Long term health effects of the Dutch famine of 1944-45: A summary of research findings

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Abstract

Studies of the Dutch famine of 1944-1945 (also known as the Dutch 'Hunger winter') provide an opportunity to look at the long-term impact of early life nutrition changes on later health and disease. This contribution gives a summary of research findings from study cohorts in the famine followed from birth to adolescence and later age with medical examinations and DNA methylation analysis. The studies show a relation between prenatal famine and body size, type 2 diabetes, lipid metabolism, and DNA methylation at age ~60 years and to current mortality through age 63 years. Long-lasting epigenetic changes in DNA methylation could provide a biological pathway to explain some of these epidemiologic observations. Our study findings point towards the early gestation period as being especially sensitive to environmental changes for later health effects.

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Introduction

One aim of our studies of the Dutch famine of 1944-45 is to address unresolved questions about the nature of 'fetal programming' (Barker and Martyn 1992, Lucas and Cole 1999, Kermack, McKendrick and McKinlay 1934, Forsdahl 1977). This is the idea that there are critical time periods in gestation that are important for life-long health.

According to the fetal programming hypothesis, undernutrition in pregnancy can have permanent effects because the developing fetus is highly responsive to its environment. Possible future growth and development trajectories are adjusted based on the prevailing conditions in the womb. In an adverse environment, the fetus can make adjustments to its nutrition requirements that may be beneficial in the short run. If however the adjustments cannot be reversed over time, they may be harmful in the long run should the circumstances improve after birth. As an example, changes in fetal nutrition may have an effect on the regulating mechanism of one or more genes. Animal studies show that this may lead to differences in gene expression and in the synthesis of important enzymes (Waterland and Michels 2007).

From a life course perspective, the changes in the prenatal environment could be the first among a series of cumulative insults; they may initiate a chain of events which over time increase the risk of disease; they may also create an increased susceptibility to other exposures later in the life course (Ben-Shlomo and Kuh 2002, Lynch and Smith 2005).

In the setting of the Dutch famine of 1944-45, individuals who were exposed to extreme undernutrition in the womb can be followed over time. This provides an opportunity to evaluate long-term health effects of prenatal undernutrition in general (Lumey, Stein and Susser 2011) and to address important questions related to the fetal programming hypothesis.

