Prenatal exposure to the Dutch famine and glucose tolerance and obesity at age 50
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Chapter 3

DUTCH FAMINE STUDIES
The Dutch famine is unique among other periods of famine that have occurred in the past, as it meets the criteria for an “experiment of history”.1 The famine struck at a circumscribed time period. During the Dutch famine there was a severe nutritional deprivation. The famine was short in duration and was preceded and followed by adequate nutrition. The Netherlands were those times a highly organized society and people born during the time of the Dutch famine grew up in a time of affluence. The population was ethnically homogenous, as almost all were Caucasians. Birth records of people born during the famine period still exist and long term follow-up is possible because all inhabitants of the Netherlands are registered in the population registers.

It is not the first time that health effects of the Dutch famine are studied. In this chapter an overview is given of other epidemiological studies. We start with the early famine studies on birth outcomes performed shortly after the war. Stein and Susser studied the mental performance in a population of men 19 years after the famine. Lumey studied the obstetric performance of women who had been exposed to famine in prenatal life. Susser, Hoek and Brown studied the effects of the Dutch famine on the occurrence of schizophrenia. We end this chapter with some studies that have looked at associations between exposure to famine in postnatal life and outcomes later in life.

1. The early famine studies

The nutritional status of the Dutch population was assessed three weeks after the war by three nutritional teams from the Allied forces.2 They found that 200,000 to 250,000 persons in Western Holland suffered from famine oedema. Loss of weight varied from 20 to 25% of the total body weight. The incidence of tuberculosis, enteritis, peptic ulcers and hernia was greatly increased. No clear-cut signs of vitamin deficiency, scurvy or pellagra were seen. Pregnancy related diseases like eclampsia and toxocose had greatly diminished and the incidence of adult diseases as hypertension and obesity was decreased during the famine period.3,4 Mortality was three times higher in February 1945 than in preceding years and remained twice as high in March and April 1945. Mortality was highest among infants and elderly people.5

Shortly after the end of the World War II, the effects of prenatal exposure to famine on fetal growth were described. Impaired nutrition of pregnant women during the famine had resulted in a decrease in birth weight of hospital born infants of about 200 gram in Utrecht.6 Smith found a reduction in birth weight of about 240 gram in Rotterdam and in The Hague.7 In The Hague 41% of the children had a birth weight less than 3000 gram in the first half year of 1945. This percentage was nearly doubled compared to the 24% found in 1942.7 In Amsterdam birth weights declined on average by 340 gram. The decrease in birth weight was higher in boys than in girls.8

2. Studies by Stein and Susser

Zena Stein and Mervin Susser started their study; “Famine and Human Development. The Dutch Hunger Winter of 19459 in the sixties.10 They studied the effects of prenatal exposure to famine on fetal growth, mental performance, obesity and mortality at age 19. They used available hospital records for deliveries, the records of military induction made of Dutch males 19 years after the famine, and the mortality information from the Central Bureau of Statistics.11

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The data on delivery in hospitals in famine and non-famine cities provided information about the size of the baby after famine exposure. Generally the famine had reduced birth weight with 300 gram. They found that fetal size was reduced only by third trimester famine exposure. Birth weight was relatively more reduced than crown-to-heel length; more thin babies with reduced placental weight were born after third trimester famine exposure. Isolated first and second trimester exposure did not reduce birth weight.\(^1\)\(^2\)

The records of the military examination of all men in the Netherlands at 19 years of age formed the main source of data for the analysis of long-term effects of prenatal exposure on mental performance. At the age of 19 years there were no detectable adverse effects on cognitive ability. Nor was there an increased prevalence of mental retardation.\(^3\) Obesity rates in 19-year-old males varied by timing of prenatal exposure. Increased obesity rates at age 19 were seen in subjects exposed to famine in the first half of pregnancy and decreased obesity rates in subjects exposed in late pregnancy or early infancy.\(^4\)

Exposure to famine in the third trimester of gestation was followed by an excess of fetal deaths and deaths in the first three months of life. Famine exposure in the first trimester of gestation was related to an excess of premature deliveries, perinatal deaths and malformations of the nervous system.\(^5\)\(^6\)

3. Obstetric performance of women after in utero exposure

Lumey has studied the effects of prenatal exposure to famine on the obstetric performance of women. The first study of Lumey included all obstetric outcomes of firstborn singleton infants born in Amsterdam at the Wilhelmina Gasthuis between 1960 and 1984 of mothers who had been born between January 1944 and July 1946 in the Netherlands. Famine exposure of these women as fetuses during third trimester of gestation had produced marked effects on their own birth weights. The second-generation effect of in utero exposure to famine was found only in the offspring of mothers who were in utero exposed in the first and second trimester. Famine exposure of these women as fetuses, which had no effect on their own birth weights, did have a decreasing effect on their offspring birth weights.\(^7\)\(^8\)

