Prenatal exposure to the Dutch famine and health in later life
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General Discussion

So it is when my life began.
So it is now I am a man.
So be it when I shall grow old, or let me die!
The Child is the Father of Man.
(Wadsworth 1802)
Prenatal exposure to undernutrition appears to have permanent effects on health. The effects of undernutrition, however, depend upon its timing during gestation and the organs and systems developing during that critical time window. Our findings suggest that risk factors for coronary heart disease, such as hypertension, hypercholesterolaemia and hypercoagulation, which often co-exist, have their origins in utero, but that they are programmed through different environmental influences. We found effects of undernutrition during gestation on adult health even in the absence of effects on body size at birth. This implies that adaptations that enable the fetus to grow can nevertheless have adverse long-term consequences. These findings broadly support the fetal origins hypothesis.

This chapter will focus on some methodological issues. We will furthermore elaborate on the implications of our findings for the fetal origins hypothesis and future research that should be performed. Finally, we will consider the implications of our findings for chronic disease epidemiology and public health.

**The Dutch famine: methodological issues**

We mimicked a scientific experiment by comparing the health of people born at different times in relation to the famine. An ideal experiment creates circumstances across which only one factor (in this case the famine) affecting the outcome of interest (in this case adult health) varies. However, the analogy with an experiment is violated to some extent because the famine affected fertility and early mortality. 5 Selective fertility did not seem to explain our findings as adjustments for maternal characteristics that might be proxies for fertility (age, parity, maternal weight and socio-economic status) hardly altered the results. Nor did we find indications that differences in early mortality had caused differences in adult health: there were no differences in adult health between people who were born before the famine and those who were conceived after the famine, whereas early mortality differed most strongly between these two groups.

In our study, the hypothesised factor affecting the outcome was prenatal undernutrition due to maternal exposure to famine during gestation. Although the famine was characterised by extreme shortage of food, the availability of food was not the only aspect that varied with the famine. The famine
coincided with a very cold winter during which infections were widespread. Also, the stress experienced by pregnant women during the famine due to lack of food, the war, and the absence of their spouses will have been more extreme than in those who were pregnant before or after the famine. We cannot rule out effects of exposure to stress as a possible cause of long-term effects on health. We do not, however, consider stress to be a major cause of the effects we found since we did not find differences in health between people who were born before the famine and those conceived after the famine, whereas one would expect differences in the levels of exposure to stress between these groups. Moreover, we observed effects on health predominantly in the offspring of women exposed to famine in early gestation. One would expect at least the same or even higher levels of stress in pregnant women exposed to famine in late or mid gestation, yet, we did not find that offspring of these women had a poorer health. Furthermore, we found that the balance of nutrients in the maternal diet during late gestation was linked to blood pressure both in people who had been exposed to famine and those who had not been exposed prenatally, which suggests that maternal nutrition rather than stress is important in programming blood pressure. Finally, animal experiments have shown that not only caloric restriction during gestation, but also protein restriction during which caloric intake was unrestricted affected the health of the offspring. This suggests that nutrition rather than stress is the major cause of effects on health. Whatever the true cause of the adaptations made by the fetus that resulted in disease in later life, our findings indicate that an adverse environment in utero can have permanent effects on health.

In terms of the hypothesis of critical periods, the stage of growth and development of the fetus during which it was undernourished was an important factor in our study. Organs are most vulnerable at periods of rapid growth and development. Disturbance of development at a critical period during gestation is likely to be irreversible. Our definition of exposure to famine in late, mid or early gestation was based on the simple division of pregnancy into three equally sized periods. It is unlikely that this coincides exactly with biological critical periods corresponding to periods of rapid growth and development. This may have led to an underestimation of effects of undernutrition during a critical period of gestation.
The fetal origins hypothesis

Criticism

Notwithstanding the large number of publications supporting the fetal origins hypothesis, critics suggest that the associations found are biased and should not be interpreted as causal. Selection bias, confounding by socio-economic status and inconsistencies within and across studies are among the most frequently raised points of critique questioning the validity of findings on the fetal origins of adult disease. We will discuss these issues below.