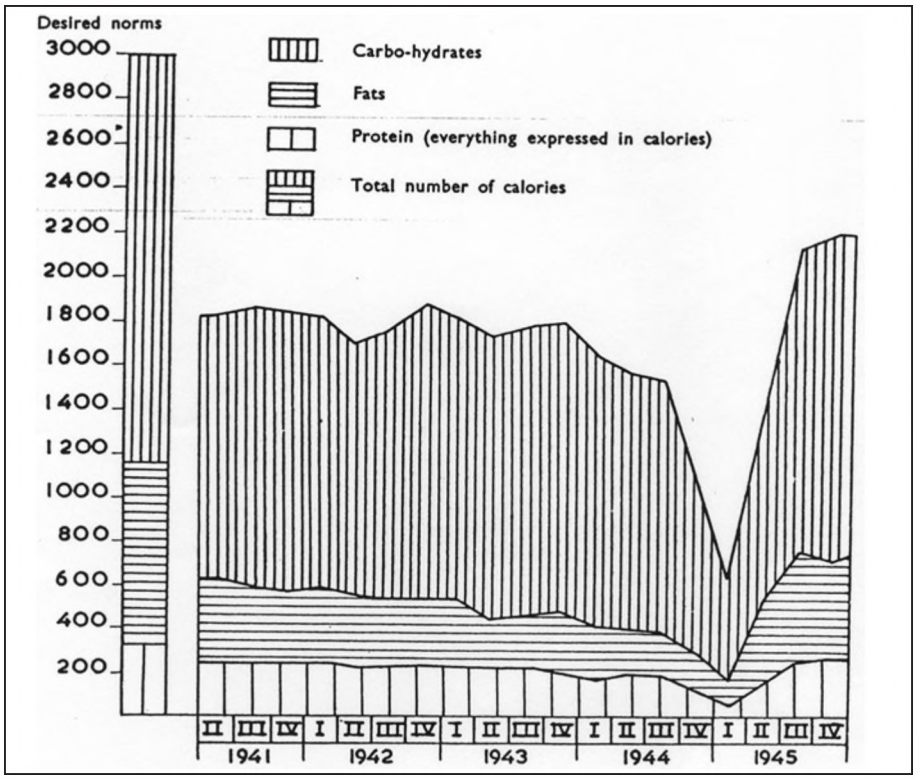

Figure 1. Distributed food rations (calories/day/person) for the Western Netherlands, 1941-1945 (Burger, Drummond and Sandstead 1948).

We here provide a summary of research findings based on the natural experiment that the Dutch famine provided.

Historical setting

The Dutch famine of 1944-45 is known as the "Hunger Winter". During WWII, the country was invaded by the German army in 1940 and remained occupied until 1945. Following the Invasion of Normandy in June 1944, the Allied troops had liberated most of the South of the country by September 1944. The advance came to a halt when supplies became overstretched and the Allies faced newly regrouped German lines at the Waal and Rhine rivers. Crossing these rivers at Arnhem and Nijmegen proved to be 'One bridge too far'. In support of the Allied advance, the Dutch government in exile in London called for a national railway strike to hinder German military transports. In retaliation, the German authorities blocked shipments of all food supplies to the occupied West of the country in October 1944. The population of this area was approximately 4.3 million people, of whom 2.3 million lived in the cities of Amsterdam, Rotterdam, the Hague, Delft, Leiden, Haarlem, and Utrecht.

Despite the war, the general nutrition of the population in the occupied Netherlands had been adequate until October 1944 (Trienekens 2000). Thereafter, food supplies became increasingly scarce in the West although supplementary rations were distributed by the Government. These rations provided the only food source for many people living in the cities in the West. They had fallen to below 1,000 kcal per day by November 26, 1944 however and to 500 kcal per day by April 1945 (Burger, Drummond and Sandstead 1948).

While some people obtained additional food from black markets and from bartering, these supplements were not generally available to most. Widespread starvation followed in the Western Netherlands, with an immediate death toll of over 20,000 (De Jong 1981, Lumey and Van Poppel 1994). The excess deaths were

