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Survival effects of prenatal famine exposure


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ABSTRACT

Background
Adverse intrauterine conditions are known to be associated with an increased risk of chronic diseases in adult life. Previously, we showed that prenatal famine exposure increased the incidence of cardiovascular and metabolic disease in adulthood.

Objective
We examined the association between prenatal famine exposure and adult mortality.

Design
We studied adult mortality among 1,991 term singletons from the Dutch Famine Birth Cohort. We compared overall and cause-specific adult mortality among people exposed to famine in late, mid, and early gestation with those unexposed to famine in utero by using Cox proportional hazard models.

Results
A total of 206 persons (10%) had died by the end of follow-up. Compared with unexposed women, women exposed to famine in early gestation had a significantly higher risk of overall adult mortality (HR: 1.9, 95% CI: 1.1 to 3.4), cardiovascular mortality (HR: 4.6, 95% CI: 1.2 to 17.7), cancer mortality (HR: 2.3, 95% CI: 1.1 to 4.7), and breast cancer mortality (HR: 8.3, 95% CI: 1.1 to 63.0). In men exposed to famine in early gestation, these associations were as follows compared with unexposed men: overall adult mortality (HR: 0.4, 95% CI: 0.2 to 1.1), cardiovascular mortality (HR: 0.9, 95% CI: 0.3 to 3.1), and cancer mortality (HR: 0.3, 95% CI: 0.0 to 1.9).

Conclusions
Women exposed to famine in early gestation had a higher overall adult, cardiovascular, cancer, and breast cancer mortality risk than did women not exposed to famine. No such effects were observed in men exposed to famine in early gestation.
INTRODUCTION

Maternal undernutrition during pregnancy can cause an imbalance between fetal demands and nutrient supply resulting in fetal undernutrition. In response to undernutrition, the structure and function of many key organs change in the fetus. In the short-term, these adaptations may be beneficial for fetal survival. In the long-term these changes have consequences for the physiology and structure of the key organs, which eventually leads to the development of chronic diseases in adult life. In total, this mechanism is known as fetal programming.

Experiments in animals have shown that maternal undernutrition during gestation reduces offspring lifespan. In humans, associations between maternal gestational undernutrition and offspring lifespan are less well studied. A study in three Gambian villages showed that people born during the ‘wet’ (hungry) season are ten times more likely to die prematurely as are people born during the ‘dry’ (harvest) season. Most of these deaths were due to infectious diseases. Comparable studies among Bangladeshi and Senegalese populations could not replicate these findings. A Finnish study examining the effects of prenatal famine exposure also found no evidence of increased adult mortality. Other studies examined the association between body size at birth, as a marker of adverse intrauterine conditions, and adult mortality. These studies showed that the associations between body size at birth and adult mortality differ between the two sexes.

The Dutch famine may be considered a historical ‘natural experiment’, which gave us the unique possibility to study the long-term effects of environmentally imposed adverse intrauterine conditions on adult mortality. Previously, we reported on associations between prenatal undernutrition and an increased incidence of chronic diseases in later life among people born around the time of the Dutch famine. People conceived during the famine had a twofold increase in coronary artery disease compared with people not exposed to famine in utero. Women exposed to prenatal famine more often reported a history of breast cancer than did unexposed women (HR: 2.6). However, we did not detect an association with adult mortality. A practical limitation was that the members of the Dutch Famine Birth Cohort were then only 57 years of age and were likely too young for meaningful analysis of adult mortality. However, it is important to note that, although indicated by non-experimental studies such as the Hertfordshire cohort, ‘experimental’ evidence on the association in humans between prenatal undernutrition and adult mortality in offspring is currently lacking. Therefore, we evaluated the effects of prenatal famine exposure on overall and cause-specific adult mortality using extended follow-up. Because there are indications that the associations between adverse intrauterine conditions and adult mortality differ between the two sexes, we examined men and women separately.
SUBJECTS AND METHODS

Selection procedures
The Dutch Famine Birth Cohort consists of 2,414 term singletons born alive in the Wilhelmina Gasthuis in Amsterdam between 1 November 1943 and 28 February 1947. Medical birth records have been preserved, providing information about the mother, the course of the pregnancy, and the size of the infant at birth. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of the Academic Medical Center. We excluded 160 infants (6.6%) from the analysis because they were not registered as newborns in Amsterdam. Because mortality up to the age of 18 years has been described elsewhere, we have reported on adult mortality only. Of the remaining 2,254 cohort members, 1,991 (88%) persons were available for follow-up at the age of 18 years.