Selection bias

Programming studies are unique in that potential causes are temporally separated from effects by a span of some 5 decades or more. Losses to follow-up are an inevitable feature of these studies and raise the possibility of selection bias.

We studied the adult health of less than half of the original cohort. However, size of the baby and the mother at birth according to prenatal exposure to famine in the group of participants were not different from the rest of the cohort suggesting that those who participated are a representative sample of the entire cohort.

We only invited people to the clinic who were born in the Wilhelmina Gasthuis and still lived in or close to Amsterdam (within an 80 km radius), therefore those who came to the clinic are not a random sample. However, our analyses are based on comparisons within this sample. Unless the relations of prenatal exposure to famine and adult health are different among people born in or outside the hospital and between people who live close to or far from Amsterdam, no bias has been introduced.

Because of the quality of the registrations systems and the presence of a personal identity number in Scandinavian countries, complete follow up in these countries is feasible, thereby overcoming the problem of selection bias. By far the most persuasive evidence of a real association between size at birth and coronary heart disease has been provided by a study performed in Sweden. This study among 15000 men and women clearly showed that cardiovascular mortality decreased with increasing birth weight.
Confounding by socio-economic status

It has been suggested that small size at birth is simply a marker of poor socio-economic circumstances around the time of birth. Continuities in socio-economic disadvantage from birth to adulthood could be an alternative explanation for the link between small size at birth and an increased risk of disease in later life.

Most patients in the Wilhelmina Gasthuis came from lower to middle social classes, but little is known about the actual referral pattern during the period of our study. Adjustment for socio-economic status at birth and adulthood, however, did not alter our results. One could question whether occupation during wartime is an appropriate indicator of socio-economic status. Although we consider it unlikely that confounding by socio-economic status has greatly affected our results, we cannot exclude residual confounding by socio-economic status.

Others have studied whether the association between birth weight and later disease can be explained by confounding by socio-economic status. In these studies detailed information on socio-economic circumstances was available, including employment status, occupation, education, gross and disposable income, crowding, and access to car, at several points in adult life. They found that the associations between size at birth and health in later life were only slightly attenuated among men after adjustment for socio-economic status but not among women. They therefore concluded that socio-economic circumstances and behaviour can not fully explain the link between size at birth and health in later life.

Inconsistencies within and across studies

The hypothesis that a baby's nourishment influences the diseases it will experience later in life has been tested by assessing the link between a range of possible markers of a baby's nourishment and a variety of diseases in later life. The apparently opportunistic use of a range of different obstetric and perinatal measures as explanatory variables has often been put forward as a weakness of the work on the fetal origins hypothesis. Some have even referred to the work on the fetal origins hypothesis as an 'inductionist delight' as the hypothesis would be too broad to be testable and inconsistent results would lead to creative changes in the hypothesis. It is, however, a natural consequence of progression of scientific knowledge that an initial broad
hypothesis evolves and is refined to a more complex framework. Obviously, a critical evaluation of results and proper testing of specific hypotheses is obligatory for progression of scientific research. But simplistic representations of the underlying mechanisms are an unlikely explanation for the complex phenomena we are studying. Because of the complex and non-linear nature of fetal growth and development, the reductionist strategy fails. Therefore, it is crucial that the epidemiological findings are critically evaluated in the light of clinical and experimental findings in the multi-disciplinary approach that has already been taken in this field.

Implications of our findings for the fetal origins hypothesis

The fetal origins hypothesis is now a scientifically accepted concept and the initial points of critique have largely been superseded. Most of the original sceptics have been convinced by the wealth of supportive scientific information. Some of the recent support has arisen from work which originally set out to disprove the hypothesis. Many now appreciate the importance of early life factors in the aetiology of chronic disease, and some of them do so within the framework of the so-called life course approach. This places the fetal origins in a broader perspective: events during critical periods across the entire life course might affect health in later life.