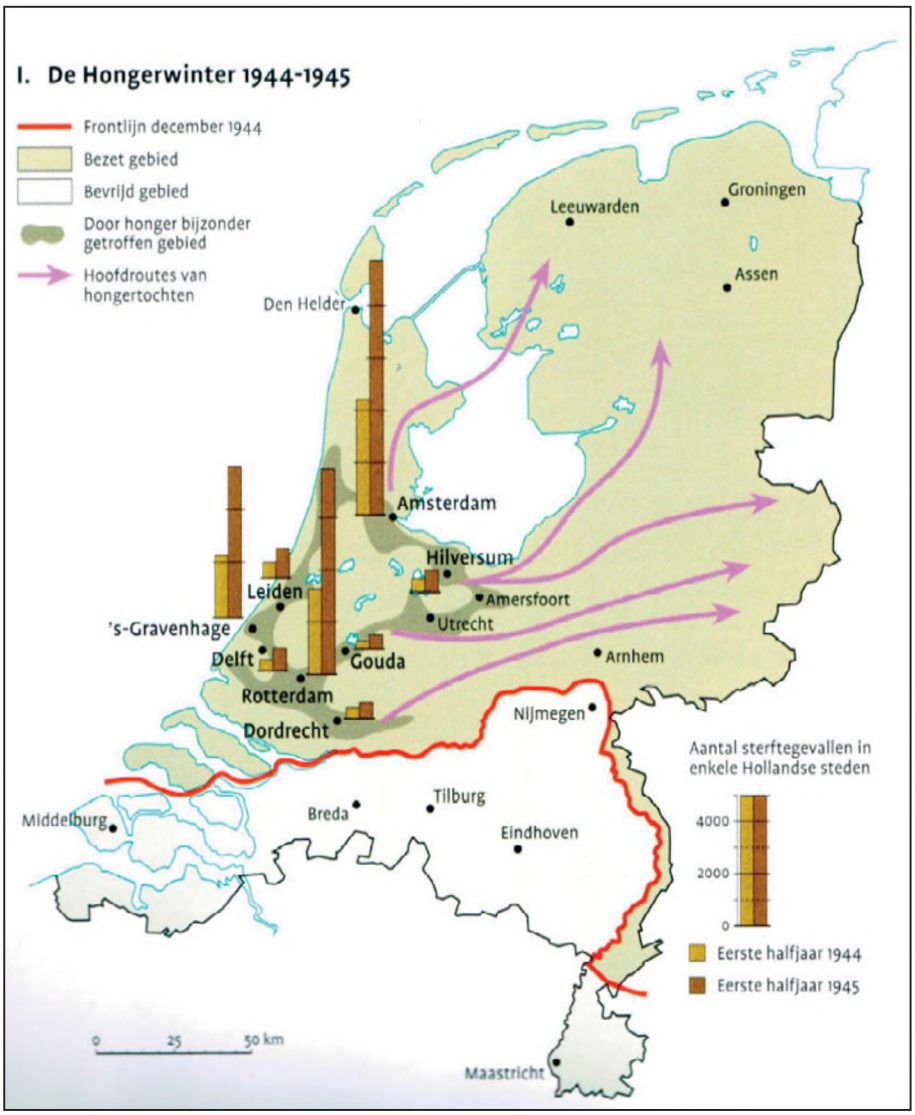

Figure 2. The Hunger Winter of 1944-1945. Map of the Netherlands with estimated number of deaths in selected cities in the Western Netherlands in the first half year of 1944 (pre-famine period; light brown columns) relative to the first half year of 1945 (famine period; dark brown columns) (Bosatlas 2011).

Top left legend translation: Frontlijn december 1944=German-Allied front as per December 1944; Bezet gebied=German occupied area; Bevrijd gebied=Area liberated by Allied forces; Door honger bijzonder getroffen gebied=demarcation of Western Netherlands area that was especially affected by famine; Hoofdroutes van hongertochten=Main food foraging routes from the Western famine area to non-famine areas in the East and North of the country.
Bottom right legend translation: Aantal sterftegevallen in enkele Hollandse steden=death counts in selected cities in Western Netherlands (Amsterdam, Rotterdam,'s-Gravenhage and others), comparing the number of deaths in the first half year of 1944 to the number in first half year of 1945.

