Undernutrition and chronic disease: the 1944-1945 Dutch famine
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General introduction
Chapter 1

GENERAL INTRODUCTION

Famine and undernutrition are still major problems in the world. The United Nations Food and Agriculture Organization recently estimated that 925 million people suffered from hunger worldwide in 2011\(^1\). The first of the Millennium Development Goals is to eradicate extreme hunger\(^2\). But, since the formulation of the Millennium Development Goals the number of hungry people worldwide has only increased. Never before in history has the number of people suffering from hunger been larger\(^3\).

Another major health problem worldwide are non-communicable chronic diseases, including cardiovascular disease, type 2 diabetes, and respiratory disease. To date, cardiovascular disease is the number one cause of death globally; it has been estimated that more than 17 million people died due to cardiovascular disease in 2008\(^4\). Furthermore, more than 300 million people suffer from type 2 diabetes worldwide\(^5\). Once, non-communicable chronic diseases were considered only a problem in developed countries. However, to date the number of people suffering from non-communicable chronic diseases is dramatically increasing in developing countries. Over 80% of the cardiovascular and diabetes deaths occur in low-and-middle-income countries\(^4,5\).

The two problems undernutrition and non-communicable chronic diseases may be linked. In the early 1980s, Professor David Barker generated a revived interest for the early origins of adult disease. He postulated that non-communicable chronic diseases can have their origin in early life. This is now known as the developmental origins of health and disease (DOHaD) hypothesis\(^6\). This hypothesis proposes that undernutrition during important periods of growth and development, including fetal life, infancy, and childhood, can lead to permanent changes in the physiology and metabolism of the body\(^6\). These adaptations may be beneficial for short-term survival, but they may also increase the risk of a number of chronic diseases in the long-term\(^6\).

Much evidence for the DOHaD hypothesis comes from human studies focusing on associations between size at birth and chronic diseases in adult life. Size at birth, including birth weight and length, serves as a marker for fetal growth rate and as a reflection of the fetal environment. A small size at birth has been associated with an increased risk of cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia\(^7\). Furthermore, the combination of a small body size at birth, low weight gain during infancy, and rapid gain in BMI during childhood has been associated with the metabolic syndrome, a body composition with low muscle mass in relation to fat mass, hypertension, and coronary heart disease in adult life\(^8,10\). Since size at birth is the product of maternal, placental, and fetal factors, it is difficult to define the impact of each of
these factors separately on later chronic disease risk. To overcome this problem, historic periods of famine, including the Dutch famine, have been used to specifically investigate the effects of acute undernutrition on health in adult life.

The Dutch famine

On the 6th of June 1944, the Allied troops invaded France. After weeks of heavy fighting the Allied forces finally broke through German lines and took possession of much of France, Luxembourg, and Belgium. By the 4th of September, the Allied forces had the strategic city of Antwerp in their hands, and on the 14th they entered the Netherlands. Everyone expected that the German occupation would soon be over. However, the advance of the Allies to the North of the Netherlands came to a halt when operation ‘Market Garden’, aimed at gaining control of the bridge across the river Rhine at Arnhem, failed. In order to support the Allied offensive, the Dutch government in exile had called for a railroad strike to thwart German transport of troops and ammunition. On the 18th of September 1944, Dutch train stations were empty and railway transport had ceased. As a reprisal, the German occupier banned all food transports. This embargo on food transports was partially lifted in early November 1944, when food transport across water was permitted again. However, the winter of 1944-1945 had started unusually early and was extremely severe. Since most canals and waterways were frozen, it had become impossible to bring in food from the rural East to the urban West of the Netherlands. Consequently, the food situation in the West of the Netherlands deteriorated rapidly from October 1944 onwards.

The official daily rations for the general adult population dropped from about 1,400 kcal in October 1944 to below 1,000 kcal 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 kcal\(^1\). 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. Children younger than 1 year were relatively protected. Their official daily rations never fell below 1,000 kcal and the specific nutrient components were always above the standards used by the Oxford Nutritional Survey\(^1\). Also, extra food came from church organizations, central kitchens, the black market and foraging trips to the countryside. With liberation on the 5th of May 1945, the food situation quickly improved, ending the famine abruptly. One month later, the rations were above 2,000 kcal.

The Dutch Famine Birth Cohort Study and the Prospect-EPIC Cohort Study

After liberation, researchers immediately realized that the Dutch famine was a unique opportunity to study the effects of acute undernutrition during pregnancy on the health of the mother and child. Clement Smith from Harvard Medical School was one of the first who began studying the
effects of the famine on the health of the Dutch population. He investigated the effects of prenatal famine exposure on pregnancy and the fetus using obstetric records from Rotterdam and The Hague. He demonstrated that babies who were born during the famine were about 200 gram lighter at birth.

Since then, a lot of research has been performed using victims from the Dutch famine to study the effects of acute undernutrition on health in humans. We used the Dutch Famine Birth Cohort Study and the Prospect-EPIC Cohort Study to investigate the long-term effects of undernutrition during fetal life, childhood, adolescence, and young adulthood on health in adult life. Since the famine lasted only for about six months, we were able to pinpoint possible effects to specific time-windows in fetal and human development (Figure 1).