The results of epidemiological research have often led to speculations on the potential mechanisms that may account for the link between proxy measures of fetal development and later disease. Although these ideas have often been post hoc, they have drawn on previous animal research and indicated its possible relevance for the development of chronic disease in humans, and, in doing so, they have built a valuable bridge between scientific disciplines. The remainder of this chapter will focus on the comparison of our findings with results from animal experiments in an attempt to understand the underlying mechanisms.

The fetal origins hypothesis proposes that chronic diseases originate *in utero* through adaptations made by the fetus in response to undernutrition during a critical period during development. Because we studied effects of undernutrition during different periods of gestation, the findings of our study provide some further insight into the critical periods of development of
different organs and systems, furthermore they illuminate the consequences of fetal adaptations to maternal starvation during different periods of gestation.

**Critical periods**

Although the growth of the fetus is influenced by its genes, it is often limited by the nutrients and oxygen it receives. Fetal undernutrition results from an imbalance between fetal demand for nutrients and the maternal-placental capacity to supply sufficient nutrients to meet that demand. Consistent with this concept, animal studies have shown that the effects of restricted supply of nutrients to the fetus depend upon the nutrient demand of the fetus. Undernutrition of the ewe in late pregnancy adversely affected the development of rapidly growing fetuses while having little effect on those growing more slowly. This shows that a fast growth trajectory makes the fetus more vulnerable to reduced supply of nutrients in late gestation. Male fetuses grow faster than female fetuses in utero. We have not been able, however, to demonstrate any difference in effects of undernutrition during gestation between men and women.

The notion that rapidly growing organs and tissues are more vulnerable to an adverse environment in utero is supported by some of our findings. For example, the bronchial tree grows most rapidly in mid gestation, and our findings might indicate that undernutrition during this period increases bronchial reactivity. The liver is formed from the 3rd week of gestation and by week 12 of gestation hepatocytes start functioning, we found that several aspects of liver function appeared to be permanently altered in those whose mothers were undernourished during this period.

Because the fetus' requirements for nutrients are small in early gestation it is often assumed that undernutrition during that period will not influence growth and development. This, however, seems not to be the case. Experiments in rats have shown that a low protein diet during the first 4 days after conception (i.e. even before implantation) permanently changed the fetal growth trajectory by altering the allocation of cells between the inner cell mass that develops into the fetus and the trophectoderm that becomes the placenta. Furthermore, these fetuses appeared to have higher blood pressures after birth. This suggests that maternal undernutrition influences the embryo in such a way that, irrespective of the supply of a normal diet for the remainder of pregnancy, the embryo may be comprised in its
cardiovascular physiology. Our finding that those exposed in early gestation had a more atherogenic lipid profile, reduced plasma concentrations of factor VII, somewhat higher fibrinogen concentrations, a poorer perception of their health and an increased prevalence of coronary heart disease suggests that even undernutrition during periods of gestation in which demand is small can have permanent effects on health.

_Fetal adaptations to an adverse environment_

In our study, the effects of prenatal exposure to famine could not be explained by its effects on the size of the baby at birth. Babies born during the famine period – and therefore exposed to famine in late gestation – were on average only about 250 grams lighter at birth than babies who had not been exposed to famine _in utero_. This famine-related reduction in birth weight is relatively small compared to the routinely observed variations in birth weight. Therefore, the Dutch famine should be considered as a short but severe nutritional challenge superimposed on other determinants of the supply of nutrients to the fetus. This might also explain why – despite an association between small size at birth and raised blood pressure in later life – we could not demonstrate a significant effect of prenatal exposure to famine on blood pressure in later life.