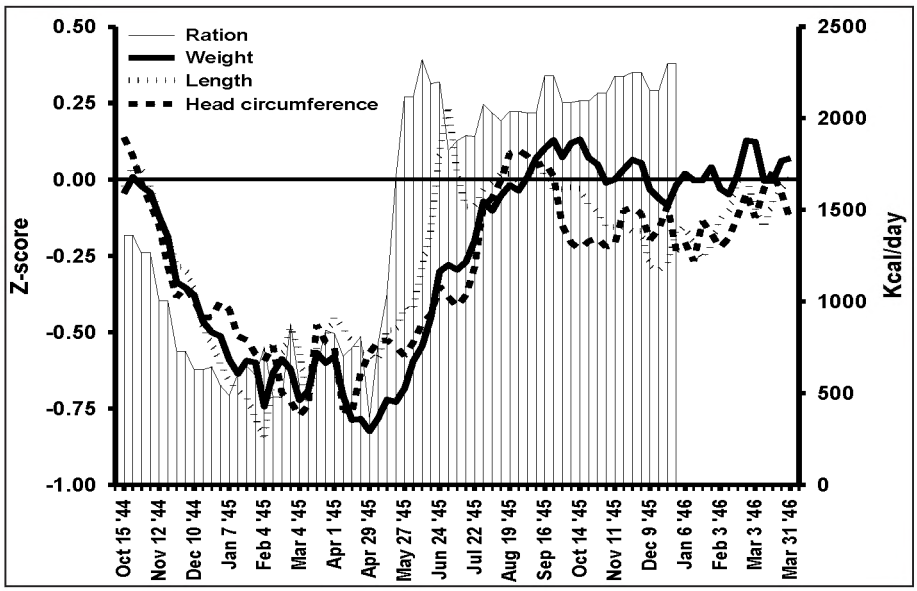

Figure 3. Weekly caloric rations (kcal/day) and averages of z-scored linear measures of weight, length, and head circumference at birth, for births in two clinics in the Western Netherlands, 1944–1946. The reference population (births in 1943) has a mean Z-score of 0 (Stein et al. 2004).

mostly seen in the large cities in the Western Netherlands that could no longer be supplied with food. Supplies were restored very soon after liberation on May 5, 1945.

The famine had a strong impact on size at birth. Infants born at the end of the famine showed a birth weight decrease of about 300 gm (Sindram 1953, Stein and Susser 1975). Together with the birth weight changes there was a decline in length at birth and in head circumference. The decline was only seen in infants exposed to famine during the last trimester of pregnancy. Birth weights recovered immediately after Liberation and infants conceived during the famine and born after the war had normal birth weights again (Stein et al. 2004).

The famine as a natural experiment

The Dutch famine can be investigated as a 'natural experiment'. A large number of individuals in the Western Netherlands were exposed by circumstances beyond their control to increasing levels of starvation. Pregnant women were exposed during different stages of pregnancy. The dates of birth of their infants provide information on the timing of exposure in relation to the stage of gestation. These stages represent potential 'critical periods' for development and long-term health. Possible long-term effects can be evaluated by comparing health outcomes in individuals exposed to prenatal famine with health outcomes in unexposed controls. These controls can comprise individuals born before or after the famine (time controls) or individuals born at the time of the famine but in non-famine areas (place controls). In addition, outcomes can be compared in siblings without famine exposure (sibling controls).

In this setting, there are several ways to define critical exposure periods. Most studies of the Dutch famine define prenatal famine exposure by place and date of birth (Stein et al. 1975). This assumes a gestation of 40 weeks for each pregnancy. Sometimes mothers' reported Last Menstrual Period (LMP) rather than birth weight can be used to estimate the time of conception (Lumey et al. 2007). If LMP is available this can be more helpful for studies of famine exposures during the periconceptional period or very early pregnancy.

In famine studies of individuals with hospital birth records (Lumey et al. 2007) we characterized prenatal famine exposure by determining the gestational ages (in weeks after LMP) during which the mother was exposed to distributed food rations of less than 900 kcal/day. Accordingly, we considered the