The second study by Lumey and colleagues included a birth cohort of 1116 female infants born in the Amsterdam Wilhelmina Gasthuis university hospital between 1 August 1944 and 15 April 1946 and their first and second born offspring.\(^9\) The conclusion was that a substantial 200 gram or more impact of severe in utero maternal undernutrition on offspring birth weight can be ruled out. There may however be parity specific effects. Birth weights of firstborn infants of women exposed in the first trimester of pregnancy were higher than non exposed firstborn children and second born infants of these mothers were lighter than non exposed second born children.\(^10\)\(^11\)

In a comparison within sibships it was concluded that the expected increase in offspring birth weight with increasing birth order was not seen after maternal intrauterine exposure in the first trimester of pregnancy.\(^12\) Acute famine exposure in utero had no adverse consequences for subsequent fertility of the women born or conceived during the famine period.\(^13\)

On the basis of the maternity records of the women collected for the second reproductive study the effects of maternal weight gain during gestation on the size of the female infants were studied. Aryeh Stein described how in the presence of adequate preconception nutrition fetal growth is protected until maternal nutritional
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deprivation becomes extreme. Last trimester weight loss or low to moderate weight gain of ≤0.5 kg/week was found to be strongly associated with the birth weight, length and ponderal index of the babies. It was suggested that acute maternal nutritional deprivation affects fetal growth only below a threshold.22

4. Schizophrenia studies

Ezra Susser, Hoek and Brown studied the effect of prenatal exposure to the Dutch famine on schizophrenia and neurodevelopmental disorders.23 They started with the finding of Stein and Susser that there was an increased prevalence of spina bifida and hydrocephalus in the cohort exposed to famine in the first trimester of gestation.24 An association was found between early prenatal exposure to famine and adult schizophrenia and schizophrenia spectrum disorders.25-28 Men and women conceived at the height of the famine had increased risk of schizophrenia and neural tube defects.29 This increased risk was specific for schizophrenia and not observed for other psychiatric disorders.28

5. Exposure to famine in postnatal life

In some studies the relation between exposure to famine in postnatal life and later health effects has been described. Health effects after exposure to the Dutch famine in postnatal life were studied in 18,000 women born between 1911-1945 who participated in the DOM study in 1974. The study showed an increase of 8 months on mean age at menarche during the war period of 1940-1945. There was no additional increase in age of menarche during the Dutch famine period of 1944-45.29 The same DOM study showed a decreasing effect of exposure to the Dutch famine in infancy on adult height. Women exposed to the famine before the growing period, between the age of 0-9, and after the growing period, between the age of 12-16, had a smaller adult height, leg length and arm span width.30

The risk of breast cancer was studied in a prospective cohort study consisting of 62,735 women at age 55-69 years who were interviewed in 1986. The hypothesis that energy restriction during adolescence could be associated with a decrease in the risk of breast cancer was studied. This hypothesis could not be confirmed. Compared to residents living in the North and South of the country in 1944-45, residents of the Western rural area had an increase in breast cancer risk (RR=1.45 (95%CI 1.13 to 1.87)) and residents of the Western cities had no significant increase in breast cancer risk (RR=1.12 (0.91 to 1.38)).31

Associations between exposure to famine in adolescence and young adulthood and adult health were studied in a cohort of 3107 people from the Longitudinal Ageing Study Amsterdam. Participants who were exposed to famine at ages 20-36 years were more likely to have cancer and depressive symptoms at ages at ages 68-84, but less likely to have diabetes. When subjects were exposed to famine in adolescence, at ages 10-14 years, they had more respiratory diseases and vision problems at ages 58-62.32-36
6. Conclusion

It can be concluded that the Dutch Famine period has been studied in a long tradition of scientific research. The unique short duration of the famine in combination with good documentation of food rations and birth outcomes will continue to provide an ideal environment for testing new hypotheses. Previous studies of long-term effects of maternal malnutrition during gestation looked at birth outcomes, mental performance, schizophrenia and the effects on the birth outcomes of the next generation. In the new Dutch famine study described in this thesis we studied diabetes, obesity and other cardiovascular risk factors around age 50 of men and women who were exposed to famine in prenatal life.

References