Prenatal exposure to the Dutch famine and glucose tolerance and obesity at age 50
Ravelli, A.C.J.

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Chapter 1

INTRODUCTION
An early indication that adult cardiovascular diseases might be linked to prenatal life came from geographical studies. In 1986 Barker reported a close geographical similarity between past infant mortality rates and current mortality rates from coronary heart disease in England and Wales. With his geographical studies Barker and his team from Southampton set a new point of departure for cardiovascular research. Other geographical studies had also focused on the early environment. The influence of poor living conditions during childhood, such as illnesses in childhood, child diets and child homes on adult cardiovascular disease had been identified. Barker interpreted the findings from the dominant environmental influence of mothers on babies during gestation, which could be the cause of cardiovascular disease in adult life.

More indications that some of the origins of cardiovascular disease can be found in the environment experienced in utero came from follow-up studies of historical birth cohorts. In Hertfordshire low birth weight was found to be associated with impaired glucose tolerance, non-insulin-dependent diabetes mellitus and hypertension in adult life. Further studies in Preston and Sheffield showed that people who were thin at birth tended to become insulin-resistant and developed the insulin resistance syndrome: diabetes, obesity, hypertension and abnormal lipid profile. The association between small size at birth and adult disease did not depend on length of gestation. The conclusion was that reduced fetal growth at particular stages of gestation was associated with adult disease.

In recent years, a growing number of independent epidemiologists in different countries have found size at birth to be inversely associated with cardiovascular mortality and cardiovascular risk factors, such as non-insulin-dependent diabetes mellitus, obesity, hypertension and an abnormal lipid metabolism. These associations are specific, strong and span the whole of the birth weight range. The associations with size at birth and adult disease are independent of social class and adult life style. Adult lifestyle, however, adds to the effects established in early life. For example, the prevalence of impaired glucose tolerance is highest in people who had a low birth weight but become obese as adults.

The findings of epidemiological studies are strongly supported by the results of animal studies. Studies in animals have shown that undernutrition in utero or during early postnatal life may reduce the secretion of insulin or exhibit insulin resistance. Animal experiments have also shown that rats whose mothers had restricted food intake during the first two weeks of pregnancy became markedly obese.

Fetal growth depends on many factors. Fetal size is controlled more by environmental influence of the mother than by parental genes. The supply of nutrients...
and oxygen to the fetus is the major influence that regulates its growth. It depends on the mother’s body composition and size, her lifelong nutrient stores, food intake during pregnancy, the transport of nutrients to the placenta, the transfer across the placenta and the supply of nutrients to the fetus. This long and vulnerable series of steps is known as the fetal supply line. This indicates that maternal nutrition during gestation is but one of the factors in the chain affecting fetal nutrition.

Different tissues and organs have different periods of rapid cell division which determine their sensitivity to nutritional insults. The effect that undernutrition in utero has on the structure and metabolism of the fetal body depends on its timing. The term “programming” is used to describe the process whereby a stimulus or input during a sensitive critical period of development has permanent effects on the structure, physiology and metabolism of the body. The specific adaptation effects of undernutrition depend on the time in development in early life at which it occurs. The effects of undernutrition in early life include a reduction in cell numbers, alteration in organ structure and changes in the patterns of hormone release and of tissue sensitivity to hormones. These adaptations may permanently alter adult metabolism in a way that contributes to survival under conditions of undernutrition but is detrimental when nutrition is abundant.

Previous epidemiological studies have described the associations between small size at birth, as a proxy for poor fetal growth, and adult glucose tolerance. No human studies have directly linked maternal nutrition during specific periods of gestation with glucose tolerance in adult life. The Dutch famine 1944-1945 provides a unique opportunity for studying the effects that severe maternal malnutrition during gestation has on adult glucose tolerance, obesity and other cardiovascular risk factors.

The Dutch famine occurred between the end of November 1944 and the beginning of May 1945 during World War II in the Western part of The Netherlands. The famine was severe and short in duration. The detailed weekly records of the food rations distributed in the Western Netherlands during the famine period reflect the amount of food available to the population as a whole and can therefore be used to define whether people were exposed to maternal nutrition in fetal life or not. The birth records of babies born in that period are still available, and the Dutch population registers are, in principle, capable of finding out whether these people are still alive and where they live. As a consequence the Dutch famine can be considered as an “experiment of history” to test the fetal origins hypothesis.

The aim of the Dutch famine study, reported in this thesis, was to examine the effects of nutritional deprivation at different stages of gestation on major risk factors for coronary heart disease in general and glucose tolerance and obesity in particular. We have investigated possible associations of exposure to famine during late, mid or early gestation with differences in body size at birth, glucose tolerance and obesity in adult life. Furthermore we have investigated if infant feeding in early life is associated with glucose tolerance, obesity, lipid profile and blood pressure in adult life. To answer the research questions we studied singleton people born at term in the Wilhelmina Gasthuis in Amsterdam shortly before, during and shortly after the Dutch Famine of 1944-45. Data on prenatal visits, sizes at birth and infant feeding were abstracted from the medical records. Glucose tolerance, obesity, blood pressure, lipid profile and other cardiovascular risk factors were measured around age 50.
Chapter 1

In chapter 2 the food rations, composition and intake during the Dutch famine period and the prenatal exposure to famine definition are described. Chapter 3 contains an overview of previous studies on the health effect of prenatal exposure to the Dutch famine. In chapter 4 the material and methods of the current Dutch famine study are described. In chapter 5 we present the results of maternal malnutrition on body size at birth. The effects of prenatal exposure to maternal malnutrition on adult glucose tolerance at age 50 are reported in chapter 6. In chapter 7 the effects of maternal malnutrition on obesity at age 50 are described. The effects of infant feeding during the first weeks after birth on glucose tolerance, obesity, lipid profile and blood pressure at age 50 are described in chapter 8. In chapter 9 some methodological aspects of the study are discussed. This chapter closes with the implications of the study findings for the fetal origins hypothesis.

References