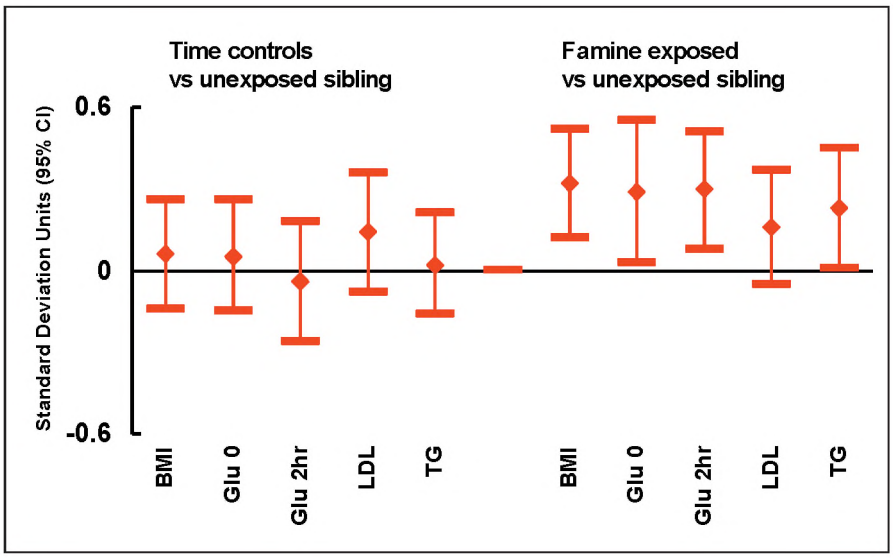

Figure 4. Between sibling outcome differences in Body Mass Index (BMI), fasting Glucose (Glu 0), 2hr Glucose from Glucose Tolerance Test (Glu2 hr), fasting LDL cholesterol (LDL) and Triglycerides (TG), all measured at age ~58 years. Point estimates in Standard Deviation (SD) Units with 95% Confidence Intervals. Left panel: Unexposed time controls vs siblings; Right panel: Famine exposed individuals vs siblings. Data from several studies combined (Stein et al. 2007, Lumey, Stein and Kahn 2009, Lumey 2009).

mother exposed in gestational weeks 1-10, 11-20, 21-30, or 31 to delivery if these gestational time windows were entirely contained within this period. Pregnancies with LMP between 26 November 1944 and 4 March 1945 were thus considered exposed in weeks 1-10; between 18 September 1944 and 24 December 1944 in weeks 11-20; between 10 July 1944 and 15 October 1944 in weeks 21-30; and between 2 May 1944 and 24 August 1944 in weeks 31 to delivery. No individuals were exposed during the entire gestation period.

In famine studies of individuals without birth records, including military conscripts (Ekamper et al. 2014, Ravelli, Stein and Susser 1976, Stein et al. 1972), prenatal famine exposure can only be classified by the date of birth in relation to distributed food rations.

Follow-up studies of clinic populations

As described elsewhere (Lumey et al. 2007), we identified for one study all live-born infants in three clinics in the famine cities Amsterdam, Rotterdam, and Leiden who were born between February 1945 and March 1946. In addition, we sampled births in 1943 and in 1947 in these clinics as unexposed time controls. A current address was obtained by population register tracking and traced individuals were invited to participate in a telephone interview and in a clinical examination, together with a same-sex sibling not exposed to the famine serving as a family-control. We conducted about 1,000 interviews and clinical examinations between 2003 and 2005.

Body size and glucose and lipid metabolism

The study showed an increase in body weight, BMI, and waist circumference after prenatal famine exposure, especially in women (Stein et al. 2007). These findings are in agreement with other studies (Ravelli et al. 1999).

In addition, we found elevated serum levels of fasting and 2hr glucose in a glucose challenge test (Oral Glucose Tolerance Test, OGTT) among famine-exposed subjects compared to unexposed controls and associations with type 2 diabetes (Lumey, Stein and Kahn 2009) and LDL-cholesterol and triglycerides (Lumey 2009). With earlier diabetes findings (Ravelli et al. 1998), several studies in the Netherlands point towards a link between prenatal famine and glucose metabolism. More work is needed however in aggregated data with larger numbers to refine critical exposure windows in pregnancy and to evaluate sex-specific effects.

