Summary
Fetal origins hypothesis

Chronic diseases are the main public health problem in Western countries. Coronary heart disease, cancer and respiratory disease are the most common causes of death in developed countries, accounting for three-quarters of all deaths at adult age. Much of the research into the aetiology of these diseases has focussed on adult risk factors, such as smoking, diet and physical activity. These factors, however, are limited in predicting individual risk and only partly explain the striking social and geographical inequalities in health.

There are now indications that coronary heart disease originates in utero. Studies in several populations have shown that people who were small at birth have an increased risk of coronary heart disease in later life. And, they also have higher blood pressure, higher cholesterol levels and more often suffer from diabetes than those who had been larger at birth.

These findings have led to the fetal origins hypothesis. Undernutrition of the fetus during critical periods of development would lead to adaptations in the structure and physiology of the fetal body, and these adaptations would increase the risk of coronary heart disease, hypertension, hypercholesterolaemia and diabetes in later life. It is not surprising that such a phenomenon – that is also known as programming – occurs when human development is considered from conception to death. Before birth some 42 cycles of cell division takes place, after birth only another 5 are needed.

The fetal origins hypothesis is supported by findings from animal experiments that show that undernutrition during pregnancy has permanent adverse effects on health of the offspring. There is however no direct evidence in humans that undernutrition during gestation has permanent effects on health. The Dutch famine – though a historical disaster – provides a unique opportunity to study effects of undernutrition during gestation in humans. Famine has seldom, if ever, struck where extensive, reliable and valid data allow the long-term effects to be studied. The famine was sharply circumscribed in both time and place, it had a sudden beginning and end and struck the entire population irrespective of social class. And, the type and degree of nutritional deprivation during the famine were known with a precision unequalled in any large human population before and since. All these characteristics bring about that the Dutch famine can be considered as a
unique ‘experiment of history’ to test the fetal origins hypothesis. This thesis describes the effects of prenatal exposure to famine on health in later life.

**Effects of prenatal exposure to famine**

The objective of the study described in this thesis was to assess the effects of exposure to famine during different periods of gestation on adult health and disease in general, and coronary heart disease and its risk factors in particular. The effects of prenatal exposure to famine on adult glucose tolerance and obesity have been described elsewhere. We traced a group of people born between November 1943, and February 1947, in the Wilhelmina Gasthuis in Amsterdam, for whom we had detailed birth records. We compared the health of people who had been exposed to famine in late, mid or early gestation with the health of people who had not been exposed to famine during gestation (people who were born before the famine or people who were conceived after the famine).

We could not demonstrate an effect of prenatal exposure to famine on blood pressure (*chapter 2*). 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 (*chapter 3*). Children whose mothers ate relatively little protein in relation to carbohydrates 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.

We found that people exposed to famine in early gestation had a more atherogenic lipid profile (*chapter 4*), somewhat higher fibrinogen concentrations and reduced plasma concentrations of factor VII (*chapter 5*), and they appeared to have a higher risk of coronary heart disease (*chapter 6*). Though the latter was based on small numbers, as could be expected from the relatively young age of the cohort in terms of coronary heart disease. Nevertheless, this is the first evidence in humans that undernutrition during gestation is linked with the risk of coronary heart disease in later life. Moreover, people who had been
exposed to famine in early gestation more often rated their health as poor (*chapter 8*). This indicates that they are not only less healthy in terms of objective measures of health, but that they also feel less healthy. Because the famine ended abruptly, the women who conceived during the famine (and were thus exposed in early pregnancy) were well nourished in later pregnancy, which may have contributed to the above average birth weight of their babies. The transition from nutritional deprivation in early gestation to nutritional adequacy later on may have led to metabolic conflicts resulting in disease in later life.

We found that people who had been exposed to famine in mid gestation had an increased prevalence of obstructive airways disease (*chapter 7*). 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.

Although we found that prenatal exposure to famine affected several aspects of adult health, we were not able to demonstrate any effects of famine on either overall or cause specific mortality after the age of 18, while there were differences in mortality during the first years of life (*chapter 9*). Because people who had been exposed to famine in early gestation felt less healthy, and perceived health is known to be a strong predictor of future mortality, we might expect an increased mortality in the future among these people.

**Interpretation**

Our findings 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 intra-uterine 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.