Prenatal exposure to the Dutch famine and health in later life
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Introduction

*Man brings all that he has or can have into the world with him.*

*Man is born like a garden, ready planted and sown.*

*(William Blake 1757–1827)*
Early origins of adult disease: a historical perspective

It has long been recognised by poets and prophets that events before birth are of lifelong importance. One of the first records of this thought is found four centuries BC, in Plato's philosophy suffering in life is the result of the evil experienced before birth. In the Bible, this was also the premise upon which the disciples based their question about the blind man: 'Master, who did sin, this man or his parents, that he was born blind?'. Still, old wives' tales from Asia claim that how the pregnant woman behaves or what she eats could affect the child's qualities. The concept that events during early life may have lifelong consequences for health in adult life is also established in medical research.

At the beginning of the twentieth century, the idea that early life conditions and experiences affect adult health was an important component of the prevailing public health model. In 1914, the British Chief Medical Officer to the Board of Education wrote that 'the health of the adult is dependent upon the health of the child ... (and) ... the health of the child is dependent upon the health of its mother'. This idea went hand in hand with the expanding knowledge on nutrition in the 1930s with its emphasis on the importance of nutrition in childhood. It appeared to be self-evident that poor nutrition in childhood would lead to poor health in later life. The importance of early life experiences for public health was complementary to the ideas that emerged in psychoanalysis, behavioural psychology and the biological sciences at that time. The concept of a critical period in biological development, a time when some specific experience affects the development of an organism more than it would at other times, became a central theme in studies concerning behaviour and growth. A well-known example of programming during critical periods of development is the observation made by Lorenz showing that ducklings can be imprinted upon the first moving object they see after hatching. In the early seventies, Stein and Susser aimed to test the hypothesis, newly fashionable in the mid 1960s, that nutritional deprivation during fetal development depressed mental ability in their study of military conscripts born around the time of the Dutch famine. In 1977, Anders Forsdahl found a geographical link between past infant mortality and subsequent adult mortality from heart disease, and he therefore postulated that poverty in early life followed by later affluence might result in an increased risk of heart disease. This public health interest in early life determinants of
susceptibility to adult disease then diminished, however, as attention was drawn to the poor health of adults which occurred despite improvements in child health.

In the last decades, chronic degenerative disease has been the main public health problem in Western countries. Cardiovascular disease, cancer and respiratory disease have become the most common causes of death in the developed world, accounting for three-quarters of all deaths at adult age.\textsuperscript{13} Much of the research into the aetiology of these diseases has focussed on adult risk factors, such as diet, physical exercise and smoking. However, these risk factors are limited in predicting individual risk and only partially explain the striking social and geographical inequalities in health. Since the 1980s, there has been a revived interest in the early origins of adult disease. A growing body of evidence suggests that poor living conditions in early life, and more specifically poor growth, and undernutrition, increase the risk of adult cardiovascular and respiratory disease. People who were small at birth have been shown to have an increased risk of coronary heart disease and people who experienced early respiratory infection were found to have an increased risk of chronic bronchitis and abnormal lung function in adult life.\textsuperscript{14} Professor David Barker has given the early origins hypothesis a new impulse. He hypothesised that many chronic diseases originate in the womb. Because of poor nutrition and health among women, both before and during pregnancy, many human fetuses have to adapt to a limited supply of nutrients. In doing so, they permanently change their physiology and metabolism. These adaptations may be the origins of a number of diseases in later life, including coronary heart disease and the related disorders stroke, diabetes, and hypertension.\textsuperscript{14} From a developmental point of view, it is not surprising that circumstances during intra-uterine life permanently affect the body’s structure and metabolism. Between conception and birth the fertilised ovum goes through some forty-two cycles of cell division to develop into a term infant; after birth only another five are needed to attain adult size.\textsuperscript{15}

Evidence for the fetal origins hypothesis comes from observational studies in humans, which use size and body proportions at birth as a proxy for fetal nutrition. These studies have shown that people who were small at birth have an increased risk of coronary heart disease and its biological risk factors, hypertension, diabetes and hypercholesterolaemia in adult life.\textsuperscript{14} These associations have extensively been replicated in studies in several European
countries, but also in the US and in India.\textsuperscript{16-20} They extend across the normal range of size at birth and depend on small size for gestational age rather than on prematurity.\textsuperscript{21} Furthermore, a study in Finland has shown that men who were thin at birth had high death rates from coronary heart disease, and if, in addition, their mothers were short and fat they had even higher death rates.\textsuperscript{22} Another study in Finland showed that the path of growth in childhood modifies the risk of coronary heart disease associated with size at birth. Death rates from coronary heart disease were highest among men who were thin at birth but had accelerated weight gain in childhood.\textsuperscript{23} The effect size, a more than five fold increase in mortality among men with the lowest ponderal index at birth and the highest BMI at age 11 compared to men with the highest ponderal index at birth and the lowest BMI in childhood, is among the largest found in cardiovascular epidemiology. These findings may be a new explanation for the epidemics of coronary heart disease that accompany Westernisation. Chronically malnourished women are short and light and their babies tend to be thin. The immediate effect of improved nutrition is that not only women but also children become fat, whereas fetal nutrition remains limited by intergenerational constraints on placental growth. These changes are associated with an increased risk of coronary heart disease. With continued improvements in nutrition, women become taller and heavier; their babies are adequately nourished, and maternal fatness no longer increases the risk of coronary heart disease.