The impact of prenatal famine on Body Mass Index (BMI), blood glucose levels, LDL-cholesterol

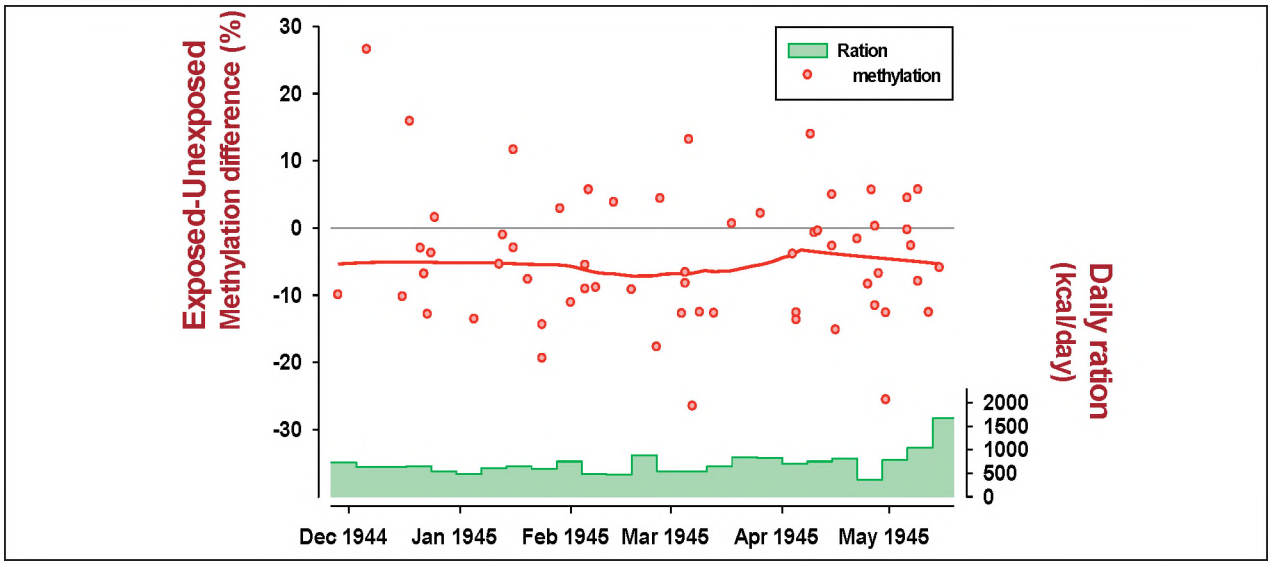

Figure 5. Differences in IGF2 DMR methylation at age ~58 years between individuals prenatally exposed to famine and their same sex siblings. X axis: date of mother's last menstrual period of the famine exposed pregnancy. Each red dot depicts the methylation difference of a same-sex sibling pair comprising a famine exposed individual and its unexposed sibling. To describe the difference in methylation according to estimated conception dates, a smoothed lowess curve (red) is drawn. The average distributed rations (kcal/day) (scaled on Right y-axis) between December 1944 and June 1945 are depicted in green (Heijmans et al. 2008).

and triglycerides is especially clear when the outcomes are contrasted with unexposed sibling controls who took part in the same examination. This comparison shows an adverse famine effect at age ~58 years controlling for maternal genes and early family environment. In the time-controls, born in the famine cities but before or after the war, we see no differences with their unexposed siblings. This is reassuring as neither the time-controls nor the sibling controls were exposed to prenatal famine.

DNA methylation

Gene expression is sensitive to environmental signals. Regulating mechanisms can increase or decrease gene expression depending on environmental conditions at critical phases over the lifecourse. It appears that the pre-natal period may be one of these phases.

We studied the Insulin-like growth factor II (*IGF2*) gene in men and women who had been exposed to famine in early pregnancy or in late pregnancy. The *IGF 2* gene is under epigenetic control and has been used in many studies of growth dysregulation and cancers, some of which show hypo-methylation of this locus.

We selected unexposed same-sex siblings as study controls. For each study pair, comprising an exposed individual with an unexposed sibling control, the outcome of interest was the difference in methylation between the siblings (Heijmans et al. 2008).

