a maternal intervention in obese pregnant women will have considerable impact in the academic community and potentially also in the commercial sector, providing a target for interventions in pregnancy to prevent childhood obesity.

The exploration of early nutrition programming through follow-up of prospective mother-offspring cohorts followed-up in childhood, adolescence and adulthood in Theme 2, including investigation of underlying mechanisms for early nutrition programming effects, provided major novel findings and important insights that lay the ground for future application in human studies. These include the following:

• The world’s largest individual participant data (IPD) meta-analysis of gestational weight gain, body composition and smoking in relation to offspring adiposity/co-morbidities was performed, including as many as 39 studies. The analyses included exploring the effect of adjustment for socio-demographic and lifestyle-related characteristics and potential sex specific and ethnic specific effects. Overall the results indicate that a high BMI at the start of pregnancy is a major risk factor for adverse offspring outcomes that has greater predictive importance than high gestational weight gain. These findings have direct implication for preventive strategies and programmes and for commercial application.

• Assimilated data from the UK SWS and from a US study funded by the National Institutes of Health enabled examination of maternal diet, physical activity and stress in pregnancy in relation to offspring body composition, including novel metabolomic studies.

• Data from the Danish National Birth Cohort, the SCOPE/BASELINE study and the US Project Viva cohort, examined whether long-chain n-3 polyunsaturated fatty acids during pregnancy interact with maternal glycaemia to influence offspring adiposity/co-morbidities.

• Detailed phenotyping of the UK SWS cohort in late childhood enabled characterisation of the sensitive periods for programming of adiposity/comorbidities before and after birth.
Moderate ethnic differences have been detected in maternal pre-pregnancy overweight, obesity and gestational weight gain; socio-demographic, lifestyle and pregnancy related characteristics partly explained these differences. Childhood follow up of the Generation R cohort showed that all ethnic minority groups had higher risks of overweight and obesity than Dutch children. Moroccan, Surinamese-Hindustani, and Turkish children also had adverse body fat and cardiovascular profiles. These differences were largely explained by parental pre-pregnancy factors, pregnancy factors and childhood BMI. The results are important for refinement of preventive strategies.

Higher weight gain in early pregnancy was particularly associated with an adverse cardio-metabolic profile in offspring, largely mediated through childhood adiposity. The result is highly relevant for informing trimester specific approaches of pregnancy care.

An association between maternal smoking and increased cardiovascular risk in the offspring was mainly seen in girls, which adds further arguments and weight to strategies and programmes tackling smoking before and during pregnancy.

IPD meta-analysis resulted in construction of new gestational weight gain reference charts for underweight, normal weight, overweight, and grade 1, 2 and 3 obese women. A higher maternal BMI was associated with higher offspring BMI SDS and higher risks of overweight throughout childhood, with the strongest effect estimates in late childhood.

Measures of higher maternal physical activity (e.g. faster walking speed) in early pregnancy are associated with lower offspring percent fat mass and greater total lean at 6 years, alongside associations of maternal late pregnancy vitamin B and D insufficiency with greater offspring total and percent fat mass in early childhood. These data inform strategies for targeting sedentary and physical activities in women before and during pregnancy.

Physical activity levels in most studied children met guidelines, but most activity was “light activity” that did not appear to protect from high adiposity. In contrast, levels of protective moderate/vigorous activity were low in most children. These results are important for targeted approaches to enhance protective levels of physical activity.

Regarding maternal diet effects, dietary glycaemic load in early but not late pregnancy was found linked with childhood adiposity. No consistent relations were found between long-chain omega-3 fatty acid intake in pregnancy and adolescent adiposity or early type-2 diabetes, but there was limited evidence suggesting that children of women with poor glucose tolerance may be more susceptible to changes in prenatal n-3 long chain fatty acids status.

Higher maternal stress markers during pregnancy, such as cortisol and IL6, was found associated with greater infant adiposity. A healthy diet during pregnancy was associated with lower maternal IL-6 and cortisol concentrations.

Combined analyses of multiple risk factors had led to new publications from the Theme, demonstrating that a greater number of modifiable early life risk factors are associated with large differences in childhood adiposity/obesity risk, with major policy implications.