In common with other living creatures the human fetus is plastic, it is able to adapt to external stimuli. The fetus adapts to variations in the availability of nutrients and oxygen. These adaptations – though unfavourable in the long-term – primarily aim to optimise the fetus’ survival, and may include morphologic, structural and endocrine changes. 14

- _Morphologic changes_

  Many aspects of liver function, including cholesterol synthesis and fibrinogen production, are differentially expressed in the periportal and perivenous zones. Animal studies have shown that undernutrition during gestation induces changes in the liver which might be related to altered zonation. Undernutrition during gestation reduced glucokinase and increased phosphoenolpyruvate carboxykinase activity. These were not restored in adult rats 24 and were responsible for changes in the regulation of hepatic glucose output. 25 Altered zonation is likely to be linked to other important changes in hepatic function. Our finding that those exposed in early gestation had increased cholesterol and fibrinogen concentrations and
reduced factor VII concentrations is compatible with permanent effects of undernutrition during early gestation on the morphology and function of the liver.

- **Structural changes**

  Animal experiments have shown that undernutrition during gestation reduced the size and weight of the kidney as well as the number of mature glomeruli. The number of renal glomeruli is also reported to be reduced in infants who are malnourished in early life as well as in adults with hypertension. Structural alterations in the developing kidney may thus play a critical role in the programming of blood pressure. The full adult number of nephrons is determined early in life and any insults interfering with nephrogenesis may reduce the filtration capacity of the mature organ. For a kidney with a reduced nephron number to maintain normal excretory function, pressures within the individual glomeruli must be higher. This, on the one hand, promotes higher systemic blood pressures and, on the other, leads to glomerulosclerosis and hence a vicious circle of nephron loss and further rises in blood pressure.

  Other structural changes such as alterations in the blood vessel have also been suggested to underlie the intrauterine programming of blood pressure. The elastic recoil of the aorta is important in maintaining blood flow in the peripheral blood vessels and in the coronary arteries during diastole. Reduced compliance in the aorta is a marker of cardiovascular disease. It is associated with hypertension, and also with left ventricular hypertrophy. People who were small at birth have been shown to have less compliant arteries. It was suggested that impaired synthesis of elastin may be one of the mechanisms underlying the link between small size at birth and raised blood pressure in later life. The compliance of large arteries largely depends on its elastin content, which is laid down in utero and during infancy. Reduced elastin deposition leads to less compliant arteries, which will lead to an increase in blood pressure. Both a reduced nephron number and reduced elastin deposition might underlie our finding that those who were small at birth, and those whose mothers ate relatively little protein in relation to carbohydrate during late gestation had higher blood pressures in later life.
Endocrine changes

Glucocorticoids are thought to play an important role in the programming of adult disease. Under normal conditions glucocorticoids in the maternal circulation are prevented from gaining access to the fetus by the placental enzyme 11β-hydroxysteroid-dehydrogenase which catalyses the rapid metabolism of cortisol and corticosteroids to inactive products. Animal studies have shown that undernutrition during gestation down regulates the expression of placental 11β-hydroxysteroid-dehydrogenase. The ensuing overexposure of the fetus to glucocorticoids may have lasting effects on the hypothalamic-pituitary adrenal axis. These changes in the hypothalamic-pituitary adrenal axis could in turn reset homeostatic mechanisms including blood pressure regulation and glucose metabolism. For example, lambs born after periconceptual undernutrition have higher blood pressures and exaggerated blood pressure responses to a challenge of the hypothalamic-pituitary-adrenal axis. Their ACTH and cortisol responses are also greater. Not only undernutrition of the ewe but also placental restriction by carunclectomy appeared to have permanent effects. The carunclectomised sheep fetuses had higher plasma levels of adrenaline and noradrenaline, suggesting greater sympathetic activity. Their higher levels of cortisol without increased ACTH and suppressed pituitary pro-opiomelanocortin expression suggest that feedback of the hypothalamic-pituitary-adrenal axis may have been altered. Evidence for the programming of the hypothalamic-pituitary adrenal axis in man comes from a study among men born in Hertfordshire that showed that those who were light at birth have raised cortisol levels, and that these raised cortisol levels were linked with raised 2 hour plasma glucose concentrations and insulin resistance. The increased blood pressure and reduced glucose tolerance of those who were small at birth might be related to permanent alterations of the hypothalamic-pituitary adrenal axis.