In Figure 5, each within pair difference in methylation % is represented by a dot, and the average difference over time is represented by a solid line. Pairs are arranged by mother's last menstrual period in relation to the famine. In individuals exposed to famine early in pregnancy, the average methylation of the gene was 5% lower compared to an unexposed same-sex sibling (Heijmans et al. 2008).

These findings suggest that nutrition very early in life can cause permanent epigenetic changes in humans. Additional studies show that persistent chan-

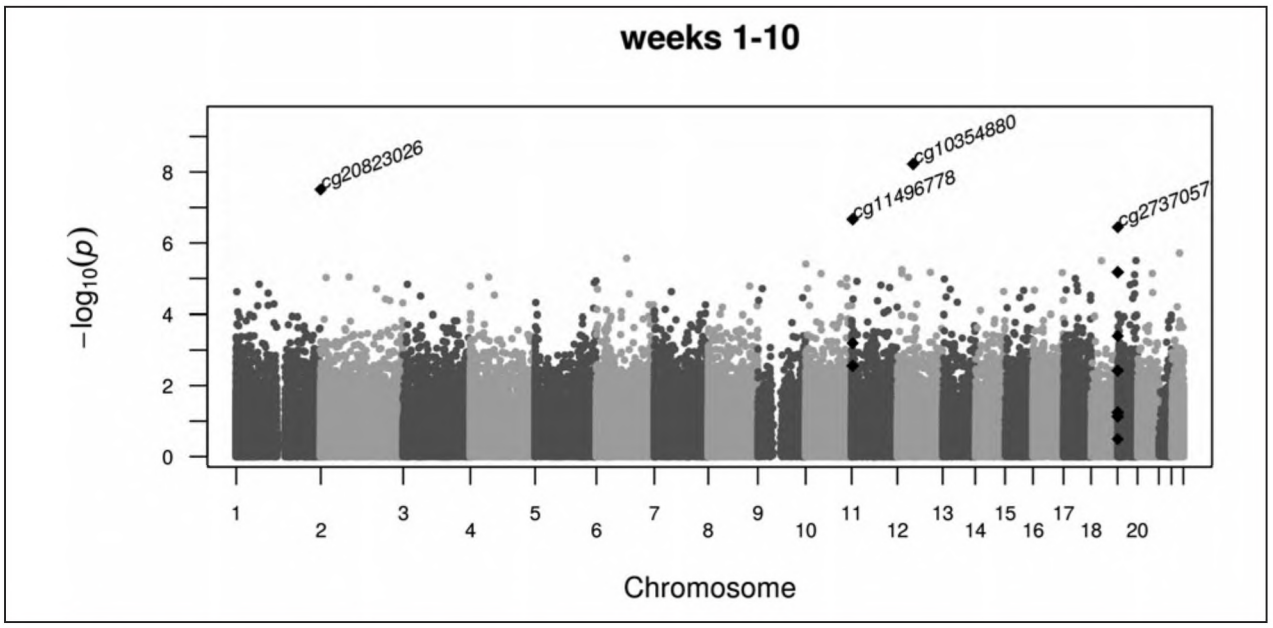

Figure 6. Manhattan plot of specific CpG associations at age ~58 years with prenatal famine exposure during weeks 1-10 of gestation. Shown are the -log10 P-values (y-axis) of the association between DNA methylation at single CpG dinucleotides and famine exposure along the autosomal chromosomes (x-axis). Marked by the CpG dinucleotide identifier are the CpG dinucleotides significant after multiple testing. These and adjacent nominally significant CpG dinucleotides are depicted as black diamonds (Tobi et al. 2015).

ges in DNA methylation elsewhere in the genome may be common, depending on sex and the timing of the exposure (Heijmans et al. 2009, Tobi et al. 2009).