Collectively, the findings indicate that higher maternal prepregnancy body mass index and smoking during pregnancy, psychosocial stress, and to a lesser extent higher gestational weight gain, are major risk factors for adverse birth outcomes, childhood obesity and an adverse childhood cardio-metabolic profile.

Technical challenges in nutritional analysis of inter-individual variation in breast milk composition, were resolved and analysis of breast milk composition in 597 samples from women in 5 European countries were completed. Unique data on breast milk composition and its variation and on prediction of contents of some milk components by maternal body size were created, which serve as a reference point both for
further research studies on human lactation, and for commercial attempts to improve the composition of infant formulae. Analyses of the nutritional and metabolic content of human breast milk have shown many new findings, including correlations between pre-pregnancy weight and milk insulin/IGF-II levels. Relating human milk metabolites to the growth patterns of the children demonstrated the complexity of the relationship between breast milk composition and growth. No clear and consistent associations were found between milk composition and the BMI, weight, length and weight for length scores of the children; this may be a reflection of the variability that was found in milk composition during the lactation period and within the day, but also within individual women. These have already led to refined approaches taking breast milk volume into account in analysing these potential relations.

- In depth analyses of growth velocities have shown independent influences on childhood adiposity of high velocities of both prenatal and early infancy soft tissue accretion, and characterized early infancy as a period when greater abdominal circumference gain associates with higher childhood blood pressure. Importantly, the analyses have provided novel evidence for interaction between faltering of fetal growth and an obesogenic childhood nutritional environment. Thus, a highly quality childhood diets was found to be strongly protective against late childhood adiposity in those with a lower velocity of fetal abdominal circumference growth in late gestation, while having no influence in those with a high velocity of abdominal circumference growth in late gestation. In keeping with this, our other analyses demonstrated that fetal growth deceleration followed by infant growth acceleration was associated with an adverse body fat distribution in childhood. Together, this provides the most compelling evidence to date for a contribution of “developmental mismatch” to the programming of childhood adiposity.

May of the results of the Theme 2 work will be highly relevant to future work of researchers and to translational application in health promotion and disease prevention strategies and programmes. Commercial application by companies engaging in health promotion services, assessment of physical activity, body composition, laboratory analyses and the development, production and marketing of food and dietetic products is expected.

The randomized clinical trials in Theme 3 investigate pre- or postnatal interventions partly with long term follow up in respect to the anthropometric and metabolic development of the offspring. All randomized clinical trials have successfully completed recruitment during the project funding period and data collections have been completed, except for the NIGO trial which could only be started with a delay and which suffered from slower than planned recruitment, leading to a last patient out date in the first quarter 2018. With funding provided by partner ABT, the trial will be completed and data analysed, as has been expressively confirmed by partner ABT and is supported by partner UGR. Although in all studies the data evaluation and interpretation is still in progress, some valuable findings have already been reported. Selected key points are highlighted below.

- The prenatal interventions tested in randomized clinical trials were all shown to be safe, which enables their further application.
- Mechanistic studies have produced novel insights indicating an association of lysophospholipids in cord blood with fetal growth, which point to a potential causal growth promoting effect of omega-6 polyunsaturated fatty acids.
- The follow up of the randomized controlled CHOP study which tested the effects of modifying milk protein supply in infancy was extremely successful. Detailed investigations demonstrated that dairy protein intake during infancy is of specific, lasting importance for anthropometric development and long-term obesity risk, with very high effect sizes.
• The CHOP study results also show that the physical activity of 2/3 of the children complied with the recommendations and seems appropriate to prevent obesity, but a further decrease of sedentary time should be recommended.

• A randomized trial to test the safety and feasibility of using novel infant formula with optimisation of both protein content and amino acid composition demonstrated safety and non-inferiority with regards to growth measures. These results now enable moving forward to the next step of performing a large efficacy study as a prerequisite for implementation this strategy for promoting healthy growth and reducing obesity risk, and potentially moving to a commercial application and wide implementation.

