The fetal origins of adult disease, the evidence and mechanisms
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Introduction
Many studies have demonstrated that prenatal undernutrition is associated with the development of a number of age-related diseases in later life. In the late 1980’s David Barker was the first to describe an association between fetal development and adult disease. Using birth weight as a proxy for fetal development, he found that birth weight was inversely associated with adult systolic blood pressure. Moreover, in a cohort of men born in Hertfordshire between 1911 and 1930, he reported that those born with the lowest birth weights had the highest risk of death from ischemic heart disease. With this observation, the fetal origins hypothesis was born, suggesting that undernutrition early in development, and particularly during intrauterine life, can lead to permanent changes in physiology and metabolism, which result in increased disease risk in adulthood. After initial scepticism and much debate the fetal origins of adult disease hypothesis became widely accepted and supported by many similar findings in populations worldwide.

To experimentally test the fetal origins hypothesis animal experiments are necessary. The field of animal research regarding the fetal origins hypothesis has expanded rapidly over the years, using different species and exposures. Initially these were descriptive, providing evidence for the causal relationship between early life exposures and metabolic risk factors in later life. In the more recent years the focus has changed to unravelling the underlying mechanisms. This has led to an abundance of studies with not always agreeing results. To study the fetal origins hypothesis in humans, we can study people that have been exposed to the Dutch famine in utero.

**THE DUTCH FAMINE**

The Dutch famine was a five month period at the end of World War II during which the urban western part of the Netherlands was struck by a severe famine. After the south of the Netherlands had been liberated by the Allied forces in September 1944, the Dutch government in exile called for a railway strike to aid the liberation of the provinces still occupied by the German forces. Despite the railway strike, the Allies were not able to pass the river Rhine. As a reprisal, the German administration put an embargo on all food transports. Food stocks ran out in a matter of weeks. Rations dropped to 400 to 800 calories per day, less than a quarter of the pre-famine levels. After liberation, the food situation quickly improved and rations rose to 2000 calories. The famine was no doubt a humanitarian disaster, but turned out to be a unique opportunity to study the consequences of prenatal undernutrition on health in later life. The fact that the famine lasted 5 months and struck a population that was well fed before the famine in combination with the fact that food supplies improved quickly after liberation, allowed us to study the effects of prenatal undernutrition on specific parts of gestation.

The Dutch famine birth cohort is a cohort of 2414 babies, all born as term singletons in the Wilhelmina Gasthuis in Amsterdam whose birth records have been kept. This cohort gave us the
Introduction

Two previous rounds of data collection at age 50 and 58 have shown that maternal undernutrition during gestation has lasting negative consequences for the offspring’s health. The effects depend on the timing during gestation and the organs and tissues developing at that time. Exposure to famine during any part of gestation was associated with raised glucose levels at adult age, possibly due to an insulin secretion defect. People exposed to famine in early gestation had altered blood coagulation and a more atherogenic lipid profile. Exposure to famine in early gestation was also found to be associated with increased blood pressure response to stress and an increase in, and earlier onset of coronary artery disease. Women who were exposed to famine prenatally had more children, more twins and started reproducing at an earlier age compared to unexposed women. These women also less often remained childless. A striking finding was the fact that the effects found were independent of the size of the baby at birth, which may imply that adaptations that enable the fetus to continue to grow in unfavourable circumstances may have adverse health consequences in later life.

In the latest round of data collection, the first evidence of transgenerational effects of famine exposure became clear. Grandmaternal exposure to famine during gestation did not affect birth weight or prevalence of cardiovascular or metabolic disease. But grandoffspring was more adipose at birth, and children of women that had been exposed to famine in utero had poorer health. This first indication of transgenerational effects of famine exposure is in line with evidence from animal experiments where adverse events during gestation not only affect the offspring of that pregnancy, but also has effects on the next generation. The effect of feeding rats a low protein diet during pregnancy for several generations took three generations of normal feeding for fetal growth and development to return to normal. The underlying mechanism that is thought to serve as a memory of early life exposures and leading to (transgenerational) changes in gene expression and potentially disease in later life is epigenetics.

EPIGENETICS

Epigenetics refers to processes that induce heritable changes in gene expression potential without altering the gene sequence. One of the major epigenetic mechanisms is methylation of CpG nucleotides. Methylation of CpG’s within gene promoters is associated with transcriptional inactivation, in contrast, unmethylated promoters are potentionally transcriptionally active. In addition to gene silencing by promoter methylation, differential methylation of individual CpG’s can induce subtle changes in transcriptional activity.

For example, feeding pregnant rats a protein restricted diet induced hypomethylation of the peroxisomal proliferator-activated receptor α (PPAR α) and glucocorticoid receptor (GR) promoters and increased the expression of PPARα and GR in the livers of juvenile and adult
offspring\textsuperscript{16,17}. The first evidence of epigenetic programming after prenatal famine exposure in humans came from the Dutch famine families study\textsuperscript{18}. Men and women who had been exposed to famine in early gestation had hypomethylation of the differentially methylated region of insulin-like growth factor-2 gene compared to unexposed same-sex siblings\textsuperscript{18}. Further studies from this group suggested that the effects of prenatal famine exposure on methylation are sex- and timing specific\textsuperscript{19}. Thus, both animal and human studies suggest that changes in the intrauterine environment can lead to altered gene expression via alterations in DNA methylation, possibly resulting in an increased susceptibility to chronic disease in adulthood\textsuperscript{20}.

The finding that the developing fetus is sensitive to its environment may be relevant to current pregnancies. The nutritional experience of fetus exposed to famine in early gestation may resemble that of fetus whose mothers suffer from hyperemesis gravidarum, a severe form of nausea and vomiting in early pregnancy. The results from the Dutch famine study have shown that the adverse effects of prenatal undernutrition were present despite the absence of any effect on the size of the baby at birth. Therefore the assumption that long term consequences of hyperemesis gravidarum may be limited because of the normal birth weight of the baby at birth no longer holds.

**AIM AND OUTLINE OF THIS THESIS**

The work presented in this thesis explores different aspects of the fetal origins hypothesis.

Human studies on the association between birth weight and health in later life have been systematically reviewed\textsuperscript{21-24} and generally support the fetal origins hypothesis. They show that birth weight is inversely related to systolic blood pressure\textsuperscript{22}, type 2 diabetes risk\textsuperscript{23}, ischemic heart disease\textsuperscript{21} and mortality\textsuperscript{24}. The evidence for this hypothesis from animal studies has not been reviewed. There is a large body of evidence from animal studies exploring the effects of undernutrition during gestation on the health of the offspring. In these studies, different species and dietary regimens are used. We systematically reviewed animal experiments concerning the fetal origins hypothesis considering the effects on glucose- and insulin metabolism (Chapter 2) and on blood pressure (Chapter 3).

In Chapter 4 the effects of prenatal exposure to the Dutch famine on hand grip strength are reported. Chapter 5 describes whether prenatal exposure to famine alters methylation levels of promoter regions of 4 candidate genes involved in cardiovascular and metabolic disease, and whether there is an association between methylation levels of these genes and lifestyle and disease markers. The association between methylation of the promoter region of the GR receptor and stress is described in Chapter 6. Whether the adverse effects of prenatal exposure to famine are confined to the offspring or are passed on to the next generation is the subject of Chapter 7. Maternal undernutrition during pregnancy is still present in the form of hyperemesis.
gravidarum. **Chapter 8** is a systematic review of the literature on the effects of hyperemesis gravidarum on the children. **Chapter 9** is a summary of this thesis and discusses the implications of the findings reported here for further research.
Chapter 1

REFERENCE LIST