Causes of death until 31 December 2007 were provided by linking the cohort with Statistics Netherlands. They were coded according to the International Classification of Diseases (ICD) coding system used at the time of death. From 1996 onward, the International Classification of Diseases, 10th Revision (ICD-10) was used. Corresponding to our previous analyses, we categorized the primary cause of death into the following subgroups: infections (ICD-10 codes: A00-B99), cardiovascular disease (ICD-10 codes: I10-I15, I20-I25, I30-I52, and I60-I69), cancer (ICD-10 codes: C00-D48) and others or unknown cause of death.

Famine exposure
The Dutch famine was a six-month period of severe food shortage in the West of the Netherlands during the last winter of World War II. Famine exposure was defined according to the official daily food rations for the general population older than 21 years. These rations decreased gradually from about 1,800 kcal in December 1943 to about 1,400 kcal in October 1944 and fell abruptly to below 1,000 kcal in late November 1944. At the height of the famine, between December 1944 and April 1945, the official daily rations in Amsterdam were between 400 and 800 kcal. On 5 May 1945, the Netherlands was liberated. The food situation improved rapidly and rations had risen above 2,000 kcal per day by June 1945.

An individual was considered to be prenatally exposed to famine if the average daily food ration of the mother during any 13-week period of gestation contained less than 1,000 kcal. On the basis of this definition, infants born between 7 January 1945 and 8 December 1945 were considered to be exposed to famine in utero. According to the date of birth, we defined the trimester of pregnancy in which each cohort member was exposed to famine. Therefore, we delineated periods of 16
weeks each to distinguish among infants exposed in late gestation (born between 7 January and 28 April 1945), in mid gestation (born between 29 April and 18 August 1945), and in early gestation (born between 19 August and 8 December 1945). Cohort members born between 1 November 1943 and 6 January 1945 (born before the famine) and between 9 December 1945 and 28 February 1947 (conceived after the famine) were considered to be unexposed to famine in utero (Figure 1).

![Figure 1](image-url)

**Figure 1** Schematic figure of the delineation between those who were unexposed to famine (born before and conceived after the famine) and those who were prenatally exposed to famine during different gestational periods (late, mid, and early gestation) according to date of birth of the members of the Dutch Famine Birth Cohort.

**Statistical methods**

We constructed Kaplan-Meier survival curves as a function of age for the groups unexposed to famine and those exposed to famine in late, mid, and early gestation. We used Cox proportional hazard regression models to explore the effect of famine exposure on overall and cause-specific cumulative adult mortality (>18 years). Follow-up time was defined as the time from date of birth to death or censoring. The survival times of subjects who had emigrated, who did not consent to their address being made available for the study, who had an unknown place of residence, and who could not be linked to the national deaths register were censored at the date at which the municipal registry had provided information about their status. Subjects who were still alive at the end of follow-up were censored on 31 December 2007. The date of emigration was missing for 22 persons who had emigrated before 1996. For these people, the mean age of emigration was imputed (19 years). To assess whether the associations differed between sexes, we tested for interaction by introducing the cross-products of famine exposure and sex into the model. All analyses were adjusted for date of birth. We additionally adjusted for birth weight and length in
a subsequent model, because small birth size is possibly an intermediate variable linking prenatal undernutrition to adult mortality. We evaluated the proportionality of the hazards over time with 
log minus log plots. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI).

We performed all statistical analyses with SPSS 14.0 (SPSS, Chicago, IL, USA). P-values were based on two-sided tests with a cut-off level for statistical significance of 0.05.

RESULTS

From age 18 years onward, 1,991 persons were available for follow-up, of whom 206 (10%) had died by the end of follow-up in 2007 (Table 1). A total of 444 (22%) subjects were lost to follow-up, and 1,341 (67%) subjects were alive at the end of follow-up. In our study group, 683 (34%) persons had been exposed to famine prenatally. The overall adult mortality rate among those at risk at age 18 years was 10% (206 of 1,991). Mortality was 11% (139 of 1,308) for those who were unexposed to famine in utero, 10% (25 of 251) for those exposed to famine in late gestation, 8.9% (22 of 248) for those exposed to famine in mid gestation, and 11% (20 of 184) for those exposed to famine in early gestation. Overall adult mortality was higher in men than in women (12.2% compared with 8.5%; HR: 1.5, 95% CI: 1.1 to 2.0). A total of 46 deaths were due to cardiovascular disease (22%), and 93 deaths were due to cancer (45%) (Table 1).