• A randomized trial testing a novel follow-on infant formula concept with a low glycaemic load demonstrated that this approach is both safe and acceptable for parents. Insights were gained for further improving the study design of evaluation of this concept in infants. Commercial application and implementation of the results is already ongoing.

• The follow up of children whose the ROLO trial showed that neonates born to mothers receiving the low GI dietary intervention had lower thigh circumference and showed at 2yrs of age a reduction in hip circumference, but no differences in other anthropometric parameters at the follow up examinations at age 6 months, two years and 5 years. The follow up showed no evidence of harm to the child of the intervention. Some maternal biochemical parameters and maternal diet were associated with infant anthropometry which raise hypotheses on potential mechanisms and offer opportunities for testing further targeted interventions.

• The intervention tested in the randomized controlled UPBEAT trial in pregnant women, comprising a low glycaemic index diet and increased physical activity, was found to be safe for both the mothers and the infants. Among the infant anthropometric parameters only subscapular skinfold at age 6 months was found significantly reduced by the intervention, whereas other outcomes up to the age of 3 years were not affected.

• The randomized controlled UPBEAT trial in pregnant women also provided some very interesting mechanistic findings, pointing to the importance of the diet and weight gain during pregnancy and of the lysophosphatidylcholine concentrations in the cord blood for infant growth.

• Date from the UPBEAT trial also confirmed a lower weight gain of breastfed compared to formula fed infants of obese mothers.

• The randomized LIMIT trial offspring follow-up at the ages of 6, 18 months and 3 years showed no evidence of harm but also effect of the maternal intervention on child adiposity at any age.

• The NIGO pilot trial demonstrated that consumption of a lower glycaemic load beverage improves 24hr and day time glucose profiles compared to control as well as habitual diets.

• An preliminary intermediate analysis of the NIGO study reported no significant differences in the glucose tolerance tests between the Intervention and standard care groups.

• The aggregate data analysis bringing together data from the LIMIT, ROLO and UPBEAT trials reported no effects on infant anthropometric outcomes including measures of infant growth, body composition and growth velocities at 6 months of age.

Although direct effects of the tested interventions in pregnancy are modest, there is some exploitable foreground, as the lifestyle interventions which recommend a low glycemic index diet/a healthy diet and improved diet/glycemic control and reduced gestational weight gain/maternal adiposity during pregnancy have shown no evidence of harm to the child and can improve health behaviours in pregnant women. Commercial application in relation to targeted dietetic products for women before and during pregnancy
The results of infant studies indicate that substantial lowering the milk protein intake in infants has a marked benefit for obesity prevention, with a 2.6-fold lowering of adjusted risk of obesity at school age. Along with promotion of breastfeeding, this is the most powerful strategy for prevention of childhood obesity known, and it was promptly implemented in guidelines, EU infant food legislation 2016, Codex Alimentarius 2017 draft infant food standards, marketed products and in infant feeding practice. The extension of this concept to improve both the quantity and quality of infant protein supply, with a targeted modification of the dietary intake of specific amino acids, resulted in lower protein oxidation rates and higher protein efficiency, while body composition was not changed at 17 weeks or 6 months postpartum. The results indicate that lowering the protein intake substantially, while changing the amino acid composition is safe and results in adequate growth. It is planned to study the hypothesis that modified protein composition might reduce the risk of childhood obesity needs in a large efficacy trial.

The randomized, controlled, double-blind intervention study AMELIE demonstrated that the acceptance and tolerance of a follow-on formula with isomaltulose (Palatinose™) is similar to that of conventional follow-on formula. No negative or adverse effects were found for the number of events registered, including also amount of flatulence, stool frequency and consistency. With respect to metabolic outcomes, our hypothesis of differences in glycaemic and insulin response between the formulae groups were not confirmed. Conclusions were drawn and shared for future studies with refined methodology. Accordingly, there is no exploitable foreground with respect to potential metabolic benefits and no IPR measures have been taken or are intended. Further research and more data about postprandial glucose response in infants over a longer time is warranted in order to benefit the general understanding of metabolic processes in this age group. This will also be a key prerequisite for any further exploitation as well as for the investigation of long-term effects of low glycaemic load follow-on formulae.