Future research

The Dutch famine provides a unique opportunity to test the fetal origins hypothesis. It has shown for the first time in humans that undernutrition during gestation has permanent effects on several aspects of health in later life.
It has also shown that adaptations that enable the fetus to grow can nevertheless have adverse long-term consequences. We now need to know more about these adaptations and the mechanisms by which events in early life permanently alter physiology. For instance, we need to know how genetic influences and the intrauterine environment sustain the fetal growth trajectory while adapting to the environment. Modern obstetric imaging techniques may be an important new tool to observe and quantify human fetal responses to undernutrition, stress and other adverse influences in utero.

We also need to understand the influence of the environment on development in the embryonic phase. Because of the likely importance of events around the time of conception in determining both demand and supply, and because the mother's diet, activity, body composition and endocrine profile change in early pregnancy, studies of women of reproductive age who are studied before as well as throughout pregnancy will provide important new information.

Furthermore, the effect of maternal diet and body composition both before and during pregnancy on adult health should be studied. These studies may indicate that the balance of both macro- and micro-nutrients in the maternal diet may be as important as the absolute amount of nutrients.

**Future research in Dutch famine birth cohort**

The research that should be performed in the Dutch famine birth cohort can be divided into two broad domains; first we should investigate the progression of coronary heart disease and its risk factors, and, second, we should investigate the likely mechanisms underlying the programming of disease by undernutrition during gestation. Furthermore, studies of the genetic make-up of our cohort could shed light on the genetic basis for the mechanisms underlying the programming of disease.

In addition, another cohort in the AMC is likely to provide important new insights into the fetal origins of adult disease, this cohort of twins has been studied in great detail at birth and can be traced into adulthood, which offers a unique opportunity to disentangle effects of genes and prenatal nutrition.
**Progression of disease in the Dutch famine birth cohort**

We have found indications that undernutrition during gestation has permanent effects on several cardiovascular risk factors, and it also seems to affect the prevalence of coronary heart disease. These findings, however, are based on small numbers. Follow-up of this unique cohort will allow us to study whether the tendency of people who had been exposed to famine in early gestation to have an increased prevalence of coronary heart disease persists, and it will also enable us to assess effects on mortality. Furthermore, it will provide insight into the rate of functional decline.

**Mechanisms underlying the associations between exposure to famine and disease**

The mechanisms underlying the changes in physiology and metabolism found in this study are likely to include morphologic, structural and endocrine changes, as described above. Although epidemiological studies cannot illuminate the adaptations made by the fetus in response to undernutrition that led to disease in later life, they may provide more insight into the biological antecedents of adult disease. Studies of the hypothalamic-pituitary-adrenal axis may prove to be crucial in unravelling the endocrine adaptations underlying the fetal origins of coronary heart disease.

**Genetic studies**

Little is known about the genes that underlie the fetal adaptations to undernutrition. Genes that allow the fetus to adapt to undernutrition are likely to be favoured by natural selection even though they may increase the risk of disease in later life.

There is some evidence for a potential role of genes mediating the association between small size at birth and later disease. It has been shown that genetically determined abnormalities in pancreatic glucose sensing, insulin secretion, or insulin resistance, all have a substantial effect on fetal growth. Babies whose mothers had a mutation in the glucokinase gene were on average 600 g heavier at birth due to the increased fetal insulin secretion in response to maternal hyperglycaemia. Babies, however, with the same mutation were on average 500 g lighter at birth. When both mother and fetus had the glucokinase mutation, the two opposing effects cancelled out and the baby was of normal weight. 35 Analyses of the genetic make-up of people born
before, during, or after the famine, will allow us to explore aspects of the gene-
early environment interaction.

