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The Dutch famine and its long-term consequences for adult health

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Abstract Small size at birth is linked with an increased risk of chronic diseases in later life. Poor maternal nutrition during gestation may contribute to restricted fetal growth, leading to increased disease susceptibility in later life. Animal studies have shown that undernutrition during gestation is associated with reduced life span and increased disease susceptibility. The Dutch famine is a unique counterpart for animal models that study the effects of restricted maternal nutrition during different stages of gestation.

This paper describes the findings from a cohort study of 2414 people born around the time of the Dutch famine. Exposure to famine during any stage of gestation was associated with glucose intolerance. We found more coronary heart disease, a more atherogenic lipid profile, disturbed blood coagulation, increased stress responsiveness and more obesity among those exposed to famine in early gestation. Women exposed to famine in early gestation also had an increased risk of breast cancer. People exposed to famine in mid gestation had more microalbuminuria and obstructive airways disease.

These findings show that maternal undernutrition during gestation has important effects on health in later life, but that the effects on health depend on its timing during gestation. Especially early gestation seems to be a vulnerable period. Adequate dietary advice to women before and during pregnancy seems a promising strategy in preventing chronic diseases in future generations.

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1. Fetal origins of adult disease

Coronary heart disease remains a major burden on public health in the western world, and is taking on epidemic proportions in the developing countries [1]. Small babies go on to develop more coronary heart disease in adult life [2]. Restricted intrauterine growth has been identified as an important contributor to later coronary heart disease and its biological risk factors. Developing organ systems adapt in response to the reduced availability of nutrients, particularly during periods of rapid development-so-called critical periods [3]. These adaptations, while advantageous for short-term survival, can be detrimental for health in later life. Animal experiments indicate that substantial changes in cardiovascular function can result from maternal or fetal undernutrition without necessarily affecting birth weight [4]. However, most studies in humans only have access to indirect measures of intra-uterine growth, such as birth weight. By directly studying the effects of restricted prenatal nutrition during different periods of gestation on health in later life, we can gain more insight into fetal origins of adult disease in humans.

2. Dutch famine as an experimental study design

While famine is sadly not uncommon in many parts of the world, studying effects of undernutrition during specific periods of pregnancy is hampered by the fact that undernutrition is usually not restricted to pregnancy alone, and the effects of chronic undernutrition and accompanying problems of infection complicate the situation. What is unusual about the Dutch famine is; first, that the famine was imposed on a previously well-nourished population; second, that there was a sudden onset and relief from the famine; and third, that despite the adversities of the war, midwives and doctors continued to offer professional obstetric care and kept detailed records of the course of pregnancy, the delivery and the size and health of the baby at birth. Furthermore, detailed information is available on the weekly rations for the people in Amsterdam, and because birth records were kept we were able to trace those born around the time of the famine allowing us to study the long-term effects of famine. All these characteristics bring about that the Dutch famine is a unique counterpart for animal models that study the effects of

restricted maternal nutrition during different stages of gestation.

3. The Dutch famine

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 cal 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 [5]. 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. 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 [5].

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 [6]. 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.

4. Famine studies

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 [7]. 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 [8]. 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 [9]. 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 [10] and anti-social personality disorder [11]. In men, the risk of congenital neural defects was also increased [8] which suggests that permanent changes in the central nervous system might be involved. Lumey [12] 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 [13].

5. The Dutch famine birth cohort study

We traced a group of 2414 term singletons born alive between November 1943 and February 1947 in the Wilhelmina Gasthuis in Amsterdam for whom we had detailed birth records. At ages 50 and 58, we invited the cohort to come to the clinic for detailed investigations. We defined exposure according to the daily official food rations for the general population older than 21 years in Amsterdam. A person was considered to be exposed if the average daily ration during any thirteen week period of gestation was below 1000 calories. The rations for babies never fell below 1000 calories a day, therefore people born before the famine (as well as those conceived after it) are considered as unexposed. Fig. 1.

