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EARNEST

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

Instrument: Integrated Project

Thematic Priority 5.4.3.1: Food Quality and Safety

Final public report on activity 2.4.1 and 2.4.2:

Genetic studies of fetal growth

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Organisation Name of Lead Contractor for this report: Norwegian Institute of Public Health

Work-package 2.4: Genetic studies of fetal growth

Background

In the 1970s, Anders Forsdahl compared cardiovascular mortality in different areas of Norway with the infant mortality in the same areas decades before. He found that the areas, for instance Finnmark county, with increased infant mortality rates in the beginning of the last century, later had higher rates of cardiovascular mortality (1). In 1986, Barker and Osmond (2) reported data from 212 local authority areas in England and Wales, and could demonstrate a strong positive correlation between infant mortality in 1921-25 and ischemic heart disease mortality rates in 1968-78 across these areas, confirming Forsdahl's observations. These observations led to the theory of fetal programming. This theory suggests that external influences on the growth of fetal organ systems have detrimental biological consequences that predispose the child for cardiovascular disease as an adult. It is now established through cohort studies that there is a fairly strong and consistent relationship between low birth weight and increased risk of later cardiovascular disease (4,5). However, the interpretation of this relationship is under discussion. According to the theory of fetal programming, it is not birth weight in itself that causes later disease, but the observed low birth weight is a reflection of the fetal growth restriction that results from environmental factors, such as lack of nutrition. These environmental factors also increase the risk of perinatal death. Forsdahl suggested that it was the combination of poverty in early life and later affluence that had detrimental consequences (1).

It has, however, been pointed out that the observed association between low birth weight and later risk of cardiovascular disease, can be explained by other biological mechanisms. The genetic confounder hypothesis says that the environment really plays little or no role in establishing the association between birth weight and later disease. Hattersley and Tooke (6) suggested that the association between birth weight and later risk of type 2 diabetes had a genetic basis. Fetal insulin secretion is one of the key determinants of fetal growth, and this secretion is influenced by fetal genes, one of them being the gene that codes for the glycolytic enzyme glucokinase (7). To explain the association to cardiovascular disease, Hattersley and Tooke suggest that a number of fetal polygenes may be pleiotropic; i.e. they influence more than one trait. Examples can be genes that affect insulin resistance. These genes may influence both fetal growth as well as adult phenotypes. Certain alleles may cause restricted growth in utero, and later also cause insulin resistance and increased risk of hypertension, atherosclerosis and type 2 diabetes, especially in the presence of obesity, for the same individual.

For the genetic confounding hypothesis to be valid, one must present evidence that genes are causing substantial variability, both in birth weight and in the liability to cardiovascular disease. For birth weight, the effects of environmental factors appear to be surprisingly small, as summarized by Leon (8). He points out that there has hardly been any increase in mean birth weight over the past hundred years, that interventions to increase birth weight by nutritional supplementation have had little effect, and that the differences in birth weight between socioeconomic groups are relatively small, as is also found in Norway (9).

Objectives

On this background, our contribution to the EARNEST collaboration was decided to be the study of the genetic influences on fetal growth, using the possibilities inherent in the Norwegian Mother and Child Cohort Study (MoBa) (10). In addition, we have included

research question that include effects of nutritional intake and physical activity on pregnancy outcomes.

MoBa

MoBa is an ambitious family-structured cohort that aims to find causes of diseases and explain trajectories and variability of health-related traits over a life course span. In the period 1999-2009, pregnant women have been recruited to the study around the time of the ultrasound examination in week 16-18. The fathers of the children have also been invited to participate. Biological material has been collected from mothers, fathers and children and has been stored in a biobank. Data is assembled from questionnaires, analyses of biological material and linkages to health and exposure information. The cohort includes data from more than 108,000 children, 90,700 women and 71,500 men (www.fhi.no/morogbarn).

Work plan

Originally, EARNEST was planned at the same time we applied for funding to do serial ultrasound measures of a subsample of 10,000 women, in order to obtain a more detailed measure of intrauterine growth. However, our grant proposal to the National Institutes of Health in the U.S. for this extensive and very costly data-collection was not supported. We have therefore concentrated our efforts at extracting DNA from blood samples from the child at birth and from the two parents obtained from the whole MoBa cohort, in order to be able to study candidate genes for fetal growth. In addition, we received funding from The Norwegian Research Council to study candidate genes for preterm birth. These genes can also be studied in relation to fetal growth. We have published methods papers as well as papers that deal with nutritional factors, genes and physical exercise as exposures and with fetal growth, preterm birth and birth weight as outcomes. As more genotypes become available we will continue to publish on the genetics of fetal growth, after the EARNEST support period ha ended.

Some main results

We analyzed the association to spontaneous preterm birth (11) for 1430 SNPs in 143 candidate genes from 434 mother-child dyads and compared the results to those of an American cohort. A maternal allele in the prostaglandin E receptor 3 gene showed a protective effect in both cohorts, whereas a fetal allele in the paraoxonase 1 gene had a risk increasing effect (12). We will follow-up these findings as well as examine associations to fetal growth in a genome-wide association study of about 1000 case dyads and 1000 control dyads, where the genotyping has been performed in the spring of 2010, and cleaned data files are now becoming ready for analysis.

It has been suggested that a diet with abundant intake of vegetables and fruits and with olive oil as a main source of fat (Mediterranean diet) can reduce the risk of preterm birth. We tested that out in parallel papers from the Danish National Birth Cohort (DNBC) and MoBa. A certain protective effect was found in DNBC (13), but not in MoBa (14). Interestingly, we found that a diet with these ingredients appeared to have a protective effect against preeclampsia (15). These dietary studies were made possible through the validated data set based on the food frequency questionnaire administered in pregnancy weeks 20-22 (16-18).

In addition to the ordinary ingredients in foods, we have described the intake of food supplements, such as folate (19), and also measured folate concentration in maternal plasma from pregnancy week 17. Fetal growth was not associated with taking folate supplements or with the folate plasma level in pregnancy (20). On the other hand, a protective effect of taking vitamin D supplements was found for preeclampsia (21). It is also of interest that folate

supplements taken early in pregnancy may have a protective influence on language delay measured when the child is three years (22).

Hyperemesis gravidarum and preeclampsia are two potentially very serious diseases of pregnancy. We find a certain protective effect of a pre-pregnant healthy diet on the risk of hyperemesis (23), while both low and high body mass index (BMI) is associated with increased risk when compared to normal BMI (24). For preeclampsia, it is well established that obesity is a risk factor, but it has been uncertain whether the risk can be modified through regular physical exercise. Our analysis suggests that physical exercise has little effect on preeclampsia risk (25). Also, it has limited effect on the mean birth weight in a population (26), although it reduces the proportion of children with large birth weights (27).

In summary, the EARNEST collaboration has given us the possibility to study important research questions.

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