_Twin studies_

Studies in another cohort in the AMC could shed further light on the fetal origins of adult disease. A cohort of twins born between 1931 and 1975 in the Wilhelmina Gasthuis (the predecessor of the AMC) has been studied in great detail at birth and the records have been kept. The study of twins offers a unique opportunity to disentangle effects of genes and prenatal nutrition.

About two thirds of the monozygous twins have one chorion and one placenta. The remaining monozygous twins and all dizygous twins are dichorionic and have two placentas. There are thus three types of twins: monochorionic monozygous, dichorionic monozygous, and dichorionic dizygous twins. Both monochorionic and dichorionic monozygous twins are genetically identical, whereas dichorionic dizygous twins share only half their genes. Because monochorionic twins share a chorion and placenta they have a more similar intrauterine environment than dichorionic twins. A comparison between monochorionic and dichorionic monozygous twins will demonstrate the influence of the intrauterine environment on the prevalence of coronary heart disease and its risk factors, whereas a comparison between dichorionic monozygous and dizygous twins will demonstrate genetic influences. As yet, there have been no studies that have information about chorionicity among twins old enough to make the study of coronary heart disease relevant. Tracing men and women from this cohort of twins seems an obvious starting point for future research into the fetal origins of adult disease that would provide an opportunity to disentangle effects of genes and intrauterine nutrition on coronary heart disease.

_Imlications for chronic disease epidemiology_

The aetiologic research of adult chronic disease has hitherto been guided by a destructive model. The causes to be identified act in adult life and accelerate the ageing process. The model used in the fetal origins hypothesis is a developmental model. The causes to be identified act on the developing fetus. In adapting to its environment the fetus ensures its continued survival and
growth at the expense of longevity. Premature death from coronary heart disease may in this view be considered as the price paid for adaptations made by the fetus to an adverse environment *in utero*.

Interest in fetal programming in the development of chronic disease partly arose from dissatisfaction with the conventional adult lifestyle or destructive model. This model forms part of what has been called black box epidemiology, or conventional risk factor epidemiology, the main purpose of which is to relate individual exposure and outcome on the basis of statistical models with little or no attention to the underlying biological mechanisms. The strength of research into the fetal origins of adult disease is that basic, clinical and epidemiological research is integrated. This will lead to greater understanding of, and a wider interest in, the ways in which experiences in early life affect the development of many of the adult chronic diseases that are already prevalent in developed countries and becoming increasingly prevalent in the developing world.

**Implications for public health**

Research investigating the fetal origins of adult disease gives new insight into the aetiology of chronic diseases and may be an important new point of departure in the prevention of many chronic diseases. In order to prevent chronic diseases in future generations maternal nutrition and health should be optimized. Although there is widespread recognition of the importance of adequate maternal nutrition during pregnancy, there is considerable uncertainty about optimal nutrition and weight gain during pregnancy. Numerous studies have examined the effect of the diet during pregnancy on the birth weight of the baby, but the results have been various and contradictory. Libera l weight gain guidelines for pregnant women apparently aim to prevent adverse outcomes by fetal undernutrition, yet, the relations between maternal nutritional intake, maternal weight gain, size at birth and later health are complex, and causal inferences are difficult.

Our findings suggest that maternal nutrition during gestation is linked with several aspects of health in adult life independent of the size of the baby at birth. This implies that adaptations that enable the fetus to continue to grow may nevertheless have adverse long-term consequences. The conclusion for public health policy is that the contribution of fetal undernutrition to chronic
disease will be underestimated by calculations solely based on the associations between size at birth and adult disease.

Little is known about what an adequate diet for pregnant women might be. In general, women are especially receptive to advice about diet and lifestyle before and during pregnancy. This should be exploited to improve the health of future generations.
References


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