6. Long-term consequences of prenatal exposure to the Dutch famine

6.1. Glucose tolerance

We found that undernutrition during gestation was associated with reduced glucose tolerance and raised insulin

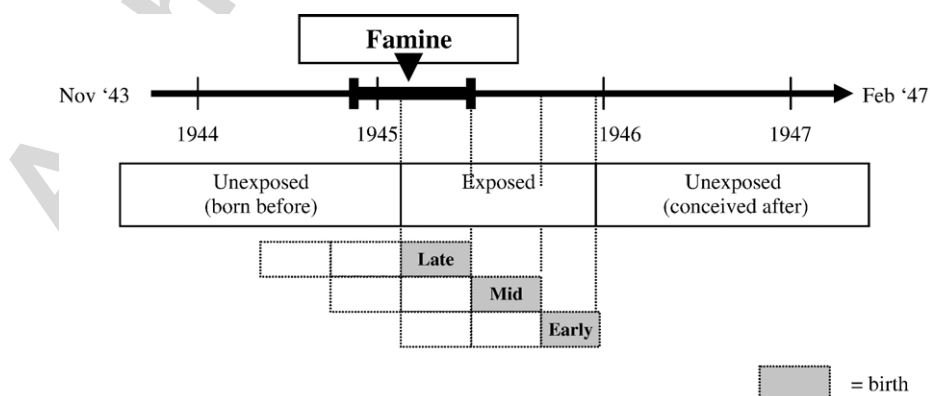


Figure 1 The Dutch famine birth cohort: famine exposure and birth in relation to the timing of the Dutch famine.

Exposure to famine		
In late gestation	In mid gestation	In early gestation
Glucose intolerance	Glucose intolerance	Glucose intolerance
	Microalbuminuria	Atherogenic lipid profile
	Obstructive airways disease	Altered blood coagulation
		Obesity (women only)
		Stress sensitivity
		Coronary heart disease
		Breast cancer

Figure 2 Long-term consequences of exposure to famine according to timing during gestation.

concentrations at age 50 and 58. We found that both 120-min glucose and insulin concentrations were higher in people exposed to famine at any stage of fetal development than in unexposed people. Importantly, this effect was larger than could be explained by the lower birth weights of babies born during the famine and by the low weight gain of their mothers [14,15]. To determine whether this association is mediated through alterations in insulin secretion, insulin sensitivity or a combination of both we performed a fifteen sample intravenous glucose tolerance test in a sub-sample of 94 normoglycaemic men and women from the Dutch famine birth cohort [16]. We used the Disposition Index (DI), derived as the product of insulin sensitivity and the first-phase insulin response to glucose, as a measure of the activity of the β cells adjusted for insulin resistance. People exposed to famine during mid or early gestation had a lower DI compared to people unexposed to famine. We therefore conclude that impaired glucose tolerance after exposure to famine during mid and early gestation seems to be mediated through an insulin secretion defect. Fig. 2.

6.2. Blood pressure

We could not demonstrate an effect of prenatal exposure to famine – during which the caloric intake from protein, fat and carbohydrate was approximately proportionally reduced – on systolic and diastolic blood pressure either taken in the clinic or at home [17]. We did find, however, that people who had been small at birth had high blood pressures in later life, which is in agreement with results from many other studies. A more elaborate analysis revealed that blood pressure of the offspring was inversely associated with the protein/carbohydrate ratio of the average ration during the third trimester of pregnancy, whereas it was not associated with any absolute measure of intake during pregnancy [18]. Children whose mothers ate relatively little protein in relation to carbohydrate in the third trimester of pregnancy had higher blood pressures at adult age. This may imply that blood pressure is not so much linked to absolute amounts of nutrients but to variations in the balance of macro-nutrients in the maternal diet during late gestation.