Potential Impact:
The results and recommendations produced by EarlyNutrition contribute to improving the quality of life and lifelong health for European children and their families through evidence based approaches to reducing the risk of obesity and associated NCDs, and reducing psychosocial burdening and mental health disorders linked to obesity. Facilitated by the unique strength of our international collaboration and our open access e-learning platforms, we have established a global network of preventive childhood obesity knowledge and action that will also reach low- and low-middle-income countries where childhood obesity has already become as great a challenge as malnutrition. We expect that the results achieved will also leverage a marked economic benefit by reducing costs for health care, unemployment, loss of productivity, and social services, given that obese children are likely to become obese adults and are at high risk of associated long-term morbidity and mortality, all of which incurs an enormous EU and global economic burden. According to the EU Action Plan on Childhood Obesity 2014-2020, ≈7% of health budgets in EU countries go towards health costs related to treating obesity. Several of our project results have the potential for underpinning innovation in European businesses and strengthening leadership in enabling industrial capability, with long-lasting commercial exploitation. These include e.g. methodological inventions, intervention programmes that can be rolled out in public-private-partnership, predictive tools and identified biomarkers, and novel nutritional products. The achieved expansion of the evidence base and mechanistic
knowledge enhances the understanding of the complex interactions between the factors influencing obesity in populations and in particularly susceptible individuals, considering a broad range of geographic, socio-economic, behavioural and cultural factors, and gender effects. Our project results will contribute to decrease the number of obese children by

- Improving diet and lifestyle before and during pregnancy,
- Achieving higher rates and longer times of breastfeeding, and
- Offering improved pre-pregnancy, pregnancy, infant and toddler nutritional products.

Through identification of pathways and risk factors, EarlyNutrition has promoted our as yet incomplete understanding of the processes which underlie development of childhood obesity using data from experimental approaches, cohort studies and randomized controlled trials synthesizing known and previously unrecognised early life dietary, lifestyle and environmental risk factors. A breadth of expertise in ‘omics technologies and available bioresources contributed to defining molecular signatures related to the biological risk of later obesity. This information will contribute to design and refinement of interventions targeting e.g. glycaemic responses in women pre-conception and in pregnancy, and insulin and IGF-1 secretion induced by amino acid intake in infants, with the potential to markedly modify childhood growth trajectories, body fat deposition and obesity risk. These refined approaches, along with improved understanding of lifestyle and behavioural interventional elements, are likely to be far more effective than currently established practices in tackling the EU epidemic of childhood obesity, with major benefits to lifelong health and wellbeing through reduction in child and adulthood obesity related diseases.

The interdisciplinary our consortium was most valuable in effectively approaching the complex and multifaceted problem of early programming of childhood obesity, which can only be successfully addressed by thoughtfully combining the specific strengths of a broad variety of disciplines and societal actors. Impact was enhanced through major synergies with science education, including the development of our highly successful Early Nutrition eAcademy platform (early-nutrition.org/en/enea/) and the award winning Southampton LifeLab programme (southampton.ac.uk/lifelab/index.page). These platforms helped to engage widely with civil society, which was also achieved through numerous public lectures, the LMU EarlyNutrition Massive Open Online Course on Nutrition and Lifestyle in Pregnancy, television, radio and social media. and international nature of the consortium international facilitated broad and international outreach and impact and implementation of findings are in international guidelines. For example, close engagement between the EarlyNutrition and policymakers includes lead roles in the International Federation of Gynecology and Obstetrics Initiative on Adolescent, Preconception and Maternal Nutrition; this has led to the widely adopted "Think Nutrition First" recommendations on adolescent, preconception, and maternal nutrition. Evidence from EarlyNutrition was highly influential in the recommendations from the WHO Ending Childhood Obesity (ECHO) Commission, which reported in January 2016. Thus, one of the "headline" WHO ECHO recommendations was to integrate and strengthen guidance for the prevention of non-communicable diseases with current guidance on preconception and antenatal care, to reduce risk of childhood obesity by preventing low or high birth weight, prematurity and other complications in pregnancy (http://www.who.int/dietphysicalactivity/end-childhood-obesity/en/).

