Prenatal exposure to the Dutch famine and glucose tolerance and obesity at age 50
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Citation for published version (APA):
Ravelli, A. C. J. (1999). Prenatal exposure to the Dutch famine and glucose tolerance and obesity at age 50

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Chapter 9

GENERAL DISCUSSION
In this thesis we have reported the results of a series of analyses on the effects of maternal malnutrition during the Dutch famine in different periods of gestation on body size at birth, glucose tolerance and obesity at age 50. We have also reported the effects that the method of early infant feeding had on the insulin resistance syndrome at age 50.

This chapter presents a comprehensive summary of the study results. We will discuss some potential methodological issues. Subsequently the results are put in perspective by a comparison with the recent literature. We end this chapter with the discussion of the implications of our study findings for the early origins hypothesis.

**Summary of the results**

This thesis reported on a large study of health outcomes at age 50 in a cohort that was partially prenatally exposed to the effects of the Dutch famine.

Exposure to maternal malnutrition during gestation was found to be associated with differences in body size at birth. Babies whose mothers were exposed to malnutrition in mid and late gestation were short and thin, whereas babies of mothers who were exposed to malnutrition only during early gestation were heavier and longer. Head circumferences were reduced in all babies. Exposure to famine had a direct influence on the size of the babies at birth not mediated through maternal weight gain. The effects of famine exposure were especially prominent in fetuses with large placentas.

Exposure to maternal malnutrition during mid and late gestation was found to be associated with decreased glucose tolerance at age 50. We also found that thinness at birth was associated with reduced glucose tolerance. Glucose tolerance was more impaired among people exposed to famine who became obese as adults. The effects of prenatal exposure to famine were larger than can be explained by famine related variations in birth weight. Poor nutrition in utero may lead to permanent changes in the glucose metabolism in adult life even if the effect on fetal growth is small.

Maternal malnutrition during early gestation was associated with a higher level of obesity and a more central body fat distribution in 50 year old women but not in men. At age 20 maternal malnutrition during early gestation was associated with a higher level of obesity and maternal malnutrition during late gestation was associated with a lower level of obesity. We found no clear associations between body size at birth and obesity. These findings are compatible with the hypothesis that exposure to famine in early gestation results in a hypothalamic dysfunction which might lead to obesity in adult life.

Bottle feeding in the first weeks after birth was found to be associated with an impaired glucose tolerance, a higher risk of non-insulin-dependent diabetes and a more atherogenic lipid profile but had no effect on obesity nor on blood pressure at age 50. These findings suggest that people born around the famine period who were bottle fed in the first few weeks after birth have a more cardiovascular risk in later life.

Summarising the results we can say that maternal malnutrition at mid or late gestation led to thin and short babies with decreased glucose tolerance at age 50. Maternal malnutrition at early gestation led to heavy and long babies with increased obesity and body fat distribution in 50 year old women. Partial bottle feeding, compared to exclusive breastfeeding in early life, was associated with decreased...
glucose tolerance, increased non-insulin-dependent diabetes mellitus and a more atherogenic lipid profile at age 50.

Methodological issues

The Dutch famine as an “experiment of history”

Previous epidemiological studies have described associations between small size at birth, as a proxy for poor fetal growth, and adult glucose tolerance. No study had directly linked human maternal nutrition during specific periods of gestation with glucose tolerance and obesity in adult life. The Dutch famine proved to be an unique opportunity to study the effects of maternal nutrition during gestation on adult glucose tolerance, obesity and other cardiovascular risk factors.

In general, a scientific experiment is a set of observations, conducted under controlled conditions. Usually, the term experiment is restricted to situations in which these conditions are manipulated by the investigator. The objective of an experiment is to compare differences between sets of conditions in which only the factor that is relevant to the outcome varies. The observations of the Dutch famine study originate from a historical disaster that afflicted the whole population in the Western part of the Netherlands. By comparing four groups of pregnant women we emulated an experimental approach. The relevant factor here is maternal nutrition during gestation. We studied the outcomes at birth and at adult age of fetuses who were exposed to famine during late, mid or early gestation compared those who were not exposed to famine during gestation.

Admittedly, the experimental nature of the Dutch famine study was violated to some extent. Potentially important influences such as bias by selective fertility or social economic status could have influenced the findings of our study.

Selective fertility

Selective fertility means that during the famine period, in contrast to the pre- and post famine period, not all women in the reproductive age could become pregnant for physiological or behavioural reasons. During the severe famine months many women were amenorrheic. Nine months later approximately 50% fewer children were born. This means that in the most severe months of the famine fewer conceptions took place and that the famine was affecting fertility.

We found that women who conceived during the severe famine months were younger and more frequently unmarried. However these women did not differ by parity, weight at the last prenatal visit or by their pelvic size from women who were unexposed to famine during gestation. Adjusting for a large number of maternal characteristics that might relate to the biological and behavioural determinants of fertility -including age, marital status, parity and weight - the results of the described association between early exposure to famine and obesity in adult life were hardly affected.

Socioeconomic status

The possibility that during the respective time windows of the study different categories of women delivered in the Wilhelmina Gasthuis might have contributed to another form of bias. It has been objected that people of lower socioeconomic status were more severely afflicted by the famine. However, the teams of nutritional specialists by the Allied forces who investigated the nutritional conditions of the
population immediately after the liberation of the Western Netherlands did not observe that weight loss during the famine period was related to socio-economic status. Most people belonged to the lower and middle social classes, which reduced the socioeconomic heterogeneity across the exposure groups and reduced the potential bias by socioeconomic status. We did not find sources describing differences in the actual referral pattern during the famine period. Also we did not find a stronger association between maternal malnutrition and adult outcomes in the group of lower socio-economic status at birth. Furthermore, the results described in this thesis were not affected by adjustment for socio-economic characteristics both at birth and at adult age.