6.3. Renal function

We found that exposure to famine in mid gestation was linked to a 3.2 fold increase in occurrence of microalbuminuria in adulthood and a 10% increase in creatinine clearance, neither of which can be explained by cardiovascular confounders [19]. We propose that mid gestational

exposure to famine – the period of rapid increase in nephron number – may prevent formation of sufficient glomeruli and thus increase the risk for microalbuminuria and possibly affect renal function in adulthood. This supports the concept that intrauterine conditions during distinct, organ-specific periods of sensitivity may permanently determine health outcome in later life.

6.4. Airways disease

We found that people who had been exposed to famine in mid gestation had an increased prevalence of obstructive airways disease [20]. These observations were not paralleled by reduced lung function or increased serum concentrations of IgE. This suggests that the increased prevalence of symptoms and disease may be attributable to increased bronchial reactivity rather than to irreversible airflow obstruction or atopic disease. Because the bronchial tree grows most rapidly in mid gestation, our findings support the hypothesis that fetal undernutrition permanently affects the structure and physiology of the airways during ‘critical periods’ of development that coincide with periods of rapid growth.

6.5. Lipids clotting and CHD

We found that men and women exposed to famine in early gestation had a more atherogenic plasma lipid profile [21], somewhat higher fibrinogen concentrations and reduced plasma concentrations of factor VII [22] than those who were not exposed to famine in utero. Women in this group also tended to have the highest BMI, but adjustment for body mass altered the size of this effect only slightly.

Exposure to famine during early gestation was also associated with an increase in coronary heart disease in later life [23]. Persons conceived in famine not only had a higher cumulative incidence of CHD, but the disease occurred at an earlier age [24]. Models in which animals were prenatally nutrient restricted had premature aging [25] and more rapid age-related progression of biological risk factors of CHD [26,27]. There is some evidence of an association between low birth weight and increased aging rates in humans too [28,29]. Although little research has been carried out elucidating the underlying mechanisms, Jennings et al. [30] suggests that telomere shortening induced by prenatal undernutrition may be responsible for premature senescence of tissues such as the liver and kidney. These studies also pointed out that catch-up growth, such as that which may have occurred in fetuses conceived

during the famine but exposed to adequate nutrition during the remainder of gestation, could result in further telomere shortening. So far, it has not resulted in increased cardiovascular mortality yet [31].

6.6. HPA

Fetal programming of the hypothalamic–pituitary–adrenal response to stress may contribute to the increased prevalence of metabolic and heart disease in adults exposed to famine in utero. Changes in the set-point of the HPA axis during fetal life might result in long-term changes in secretion of key neuroendocrine mediators of the stress response, which in turn could predispose to cardiovascular and metabolic disease in later life. Animal experiments in a variety of species have shown that programming of the HPA axis can be induced prenatally by nutrient restriction. We found that people who were exposed in early gestation were more stress responsive in terms of systolic blood pressure compared to people unexposed to famine [32], but we found no evidence of increased cortisol responses to stress (de Rooij submitted), nor increased HPA axis responsiveness to an ACTH stimulation test [33]. These findings may indicate that fetal programming of the autonomic nervous system is more important than the HPA axis in linking prenatal exposure to famine to the increased susceptibility to cardiovascular and metabolic disease.

6.7. Breast cancer

Women who were conceived during the famine had an almost five times increased risk of breast cancer [34]. We also found a higher cumulative incidence of breast cancer among women who had been exposed to famine at any time during gestation compared to unexposed women, but the difference was not significant. The effect of maternal starvation during gestation on breast cancer incidence in the offspring was not explained by differences in known risk factors for breast cancer. Famine exposure was also linked to reproductive variables such as number of children, childlessness, age at delivery of first child and age at menopause. Although numbers are small, this is the first direct evidence that maternal undernutrition during gestation is linked to breast cancer risk in the offspring. Our findings suggest the effect of prenatal famine exposure on subsequent breast cancer is strongest among women exposed to famine in early gestation. Due to the relatively small sample size, however, we are limited in pinpointing the exact timing of famine exposure during gestation and associated breast cancer risk in later life. Little is known about the pathophysiology of the association between prenatal factors and subsequent cancer risk. High birth weight has been associated with an excess of cancer, particularly breast cancer [35,36], although other studies [37,38], including our own, could not confirm this association. Rapid postnatal growth following fetal growth restriction has been associated with permanently raised levels of growth factors [39], possibly propagating pre-malignant cell growth [40]. The restoration of an adequate diet after a period of relative growth restriction due to maternal malnutrition, as was present in women exposed to famine

during gestation, could also be associated with increased levels of growth factors, though this is speculative.