Further evidence of impact from the work in the Theme comes from the chapter in the UK Chief Medical Officer's annual report, published in December 2015. EarlyNutrition also had a large impact on the training, qualification and international interlinkage of young EU researchers, through our conferences, workshops and exchange programmes, who embraced the spirit of generous international and interdisciplinary collegiality and collaboration as their careers progress. This is a major ‘added-value’ of EarlyNutrition.
Over the years to come, our results will continue to stimulate further research and innovation related to the opportunities of early life prevention and will achieve sustainable implementation of our strategies and programmes. By this, the following impacts will be reached:

- New mechanistic insights and substantial scientific evidence will be taken up by researchers in this area and stimulate the creation of new research concepts and hypotheses.
- Policy makers internationally and nationally will consider our concepts and data related to preventive strategies for actual implementation, use our data for prioritization of measures to be undertaken and allocation of resources, and take up our scientific evidence to in respective legislation.
- Nutrition/health care professionals will be aware of the importance of adequate nutrition and lifestyle in the preconception, pregnancy, infancy and toddlerhood lifestages and actively implement the knowledge and ready-to-use tools in their clinical decision making and counselling of patients.
- Women before and during pregnancy, breastfeeding mothers and parents of infants and toddlers will be aware and informed of adequate nutrition and lifestyle choices, increasing the likelihood of changing their behaviours.

Impact on further research

The sexually dimorphic offspring metabolic and cardiovascular phenotype observed in both rats and mice born to obese mothers suggests divergent mechanistic pathways which warrant further investigation. Interventions in obese women to reduce the risk of childhood obesity should focus on interventions with greater effects on maternal adiposity and insulin resistance and should include a stronger focus on the preconception period. Further studies should investigate if and how the specific essential amino acid adjustments that allow for lowering of total protein levels will affect growth and body composition development in formula-fed infants. Although metabolomics research has increased, a lot remains unknown about the associations between early programming exposures, metabolite concentrations, and the development of obesity. Due to differences in the methodological and statistical approaches, single species identified by the different research studies differ and we recommend more research with standardized approaches. More research is needed in order to develop biomarkers as targets for personalized interventions.

The documented novel associations of maternal diet, lifestyle and metabolic responses with offspring adiposity and body composition and the results of respective analyses suggest that prepregnancy and pregnancy are critical periods for preventive strategies focused to tackle the epidemic of childhood obesity and reduce ethnic disparities in childhood adiposity. EarlyNutrition has generated important new evidence indicating that the pre- and postnatal periods, and interactions between the pre- and postnatal environments, all play roles in the developmental programming of adiposity and related co-morbidities. Taken together, the data suggest it is important to consider the potential role of intrauterine stress and stress biology in arriving at a better understanding of the developmental programming of susceptibility for obesity risk and metabolic diseases, and provide potential targets for intervention during pregnancy to ameliorate or prevent the stress-related intergenerational transmission of disease risk.

Although the tested interventions during pregnancy did not reduce markers of offspring obesity at birth, the UPBEAT study should a beneficial effect on infant body fat assessed by skinfold thickness measurements at the age of 6 months. The data show safety and some indication for improvement of maternal lifestyle and related health. In addition, mechanistic knowledge was generated. Together, these new insight will inform the design and implementation of future intervention strategies and programmes.
The potential effects of a reduction in childhood obesity through the use of a reduced protein intake in early childhood, as evaluated in EarlyNutrition, offers an easy obtainable intervention to combat obesity. High protein intakes might be an important reason for the rise in obesity prevalence and could be counteracted easily by lower protein intake through a lower protein concentration in infant formula. The data on the novel follow-on formula in which higher glycaemic carbohydrates (e.g. maltodextrin) were substituted with the low-glycaemic carbohydrate Isomaltulose enable further steps towards development and evaluation of modified infant and follow-on formula design.