The Dutch Famine Birth Cohort Study was used to investigate the effects of prenatal famine exposure on adult health. This cohort consists of 2,414 men and women who were born as term singletons in the Wilhelmina Gasthuis, a hospital, in Amsterdam between 1 November 1943 and 28 February 1947. Medical birth records of these people have been preserved, providing information about the mother, the course of the pregnancy, and the size of the baby at birth. These birth records and the Dutch population registry made it possible to retrieve these men and women and ask for their participation in the Dutch Famine Birth Cohort Study.

Previously, the Dutch Famine Birth Cohort Study demonstrated that famine exposure during any stage of gestation was associated with raised glucose levels in adult life, which may be due to an insulin secretion defect. Famine exposure in early gestation was not only associated with a higher prevalence of coronary heart disease, but the disease also occurred at an earlier age. Furthermore, famine exposure in early gestation was associated with an atherogenic lipid profile, disturbed blood coagulation, an increased blood pressure response to stress, and an increased

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risk of obesity\textsuperscript{21} and breast cancer in women\textsuperscript{22}. Exposure to famine in mid gestation was associated with an increase in the occurrence of microalbuminuria, a decrease in creatinine clearance\textsuperscript{23}, and an increased prevalence of obstructive airways disease\textsuperscript{24}. All these effects were independent of the size of the baby at birth.

Not only the fetal period, but also childhood and adolescence are important periods of growth and development. We were able to use data from Prospect-EPIC, which is a large population-based cohort of women, aged between 0 and 21 years during the famine, who were participants in a breast cancer screening program in Utrecht and its vicinity. It is one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and nutrition (EPIC). These women were asked between 1993 and 1997, when they were aged between 49 and 70 years, about place of residence and whether and how much they had suffered from hunger and weight loss during the 1944-1945 Dutch famine. A combination of these questions resulted in a three-point individual hunger score ('none', 'moderate', or 'severe' famine exposure).

Previously, using this individual hunger score the long-term effects of postnatal exposure to the 1944-1945 Dutch famine on breast cancer risk and factors that may have mediated this risk have been described. Women who were severely famine exposed between two and 13 years of age had lower chances of childbirth at any time after marriage as well as after birth of a first child\textsuperscript{25}. In addition, these women reported more often that a medical problem was the reason for having fewer children than wanted\textsuperscript{25}. Furthermore, mean age at natural menopause decreased with increasing severity of famine exposure, particularly when exposure was in childhood\textsuperscript{26}. Levels of the sex-steroids estrone, estradiol, testosterone, and 5α-androstane-3α,17β-diol tended to be slightly increased in women having been exposed to the famine as young adults, whereby the strongest relation was found for estrone\textsuperscript{27}. Furthermore, insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 levels increased significantly with degree of famine exposure, while serum levels of IGFBP-1 and -2 slightly decreased with famine exposure\textsuperscript{28}. Women who were famine exposed between two and 33 years also had an increased breast cancer risk\textsuperscript{29}. This effect tended to be stronger in women who were severely famine exposed before the age of ten years and in women who remained childless\textsuperscript{29}. 
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Outline of this thesis

The work presented in this thesis explores the effects of both prenatal and postnatal famine exposure on chronic disease risk in adult life. In part 1 of this thesis, chapters 2 to 4, we describe the effects of prenatal undernutrition on the association between placental size and hypertension, the risk of adult mortality, and the risk of hypertension in later life.

Previously, we demonstrated that placental size is affected by prenatal famine exposure. Since low birth weight and both a low and high placental weight have been associated with an increased risk of hypertension in adult life, we were interested in the effect of famine on the association between placental size and later hypertension. In chapter 2, we describe whether the association between placental size and the risk of hypertension in adult life is altered by prenatal famine exposure and whether the effects are sex-specific.

Previous studies in the Dutch Famine Birth Cohort demonstrated that prenatal famine exposure increased the incidence of cardiovascular and metabolic disease in adulthood. In chapter 3, we investigated whether prenatal famine exposure is associated with overall and cause-specific (cardiovascular, cancer, and breast cancer) adult mortality.

Numerous experiments in animals have been performed to investigate the effect of prenatal undernutrition on the development of hypertension in later life with inconclusive results. In chapter 4, we systematically reviewed and performed a meta-analysis on animal studies examining the effects of prenatal undernutrition on systolic, diastolic, and mean arterial pressure in adult life.

In part 2 of this thesis, chapters 5 to 8, we describe the effects of postnatal undernutrition on the risk of chronic diseases in adult life. The association between famine exposure during childhood, adolescence, or young adulthood and anthropometric measures and the risk of overweight in adult life is the subject of chapter 5.

In chapter 6, we describe the association between moderate and severe undernutrition during childhood or young adulthood and the subsequent risk of type 2 diabetes in adult life.

In chapter 7, we investigated the association between moderate and severe undernutrition during childhood, adolescence, or young adulthood and the risk of coronary heart disease and stroke in adult life.
The association between moderate and severe undernutrition during childhood or young adulthood and the risk of obstructive airways disease, chronic obstructive pulmonary disease (COPD), and asthma in adult life is the subject of chapter 8.

In chapter 9, we discuss anticipated implications of the results of this thesis for developing countries. We provide a global orientation on hunger and non-communicable chronic diseases, with an emphasis on low-and-middle-income countries, where both problems often coexist.

This thesis closes with a summary of the findings presented in this thesis.
REFERENCES