Evidence from large epidemiological studies has tied breast cancer to postnatal growth patterns [41,42]. We have now added to the evidence that prenatal nutrition may contribute to breast cancer risk in later life.

7. Limitations

In interpreting our findings, a number of matters need to be considered. Women were less fertile during the famine. The women who did conceive during the famine, whose offspring was exposed to famine in early gestation, may have been of a different constitution. However, correcting for markers of maternal constitution or fertility, such as maternal weight, age and parity and socio economic status did not affect the outcome.

The high rates of infant mortality during the famine affected groups born before the famine and exposed in late gestation most. The two groups with the largest contrast in early mortality (those born before the famine and those conceived after it) are homogeneous in terms of adult health outcomes, indicating that selective survival cannot have a large confounding effect on outcome in later life.

Selective participation of people that were fit enough to attend the clinic, and prior excess mortality among the most seriously affected people may have led to an underestimation of the effect of prenatal famine on subsequent disease.

Finally, there are limitations in pinpointing the exact timing of famine exposure during gestation and associated outcomes in later life, due to the relatively small sample size on one hand, and partial overlap between the three famine exposed groups on the other. However, the famine exposure period do give an estimate of the timing of the focus of effect.

8. Interpretation

The findings of the Dutch famine birth cohort study broadly support the fetal origins hypothesis. Chronic diseases originate in the womb through adaptations made by the fetus in response to undernutrition. The effects on undernutrition, however, depend upon its timing during gestation and the organs and systems developing during that critical time window. Furthermore, our findings suggest that maternal malnutrition during gestation may permanently affect adult health without affecting the size of the baby at birth. This gives the fetal origins hypothesis a new dimension. This may imply that adaptations that enable the fetus to continue to grow may nevertheless have adverse consequences for health in later life. Coronary heart disease may be viewed as the price paid for adaptations made to an adverse intrauterine environment. It also implies that the long-term consequences of improved nutrition of pregnant women will be underestimated if these are solely based on the size of the baby at birth.

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 a pregnancy. This should be exploited to improve the health of future generations.

9. Relevance

The Dutch famine study has established the importance of maternal nutrition during early pregnancy for the offspring's cardiovascular risk. The nutritional experience of babies who were exposed to famine in early gestation may resemble that of babies in developing countries whose mothers are undernourished in early pregnancy and receive supplementation later on, but also of babies in developed countries whose mothers suffer from severe morning sickness. Morning sickness is common in the first trimester, and severe morning sickness is associated with metabolic changes in the mother which are similar to those seen during starvation. Since the results of our study consistently show that the effects of undernutrition are independent of size at birth, the assumption that the long-term consequences of hyperemesis gravidarum will be limited because of the normal size of the babies at birth no longer holds.

Our findings suggest that maternal nutrition before and during pregnancy play an important role in later disease susceptibility. This suggestion is in line with evidence from animal experiments that identified preconceptional and preimplantation maternal diet as important for the offspring's adult health [43–45]. Possibly, epigenetic changes, such as imprinting, which takes place before conception and DNA methylation, may be involved. In both animal husbandry and human medicine, the rapid developments in assisted reproduction in the past decades have surpassed the available knowledge about the potential long-term repercussions. These fields could benefit from more knowledge about mechanisms of pathophysiology discussed above. Besides providing insight into the role of prenatal factors in the origins of chronic diseases, this information may also help to identify susceptible patient groups and be useful in the development of more appropriate therapies for common chronic diseases in the future. Most importantly, it will contribute to the prevention of chronic disease through the development of adequate dietary advice to women before and during pregnancy.

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