Gender dimensions were foremost throughout the project, specifically in relation to involvement of women in the design of the research, taking into account the diverse experiences of men and women in the conduct of the research, gender specific analyses, consideration of gender dimensions in the communication of the findings and reflexivity in relation to the research as a whole. The new insights will lead to stronger consideration of gender effects in future related research.

To explore the causality of the associations characterised in parent-offspring studies, sibling comparison studies, Mendelian randomization-studies and randomized controlled trials are needed. Further mechanistic studies, especially in large human populations are needed to obtain insight in the underlying mechanisms. Finally, the potential for prevention of common diseases in future generations by reducing maternal obesity and excessive weight gain during pregnancy needs to be explored using randomised trial and other study designs.

Further research is required to make use of the newly identified targets for interventions in pregnancy to reduce childhood obesity. These include breast feeding duration in obese women, maternal triglycerides, fetal cholesterol and fetal lysophosphatidylcholines and the consideration of socio-economic status in the delivery of interventions in pregnant women.

Dissemination:
One of the strengths of our partnership is the broad network of close collaborative links with relevant actors in different key sectors, which has catalysed and escalated broad dissemination and translational application of outputs.

We hosted two International Power of Programming Conferences to share project results that were very well attended with more than 500 (2016: 600) participants from all across the world. The two stakeholder forums were also very successful and brought together experts from academia, industry and general public/patient organisations. The EarlyNutrition Project website, which was launched at the beginning of month 2 and subsequently re-launched with extended content in month 5, has been visited more than 38,000 times by almost 28,000 visitors.

In order to communicate relevant project results and project-related events to different target groups (public and scientists) 15 press releases have been issued and disseminated throughout the project. Overall the press releases have generated over 60 Clipings. All press releases are collected and hyperlinked on the project’s website (http://www.project-earlynutrition.eu/eneu/index.php?site=press_corner).

In order to inform interested groups regularly about project news, and e-newsletter series has been sent out regularly – 15 newsletters over the course of the project. The EarlyNutrition Newsletter has over 8000 recipients. Where suited, further channels were used to distribute specific newsletter, such as EUFIC, EFCNI (European Foundation for the Care of Newborn Infants) DOHaD (International Society for Developmental Origins of Health and Disease) and ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition). All newsletters were well received with an excellent click rate.
(over 80%) and a more than average opening rate (more than 60%). As part of the project, the scientific foundations for evidence-based recommendations for optimal early nutrition that incorporate long-term health outcomes were developed. The recommendations focus on four target groups: women before pregnancy; pregnant women; infants (incl. breastfeeding) and young children. Four recommendations have been identified (one for each target group) to develop postcards for further distribution containing the key recommendation. The EarlyNutrition Recommendations are available for high-resolution download in eight languages on the projects website (http://www.project-earlynutrition.eu/recommendations). Furthermore the Recommendations were shared via Twitter @EarlyNutrition. A manuscript has been submitted to a scientific journal for publication. For the videos for the general public, four recommendations have been identified (one for each target group). In the videos the respective recommendation is given by one EarlyNutrition expert in the field. The EarlyNutrition Recommendation Videos for the general public are placed on YouTube as well as on the project website (http://www.project-earlynutrition.eu/recommendations).

Our digital Early Nutrition eAcademy distributed key information with >10,000 health care professionals and nutritionists/dieticians in more than 160 countries, and to parents to be, families, and the general public. Facilitated by our close links, our evidence based results have been shared with and adopted learned societies and incorporated in their authoritative, scholarly advice on policy issues and practice. Our global network of key opinion leaders together with senior representation in policy making bodies has facilitated rapid translation into several policy documents, such as the global FIGO guidelines on Nutrition in Pregnancy and the World Health Organisation Report on Ending Childhood Obesity. We achieved transfer of knowledge to consumer and industry associations, to experts involved in the panels of EFSA and national food regulatory bodies, and delegations contributing to development of global food standards at Codex Alimentarius.

List of Websites:
www.project-earlynutrition.eu/

Related documents


Last update: 18 May 2018

Permalink: https://cordis.europa.eu/project/id/289346/reporting

European Union, 2023