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COMMENTARY

Fetal nutritional origins of adult diseases: challenges for epidemiological research

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Introduction

The associations of low birth weight with cardiovascular disease, type 2 diabetes and their risk factors in adult life have been studied and reviewed extensively [1]. Some reports on the early origins of adult diseases have also recently been published in the *European Journal of Epidemiology* [2–5]. Inverse associations between birth weight and the risk of cardiovascular disease and type 2 diabetes have been shown in different age and ethnic populations [1]. Although consistent, the overall effect size of birth weight on cardiovascular risk factors seems to be small and partially explained by compensatory postnatal growth [6–8].

The developmental origins hypothesis proposes that an increased risk of adult disease is induced by fetal adaptive responses to adverse fetal exposures, such as maternal nutritional status [9, 10]. These adaptive responses include changes in haemodynamics, metabolism, hormone production, and tissue sensitivity and may affect development of various organs. The association between low birth weight and later disease risk should be interpreted as reflecting the long-term consequences of fetal adaptive responses. In this model, low birth weight itself is not the causal factor per se but merely a marker of fetal adaptive responses to suboptimal exposures. These adaptive responses are not necessarily evident at birth but may result in diseases in later life. To disentangle the mechanisms underlying the associations of low birth weight with cardiovascular disease and type 2 diabetes, various steps in the proposed pathway should be studied in more detail.

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Fetal nutrition

In industrialized countries, an adverse fetal environment may be due to maternal life style habits including suboptimal dietary intake, smoking and alcohol consumption. Several historical cohort studies have studied the associations between maternal dietary intake and cardiovascular disease in adulthood [1]. Exposure to famine in fetal life and early childhood is associated with an increased risk of cardiovascular disease and type 2 diabetes [11–15]. Critical periods for exposure to famine seem to be both early fetal life and early childhood. These findings are in line with recent results from a nutritional supplementation trial in an undernourished rural population in south-India [16]. This study showed beneficial effects of balanced protein-calorie supplementation to pregnant women and preschool children on measures of insulin resistance and arterial stiffness in adolescence. These follow up results from famine exposed and severely undernourished populations are important from an etiological perspective, but are of limited use for extrapolation to contemporary children in industrialized countries. Results in normal populations showed inconsistent associations of composition of macronutrient intake in pregnant women with development risk factors for cardiovascular disease and type 2 diabetes in their offspring [17–19].

Rather than energy and macronutrient intake, variation in dietary patterns and micronutrient intake seem to be of more relevance in industrialized countries [20]. Observational studies showed associations of lower maternal fish intake during pregnancy with an increased risk of preterm birth and delayed developmental milestones achievement in the offspring [21–25]. Thus far, no associations with development of risk factors for cardiovascular disease and type 2 diabetes have been published. The association of fish intake with developmental milestones might be explained by direct effects on brain development. Maternal and early postnatal micronutrients related to development of cardiovascular risk factors in childhood and adulthood seem to be calcium and sodium. Prospective cohort studies showed inverse associations of maternal calcium intake with blood pressure in childhood [26–29]. However, results seem not to be consistent. Sodium intake in early infancy is associated with increased blood pressure in childhood and adulthood [30–32]. Results from animal studies showing associations between maternal iron levels and blood pressure in the offspring could not be replicated in children [33, 34]. Recent studies showed that low folate acid levels and high homocysteine levels are associated with both low birth weight and increased blood pressure in children [35–37]. Folate levels seem also to be associated with endothelial dysfunction in children, which is an early risk factor for development of atherosclerosis in adulthood [38]. Thus far, no associations of maternal intake of calcium and levels of folate and homocysteine with risk factors for cardiovascular risk factors in adults have been reported. The mechanisms by which these micronutrients influence blood pressure and the future risk of cardiovascular disease are largely unknown, but may include changes in vascular tone.

Maternal smoking and alcohol consumption during pregnancy have also been studied in relation to fetal growth and cardiovascular outcomes. Maternal smoking adversely affects fetal growth, whereas moderate alcohol consumption does not strongly increase the risk of fetal growth retardation [39–42]. Associations of maternal smoking during pregnancy with increased blood pressure in the offspring have been reported, but residual confounding cannot be excluded [43–45]. The association between maternal smoking during pregnancy and blood pressure in childhood disappeared after adjustment for paternal smoking [46]. Similar effects have recently been demonstrated for the associations of maternal smoking during pregnancy with behavioral outcomes in children [47]. These studies suggest that taking into account similar exposures in fathers in studies focused on maternal life style related habits as potential determinant enables additional adjustment for potential residual confounding.

Epigenetic modifications

Fetal nutritional exposure may lead to fetal adaptive responses by epigenetic modifications, including DNA methylation [48]. Studies in sheep showed that lower levels of maternal folate and vitamin B12 supplementation are associated with alterations in methylation status of CpG islands in the offspring [49]. This may influence expression of several genes. Furthermore, the offspring sheep also developed an adverse cardiovascular and metabolic phenotype. More recently, persistent impaired methylation of the IGF2 gene was reported in adults who have been exposed to the Dutch Famine [50]. These results suggest that epigenetic modifications induced by adverse nutritional exposures in the periconceptional period may persist throughout postnatal life and could affect development of risk factors for cardiovascular and type 2 diabetes. However, whether such epigenetic modifications underlie the associations between adverse fetal nutritional exposures and diseases in adult life should be studied in further detail [51]. Because the largest variation of methylation can be expected periconceptionally, important information should come from preconceptional started cohorts [52].

Fetal adaptive responses

Most studies focused on common cardiovascular risk factors in children and adults as major outcomes. However, to identify mechanisms by which fetal exposures lead to fetal adaptive responses and subsequently to increased risk of cardiovascular disease and type 2 diabetes, new methods to assess fetal growth and development in detail are necessary. Since these measurements need to be non-invasive, ultrasound or even magnetic resonance imaging should be considered. With these methods detailed studies of fetal cardiac, vascular, brain and kidney development can be performed [53–58]. We have recently shown circulatory adaptations in response to fetal growth retardation in a population-based cohort [59]. These adaptive responses were present without overt and clinically relevant fetal growth retardation. Similar effects were found on kidney growth, which tend to persist into early postnatal life [60, 61]. Detailed measurements, which are currently available in obstetric and fetal research, offer great opportunities for detailed measurements in epidemiological research. For example, with new ultrasound methods both structure and function of early and late placentation and fetal circulatory responses from first trimester onwards can be assessed [53–58].

Conclusion

The inverse associations between birth weight and risks of cardiovascular disease and type 2 diabetes needs further study into the underlying mechanisms. Both large-scale and more in depth epidemiological studies are needed, of which several have been described in detail in this journal [62–69]. Major efforts should be made to analyze the effects of maternal macronutrient and micronutrient intake on epigenetic modifications of specific genes related to cardiovascular development and on detailed fetal adaptive responses in early and late pregnancy. This information might lead us beyond associations of markers into real underlying causal pathways and eventually to strategies to improve public health from the earliest phase of life.

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