The Dutch famine – though a historical disaster – provides a unique opportunity to study effects of undernutrition during gestation in humans. The famine was remarkable in three respects. First, famine has seldom, if ever, struck where extensive, reliable and valid data allow the long-term effects to be studied. Second, the famine was sharply circumscribed in both time and place. And, third, the type and degree of nutritional deprivation during the famine were known with a precision unequalled in any large human population before and since. All these characteristics bring about that the Dutch famine can be considered as a unique ‘experiment of history’ to test the fetal origins hypothesis.
The Dutch famine 1944 – 1945

After weeks of heavy fighting following the invasion on the 6th of June 1944, the Allied forces finally broke through German lines. With lightning speed the Allied troops took possession of much of France, Luxembourg and Belgium. By the 4th of September 1944 the Allies had the strategic city of Antwerp in their hands, and on the 14th they entered the Netherlands. Everyone in the Netherlands expected that the German occupation would soon be over. The advance went so quickly that also the commanders of the Allied forces thought it would be only a matter of days before the Germans would surrender. But the advance of the Allies to the north of the Netherlands came to a halt when attempts to get control of the bridge across the river Rhine at Arnhem (operation ‘Market Garden’) failed.

In order to support the Allied offensive, the Dutch government in exile had called for a strike of the Dutch railways. As a reprisal, the Germans banned all food transports. This embargo on food transports was lifted in early November 1944, when food transport across water was permitted again. By then, it had become impossible to bring in food from the rural east to the urban west of the Netherlands because most canals and waterways were frozen due to the extremely severe winter of 1944 – 1945, which had started unusually early. Consequently, food stocks in the urban west of the Netherlands ran out rapidly.

As a result, the official daily rations for the general adult population – which had decreased gradually from about 1800 calories in December 1943, to 1400 calories in October 1944 – fell abruptly to below 1000 calories in late November 1944. At the height of the famine from December 1944 to April 1945, the official daily rations varied between 400 and 800 calories. Children younger than 1 year were relatively protected, because their official daily rations never fell below 1000 calories, and the specific nutrient components were always above the standards used by the Oxford Nutritional Survey. 24 Pregnant and lactating women were entitled to an extra amount of food, but at the peak of the famine these extra supplies could not be provided anymore. In addition to the official rations, food came from church organisations, central kitchens, the black market and foraging trips to the countryside. 25 After the liberation of the Netherlands in early May 1945, the food situation improved swiftly. In June 1945, the rations had risen to more than 2000 calories. 24
There was a serious shortage of fuel during the war which caused a gradual decrease and finally a complete shutting down of the production of gas and electricity, and in several places even the water supply had to be cut off, while the authorities were unable to provide fuel for stoves and furnaces in homes. Throughout the winter of 1944 – 1945 the population had to live without light, without gas, without heat, laundries ceased operating, soap for personal use was unobtainable, and adequate clothing and shoes were lacking in most families. In hospitals, there was serious overcrowding as well as lack of medicines. Above all, hunger dominated all misery.

The famine had a profound effect on the general health of the population. In Amsterdam, the mortality rate in 1945 had more than doubled compared to 1939, and it is very likely that most of this increase in mortality was attributable to malnutrition. 26 But, even during this disastrous famine women conceived and gave birth to babies, and it is in these babies that the effects of maternal malnutrition during different periods of gestation on health in adult life can be studied. Because of its unique experimental characteristics, it is not surprising that people born around the time of the Dutch famine have been studied by many investigators.

