Undernutrition and chronic disease: the 1944-1945 Dutch famine
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Summary
Famine and undernutrition are still major problems in the world; around 925 million people suffered from hunger worldwide in 2011\(^1\). Another major health problem worldwide are non-communicable chronic diseases, including cardiovascular disease, type 2 diabetes, and respiratory disease. The two problems undernutrition and non-communicable chronic diseases may be linked, according to the developmental origins of health and disease (DOHaD) hypothesis. 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\(^2\). 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\(^1\).

Much evidence for the DOHaD hypothesis comes from human studies focusing on associations between size at birth and chronic diseases in adult life. A small size at birth has been associated with an increased risk of cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia\(^2,3\). 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 investigate the effects of acute undernutrition on health in adult life.

The Dutch famine was approximately a six-month period of severe food shortage in the Western part of the Netherlands at the end of World War II. The famine struck a previously and subsequently well-nourished population. At the height of the famine, from December 1944 to April 1945, the official daily rations varied between 400 and 800 kcal\(^4\). 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.

We used the Dutch Famine Birth Cohort Study 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. According to the date of birth, we defined whether someone has been exposed to famine in utero. Cohort members born between 7 January 1945 and 8 December 1945 were considered to have been exposed to famine in utero. Cohort members born between 1 November 1943 and 6 January 1945 (born before the famine) and between 9 December 1945 and 28 February 1947 (conceived after the famine) were considered as unexposed to famine in utero and acted as the control group.
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We were able to use data from Prospect-EPIC to investigate the effects of postnatal famine exposure on adult health. Prospect-EPIC is a large population-based cohort of women, aged between 0 and 21 years at start of 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, whether and how much they had suffered from hunger and weight loss during the 1944-1945 Dutch famine. A combination of the answers to these questions resulted in a three-point individual famine exposure score (‘none’, ‘moderate’, or ‘severe’ famine exposure).

Part 1 of this thesis, chapters 2 to 4, contains the results of the studies in which we examined the effects of prenatal undernutrition on health in later life. In chapter 2, we examined the effect of maternal undernutrition on the relationship between placental size and later hypertension. We showed that among men who were not in utero during the famine, hypertension was associated with a small placental surface area due to a small placental breadth. Among men who were in utero during the famine, hypertension was associated with a large placental surface area due to a large placental breadth. Among women hypertension was not associated with placental size. We hypothesized that among men who were not in utero during the famine, hypertension was related to impaired implantation, whereas among men who were in utero during the famine hypertension was related to compensatory expansion of the placental surface.

In chapter 3, we investigated the association between prenatal famine exposure and adult mortality. We found that women exposed to famine in early gestation, compared with unexposed women, had a significantly higher risk of overall adult mortality (HR: 1.9, 95% CI: 1.1 to 3.4), cardiovascular mortality (HR: 4.6, 95% CI: 1.2 to 17.7), cancer mortality (HR: 2.3, 95% CI: 1.1 to 4.7), and breast cancer mortality (HR: 8.3, 95% CI: 1.1 to 63.0). No such effects were observed in men exposed to famine in early gestation.

Chapter 4 is a systematic review and meta-analysis, summarizing the available evidence from animal experiments regarding the effects of maternal undernutrition on blood pressure in the offspring. This meta-analysis showed that maternal undernutrition, both general and protein, increased systolic blood pressure (general undernutrition: 13.6 mmHg, 95% CI: 9.9 to 17.3; protein undernutrition: 18.9 mmHg, 95% CI: 16.1 to 21.8) and mean arterial pressure (general undernutrition: 4.2 mmHg, 95% CI: 1.1 to 7.3; protein undernutrition: 10.5 mmHg, 95% CI: 6.7 to 14.2). Diastolic blood pressure was only increased after protein undernutrition (9.5 mmHg, 95% CI: 2.6 to 16.3), while general undernutrition had no significant effect. Although there was substantial
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heterogeneity in the results, this meta-analysis shows that, in different animal species, maternal undernutrition generally results in increased blood pressure in the offspring.

Part 2 of this thesis, chapters 5 to 8, contains the results of studies in the Prospect-EPIC cohort in which we examined the effects of postnatal undernutrition on adult health. In chapter 5, we relate famine exposure during childhood, adolescence, or young adulthood to anthropometric measures and the risk of overweight in adult life. Overall, postnatal famine exposure was associated with an increased body mass index and waist circumference in a dose-dependent manner (P for trend < 0.01). After adjustment for potential confounders, including age at start of the famine, smoking, alcohol intake, and level of education as a proxy for socioeconomic status, odds ratios for the risk of overweight were 1.10 (95% CI: 1.00 to 1.22) for moderate famine exposure and 1.15 (95% CI: 1.01 to 1.31) for severe famine exposure compared with no famine exposure. Additionally including total energy intake did not change these results.

In chapter 6, we show that the risk of type 2 diabetes in adult life increased with increasing severity of famine exposure during childhood, adolescence, or young adulthood (P for trend < 0.001). Relative to unexposed women, the type 2 diabetes hazard ratios adjusted for age at start of the famine for moderate and severe famine exposure were 1.36 (95% CI: 1.09 to 1.70) and 1.64 (95% CI: 1.26 to 2.14), respectively. These effects did not change after additional adjustment for the potential confounders smoking and level of education as a proxy for socioeconomic status.

Chapter 7 presents the results on famine exposure and the risk of coronary heart disease (CHD) and stroke in later life. Overall, stronger famine exposure was associated with higher CHD risk in adult life. The risk of CHD was significantly higher (HR: 1.38, 95% CI: 1.03 to 1.84) among women who were severely exposed to the famine between 10 and 17 years of age compared with unexposed women. Adjustment for the potential confounders age at start of the famine, smoking, and level of education as a proxy for socioeconomic status slightly attenuated this risk estimate (HR: 1.27, 95% CI: 0.94 to 1.71). We observed a lower risk of stroke among famine exposed women (HR: 0.79, 95% CI: 0.61 to 1.02) compared with unexposed women. Adjustment for the potential confounders produced similar results (HR: 0.77, 95% CI: 0.59 to 0.99).

In chapter 8, we investigated the association between famine exposure during childhood, adolescence, or young adulthood and the risk of obstructive airways disease, chronic obstructive pulmonary disease (COPD), and asthma in adult life. After adjustment for the potential confounders age at start of the famine, smoking, and level of education as a proxy for socioeconomic status, we found that the risks of obstructive airways disease, COPD, and asthma were increased with
more severe famine exposure in a dose-dependent manner. Associations with COPD were stronger in ever-smokers than in non-smokers. Findings were mirrored with CT scans, particularly among ever-smokers.

In chapter 9, we discuss the anticipated implications of the results of this thesis for developing countries. Both hunger and non-communicable chronic diseases (NCCD) are growing worldwide health challenges. While hunger and NCCD are substantial global health threats in their own right, there is evidence that the two are directly related and that undernutrition during critical periods of early growth and development increases the risk of various chronic diseases throughout life. Such relations may further aggravate health prospects for the longer term. In this chapter, we provide a global orientation on hunger and NCCD, with an emphasis on low-and-middle-income countries where both problems often coexist.
REFERENCES