Dutch famine
The Dutch famine period was characterised as a period of severe malnutrition. It was also a period of other severe circumstances like cold and stress. We can not rule out the possibility that the combination of maternal nutrition with the other factors during the famine period may have contributed to the adult outcomes. Nobody can recover the exact chain of events during the famine period influencing adult health outcomes. Consequently, we should apply appropriate caution in attributing all differences in adult outcomes exclusively to maternal malnutrition during gestation.

Discussion of the results

Results of maternal nutrition on fetal growth
The body proportions of a newborn are thought to reflect the timing of the adverse environmental influences during gestation. It has been suggested that "disproportionate or assymetrical" fetal growth retardation reflects inadequate supply of nutrients and oxygen (failure of the supply line) at the time of rapid increase in fetal weight at the second half of pregnancy. By contrast, it is suggested that "proportionate or symmetrical" fetal growth retardation reflects low genetic growth potential or adverse influences in early pregnancy during the time of cellular hyperplasia which set the fetus on a low growth trajectory. The idea that body proportions of a newborn body indicate the timing of fetal nutrition was the central motive to study the body proportions of newborn babies exposed at different times during gestations.

Babies whose mothers were exposed to famine in mid and late gestation appeared to be short and thin; their growth was disproportionately impaired. However, babies whose mothers were exposed to famine in early gestation and had an adequate nutrition in later gestation were heavier and longer. These results support the suggestion that disproportionate fetal growth retardation occurs after undernutrition in the second half of gestation. The apparent enhancement of fetal growth of those whose mothers were exposed to undernutrition in early gestation but experienced a rapid improvement of their diet in the later pregnancy is difficult to interpret. It is possible that it was the combination of early undernutrition with the adequate nutrition in the later part of gestation. Undernutrition that starts in early gestation generally continues at least until birth. The isolated exposure during early gestation however reflects common practice in sheep farming, where ewes are temporarily put on poor pastures early after mating in order to produce bigger lambs.

Whatever the mechanisms underlying the effects of exposure to famine in early gestation, size at birth only indirectly reflects the severity and timing of the adverse
environmental events during gestation. This means that body sizes at birth, even if body proportions like low ponderal index are taken into account, provide no more than a rather crude measure of the pattern of fetal growth.

Results of maternal malnutrition on adult disease

It has been put forward that the results of the Dutch famine study deviate from two previous negative studies on the influence of prenatal exposure to famine on health in later life. A study of about 760,000 individuals, born around the Finnish famine 1866-1868, found that nutritional deprivation in utero had no effect on survival after the age of 18 years. A second study compared 169 individuals who were exposed to malnutrition in utero with 192 individuals exposed in early life during the Siege of Leningrad 1941-1944. The authors reported no association between intrauterine malnutrition and glucose tolerance, obesity or other cardiovascular risk factors.

We think that the Leningrad famine study is hardly comparable with the Dutch famine study. As indicated before, the Dutch famine happened abruptly and lasted only six months whereas the Leningrad Siege lasted more than two years. The Dutch famine period was preceded and followed by periods of relative adequate nutrition. During the Dutch famine the children were exposed during prenatal life but not in the first year of life whereas during the Leningrad Siege children were exposed during fetal and in infant life. Those born around the time of the Dutch famine also grew up later in life in times of increasing affluence whereas this was not the case in Russia. Moreover, we think that the glucose outcomes of the Leningrad study were not totally unaffected by malnutrition during the prenatal famine period. The investigators reported a mean 120-min glucose plasma concentration of 6.1 mmol/l (95% CI 5.8-6.4) in the subjects who were exposed to famine in utero. This exceeds the mean of 5.7 mmol/l (95%CI 5.4-6.0) in those not exposed to famine in utero and born outside the famine area of Leningrad.

Implications of the results for the early origins hypothesis

The early origins hypothesis states that a baby's nourishment before birth and in early life influences its susceptibility to diseases later in life. The central element of the hypothesis is that fetal growth is predominantly determined by the supply of nutrients and oxygen to the fetus, and that the fetus slows its rate of growth as an adaptation to a lack of supply. We see two implications of the findings of the Dutch Famine study for our understanding of the links between environmental influences during fetal and early life and later diseases.

We found that fetal programming, as a result of fetal undernutrition, can occur without affecting the overall body size and proportions at birth. We found that the effects of maternal malnutrition in mid and late gestation on glucose tolerance were larger than could be explained by famine related variations in birth weight. In other words, maternal malnutrition itself is associated with impaired glucose tolerance and obesity even if the effect on fetal growth is small. These effects of maternal malnutrition on glucose tolerance and obesity in adult life might be the result of metabolic or endocrine adjustments to undernutrition in order to maintain fetal growth.
There has been support for the idea that non-insulin dependent diabetes mellitus, obesity, hypertension and atherogenic lipid profile share similar environmental antecedents, that is as springing from a common soil. Our data suggest that this common soil might be sought in utero or in early life but it does not assume one single underlying mechanism. Programming in fetal and early life could possibly contribute to both diabetes, obesity and atherogenic lipid profile later in life but these conditions seem to be the result of different adaptive processes operating at different time windows during fetal and early life.

In conclusion we can say that the results of the Dutch famine study show that there are different cardiovascular risk factors in adult life that are associated to different time windows of fetal programming by maternal nutrition or infant feeding in early life. New animal and epidemiological studies, now in progress, must increase our understanding of the cellular and molecular processes that underlie the epidemiological associations. In total, a more elaborate and detailed picture will emerge from the role and interaction of fetal nutrition in prenatal and early life with risk factors contributing during life course to the development of diseases in later life.

References