Overall effects

In both sexes combined, the risk of overall adult, cardiovascular, and cancer mortality among those born before the famine did not differ from the risk in cohort members conceived after the famine (all \(P > 0.2\)). Therefore, in further analyses, the famine exposure groups were compared with one pooled control group of people who had not been prenatally exposed to famine. This group consists of cohort members born before the famine and those conceived after the famine.

In both sexes combined, we did not observe statistically significant associations between famine exposure in general and overall adult mortality \((P > 0.3)\), cardiovascular mortality \((P > 0.3)\), or cancer mortality \((P > 0.4)\). We found no associations between famine exposure during any stage of gestation and overall adult mortality, cardiovascular mortality, or cancer mortality (data not shown).

We observed a statistically significant interaction between the effects of sex and famine exposure on overall adult mortality and cancer mortality for men and women exposed to famine in early gestation compared with the control group, which had not been exposed to famine in utero \((P\text{-interaction} = 0.01\text{ for overall adult mortality and} 0.04\text{ for cancer mortality})\).
TABLE 1  Mortality among women and men between 18 and 64 years of age according to the time of exposure to famine.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Early</td>
<td>Mid</td>
<td>Late</td>
<td>Total</td>
<td>None</td>
<td>Early</td>
<td>Mid</td>
</tr>
<tr>
<td>At birth (n)</td>
<td>708</td>
<td>109</td>
<td>150</td>
<td>158</td>
<td>768</td>
<td>96</td>
<td>128</td>
<td>137</td>
</tr>
<tr>
<td>At risk at age 18 years [% at birth]</td>
<td>633 (89)</td>
<td>99 (91)</td>
<td>132 (88)</td>
<td>138 (87)</td>
<td>675 (88)</td>
<td>85 (89)</td>
<td>116 (91)</td>
<td>113 (82)</td>
</tr>
<tr>
<td>Total accumulated observation time (years)</td>
<td>35,944</td>
<td>5,620</td>
<td>7,778</td>
<td>8,181</td>
<td>38,476</td>
<td>4,903</td>
<td>6,434</td>
<td>6,625</td>
</tr>
<tr>
<td>Overall adult mortality [% at risk at age 18 years]</td>
<td>53 (8)</td>
<td>15 (15)</td>
<td>6 (5)</td>
<td>11 (8)</td>
<td>86 (13)</td>
<td>5 (8)</td>
<td>16 (14)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Cardiovascular mortality (n)</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>23</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cancer mortality (n)</td>
<td>28</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>31</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Other/unknown mortality (n)</td>
<td>17</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>32</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>
Sex-specific effects: women
The date of birth-adjusted effects of famine exposure in late, mid, and early gestation on overall adult mortality, cardiovascular mortality, and cancer mortality in both sexes and on breast cancer mortality in women are shown in Table 2. Among women, we found that famine exposure in early gestation was associated with a significantly increased risk of overall adult mortality, cardiovascular mortality, cancer mortality, and breast cancer mortality. We found no associations between famine exposure during late and mid gestation and overall, cardiovascular, cancer, and breast cancer mortality among women. The additional inclusion of birth weight and birth length produced similar results (data not shown).

Sex-specific effects: men
We found that overall adult mortality was lower in men exposed to famine in early gestation than in men unexposed to famine in utero, although this effect was not statistically significant (Table 2). We did not observe statistically significant associations between famine exposure during any stage of gestation and cardiovascular and cancer mortality in men (Table 2). The additional inclusion of birth weight and birth length produced similar results (data not shown).
TABLE 2  
Date of birth-adjusted overall, cardiovascular, cancer, and breast cancer mortality expressed as HRs (95% CIs) for women and men aged between 18 and 64 years for those exposed to famine compared with those unexposed to famine*.