Famine studies

Dutch famine

The period of starvation ceased early in May 1945 immediately after the final surrender of the Germans. In addition to the immediate provision of food after the war, medical aid was a top priority for the Netherlands. Doctors from the UK and US were sent to survey medical needs. Clement Smith from Harvard Medical School was among the first to witness the effects of the famine on the health of the Dutch population. He immediately saw the opportunity to obtain information that would help resolve important questions on how poor maternal nutrition affects pregnancy and the development of the fetus before birth. Using obstetric records from Rotterdam and The Hague, he studied effects of prenatal exposure to famine on pregnancy and the fetus. 27 He found that babies born during the famine (and thus exposed to famine in late gestation) were about 200 g lighter at birth.
Later studies focussed on mental performance, following the increasing awareness in the late 1960s that early nutritional deprivation might cause irreversible damage to the brain. 28 This study among military conscripts did not demonstrate any effect of starvation during pregnancy on the adult mental performance. However, men exposed to famine in early gestation were more likely to be obese, whereas those exposed in late gestation were less likely to be obese. 29 More recently, it has been shown that people conceived during the famine and thus exposed in early gestation had a two-fold increase in risk of schizophrenia 30 and anti-social personality disorder. 31 In men, the risk of congenital neural defects was also increased 28 which suggests that permanent changes in the central nervous system might be involved. Lume 32 studied intergenerational effects of exposure to the Dutch famine and found that women who had spent the first six months of their own fetal life during the famine had slightly smaller babies than women who had not been exposed to famine in utero. Later results, however, were inconsistent with these findings and showed that first born babies of women who – as a fetus – had been exposed to the famine in early gestation were somewhat heavier at birth. 33

Other periods of famine

A parallel can be drawn between the situation of the Dutch famine and the siege of Leningrad. Leningrad was blockaded for 900 days from 1941 to 1944. Almost a million of its 2.4 million population died. At the height of the siege, nutritional intake was as low as 300 calories per day. Birth weights of children born during that period fell by more than 500 g. However, the lack of consistently kept records and archives, limits possibilities to study the long-term effects of prenatal exposure to the Leningrad siege. Nevertheless attempts have been made to assess these effects. Stanner 34 compared the health of people who had been exposed to the siege in utero and in infancy with that of those exposed only in infancy and also with that of people born outside the famine area. This study did not demonstrate any effects of prenatal exposure to the siege on major risk factors for cardiovascular disease, although people exposed to the siege in utero were found to have raised plasma concentrations of von Willebrand factor, which might indicate endothelial dysfunction. However, the essentially different circumstances before, during and after the famine period in Leningrad and in the western part of the
Netherlands hamper a direct comparison between those results and ours. The famine period in Leningrad lasted much longer than the Dutch famine did (more than two years versus 5 – 6 months), furthermore, it was preceded and followed by periods of relative shortage of food. And, finally, after the famine period, the standard of living in Russia remained rather poor, whereas it rapidly improved in the Netherlands. 35

Other studies on the effects of prenatal exposure to wartime starvation include a study performed in Wupperthal 36 and a study performed in Berlin. 37 The famine in Wupperthal during 1945 – 1946 was not as extreme as the Dutch famine and its effect on the size of babies at birth was smaller (a reduction in birth weight of 100 g versus 200 g in the Dutch famine). Effects of prenatal exposure to the Wupperthal famine on adult health have not been studied. The study performed in Berlin showed that among men who had been born during periods of food shortage (1941 – 1946) the prevalence of diabetes was lower than among men born during times of plenty (born between 1930 – 1939 or 1950 – 1953).

A study performed in the Gambia 38 has shown that people born during the annual ‘hungry’ season had a higher mortality than those born during the rest of the year. In the Gambia, the rain season coincides with an annual hungry period when foods from the previous harvest are seriously depleted, and undernutrition is aggravated by an intensive agricultural workload. This is reflected in the reduced birth weights of babies born during the wet hungry season. Up to the age of 17 there were no differences in mortality between those born in the wet season and those born during the rest of the year. After age 17, however, people who were born during the wet season were up to 10 times more likely to die prematurely in adulthood than those who were born during the dry season. This suggests that undernutrition during gestation may have permanent effects on adult health.

Objective

Up to now, no studies have been able to assess the effect of undernutrition during different periods of gestation on health in later life. During gestation, organs develop in a predetermined order, with different organs undergoing periods of rapid cell division, and therefore being in sensitive periods, at different times.
It is likely, therefore, that undernutrition at different times during gestation will have different effects. Because the Dutch famine lasted for only 5 – 6 months we were able to study effects of exposure to the famine during different periods of gestation. The objective of the study described in this thesis was to assess the effects of exposure to famine during different periods of gestation on adult health and disease in general, and coronary heart disease and its risk factors in particular. We traced a group of people born between November 1943, and February 1947, in the Wilhelmina Gasthuis in Amsterdam, for whom we had detailed birth records. We compared people who had been exposed to famine in late, mid or early gestation with people who had not been exposed to famine during gestation (people who were born before the famine or people who were conceived after the famine). The effects of prenatal exposure to famine on adult glucose tolerance and obesity have been described elsewhere. \(^{39,40}\) It was shown that people who had been exposed to famine during late or mid gestation had a reduced glucose tolerance at adult age, whereas people exposed to famine in early gestation were found to be more obese. In this thesis the effects of prenatal exposure to the Dutch famine on blood pressure, lipid metabolism, blood coagulation, cardiovascular morbidity, obstructive airways disease, perceived health in adult life and survival up to age 50 are described.
References