In further studies, with a focus on genomic regions with differential methylation after prenatal famine, we identified specific changes at regions with regulatory potential in the subgroup of individuals with very early famine exposure around the time of conception in relation to their sibling controls (Tobi et al. 2014). Expanding this study to all exposure trimesters, and evaluating genome-wide DNA methylation data generated by the Illumina 450K BeadChip, we established that prenatal famine can affect DNA methylation at specific CpG dinucleotides linked to genes involved in growth, development, and metabolism (Tobi et al. 2015). Interestingly, and of great importance, the changes at the loci were only seen after famine exposure in weeks 1-10 of gestation, and not after exposure in any of the other gestation weeks.

Mortality among military conscripts

30 years ago, investigators had explored the relation between prenatal famine and health measures in young adults, using the health examinations from over 400,000 Dutch men tested for military service at age 18 years. It turned out that prenatal famine was not associated with intelligence scores (Stein et al. 1972), but the men exposed to famine in early and mid-gestation did show a weight increase at the upper end of the scale compared to unexposed controls (Ravelli, Stein and Susser 1976).

Because all men in the Netherlands of the birth cohorts 1944-1946 were examined for military service, these records provide information on the entire surviving male population and the large numbers needed for reliable effect estimates.

There was also an increased risk of schizophrenia in this study population among births conceived at the height of the famine (Susser et al. 1996). The schizophrenia findings were later replicated in studies ba-

sed on the Chinese famine of 1959-1961 (St Clair et al. 2005, Xu et al. 2009).

As the conscripts grew older, there was increasing interest in evaluating the impact of prenatal famine on mortality. From the conscript records, we selected for further study the subgroup of approximately 25,000 men who had been born at the time of the famine in six affected cities in the Western Netherlands together with 10,000 unexposed time controls born before or after the famine in the same cities and 10,000 place controls born outside the famine region. These men were followed from age 18 through the national population and death records to study time and cause of death in relation to the timing of prenatal famine exposure.

We found a 10% increase in mortality after famine exposure in early gestation but not in middle or late gestation, even after adjustment for social class, education at age 18, or other risk factors at that age for later mortality (Ekamper et al. 2014).

These findings again suggest that the timing of famine exposure in relation to the stage of pregnancy is critical for later health.

Looking at the causes of death, we documented close to 2,000 deaths from cancers, 1,000 from heart diseases, 1,400 from other natural causes and 500 from external causes after more than 1,8 million person-years of follow-up. We found no increase in the mortality from cancers or cardiovascular disease after prenatal famine exposure during any stage of gestation. There was a 20-40% increase however in mortality from the combined other natural causes or from external causes such as reported suicides and accidents after famine exposure in the first trimester of gestation (Ekamper et al. 2015). The number of deaths in these subgroups is still too small however for analysis by stage of gestation. Further follow-up of these cohorts is therefore needed, as most men are still alive and a longer observation period will provide more accurate estimates for deaths from specific causes with larger numbers.

Conclusions

1. The setting of the Dutch famine offers special opportunities to study the relation between prenatal nutrition and adult disease and to address specific questions about fetal programming.

2. Even under extreme famine conditions, birth size and body proportions vary only with exposure to famine at the end of gestation and not with exposure at the beginning of gestation. In general, birth size or body proportions should therefore not be used as a marker of pregnancy nutrition in the study of adult disease.

3. Clinical examinations conducted ~60 years after the famine show unhealthy changes in weight, BMI, and glucose, LDL-cholesterol and triglyceride serum levels after prenatal famine exposure. These differences hold when the health examinations of famine exposed individuals are compared with their unexposed siblings, controlling for maternal genes and early family environment. The number of individuals with clinic examinations in separate studies is still too small to examine the impact of early, mid. and late gestation exposure with confidence.

4. Epigenetic studies indicate that the early gestation period and not middle or late gestation is the critical time-window during which the fetal environment may affect the human blood methylome in adults. The functional implications of these findings need further exploration.

5. Mortality studies of conscripts with prenatal famine show an increased mortality from 18-63 years in men exposed in early gestation but not in men exposed in mid or late gestation. This again points to a specific sensitive period of early gestation for later health effects.

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