<table>
<thead>
<tr>
<th>Cause of mortality</th>
<th>Gestational famine exposure</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (HR 95% CI)</td>
<td>P-value</td>
<td>n (dead)</td>
<td>Mid (HR 95% CI)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall adult</td>
<td>1.9 (1.1 to 3.4)</td>
<td>0.03</td>
<td>15</td>
<td>0.5 (0.2 to 1.1)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4.6 (1.2 to 17.7)</td>
<td>0.03</td>
<td>4</td>
<td>0.6 (0.1 to 5.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.3 (1.1 to 4.7)</td>
<td>0.03</td>
<td>10</td>
<td>0.5 (0.1 to 1.5)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8.3 (1.1 to 63.0)</td>
<td>0.04</td>
<td>3</td>
<td>1.5 (0.1 to 16.6)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall adult</td>
<td>0.4 (0.2 to 1.1)</td>
<td>0.08</td>
<td>5</td>
<td>1.1 (0.7 to 1.9)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.9 (0.3 to 3.1)</td>
<td>0.90</td>
<td>3</td>
<td>0.8 (0.2 to 2.7)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.3 (0.0 to 1.9)</td>
<td>0.19</td>
<td>1</td>
<td>1.2 (0.5 to 3.0)</td>
</tr>
</tbody>
</table>

* Differences between the famine exposed and unexposed groups were tested by Cox proportional hazard regression models.
† Numbers were too small for meaningful analysis.
DISCUSSION

We found that in women, but not in men, famine exposure in early gestation was associated with a significantly increased risk of overall adult mortality, cardiovascular, cancer, and breast cancer mortality compared with that in unexposed women. Among men, famine exposure in early gestation was associated with a lower risk of overall adult mortality than was non-exposure, although this effect was not statistically significant.

Before further discussion, some aspects of our study require consideration. The Dutch famine is a ‘natural experiment’ in history, which provides the unique opportunity to study the long-term effects of prenatal undernutrition on adult mortality in humans. Because the Dutch famine is well described, we were able to use detailed information about the type and degree of nutritional deprivation instead of using measures of body size at birth as a marker of adverse intrauterine conditions. However, we do not have individual data on famine exposure, but rather classified famine exposure according to date of birth. Because we only included people born in Amsterdam, a city that was severely struck by the famine, we believe that misclassification of famine exposure was limited. Furthermore, this misclassification would have resulted in an underestimation of the true associations.

During the war, people were referred to deliver in hospital ‘on social indication’, mostly if no heating or hot water was available at home. As a result, a relatively high proportion of mothers from lower and middle social economic backgrounds delivered in the Wilhelmina Gasthuis. In the current study we were not able to adjust for socioeconomic status because of the large number of missing data. However, previous studies in a subgroup of the Dutch Famine Birth Cohort found no significant differences in socioeconomic status between the different exposure groups, and adjustment for socioeconomic status at birth and adulthood did not alter the effects of prenatal famine exposure on later health. Therefore, we consider it unlikely that socioeconomic status affected our findings.

Because we studied the effects of famine exposure during different periods of gestation, there was a date of birth range of approximately 3.5 years in the cohort members. Because of this narrow range, we consider it unlikely that our findings were due to changes in health care, including the detection and treatment of diseases. Moreover, date of birth adjustment did not explain our findings.
The results for women agree with previous findings of increased morbidity in the Dutch Famine Birth Cohort. Earlier analyses showed that the risk of breast cancer in women exposed to famine in early gestation was fivefold that of unexposed women\textsuperscript{23}. Our current results indicate that breast cancer mortality is also higher in these women. Furthermore, people exposed to famine in early gestation were previously shown to have a higher prevalence of coronary artery disease\textsuperscript{27} and its biological risk factors\textsuperscript{20,21,28}. In contrast with the increased cardiovascular morbidity in both men and women, cardiovascular mortality was only higher among women exposed to famine in early gestation.

The finding of a higher adult mortality rate in women exposed to famine in early gestation is consistent with the theory of life history regulation, which postulates that body maintenance and fertility are mutually balanced\textsuperscript{29,30}. As a result, increased investment in one of these traits is traded-off by a reduction in investment in the other trait\textsuperscript{29,30}. The interrelation between longevity and reproductive success has not only been shown in non-human species, such as \textit{Drosophila melanogaster}, but also in humans by using a historical data set from the British aristocracy\textsuperscript{31}. In a previous study among people from the Dutch Famine Birth Cohort we showed an increase in reproductive success among women exposed to famine in early gestation\textsuperscript{32}. According to the theory of life history regulation, the investment in body maintenance would be reduced, yielding increased adult morbidity and adult mortality.

Among men, famine exposure in early gestation was associated with a decrease in overall adult mortality, although it was not statistically significant. Cancer mortality also seemed to be lower in men exposed to famine in early gestation, which might explain the decrease in overall adult mortality. Famine exposure during late and mid gestation was not associated with an increase in overall adult mortality, cardiovascular, or cancer mortality. The association between famine exposure in early gestation and a decrease in overall adult mortality is in contrast with previous findings of increased morbidity in both men and women exposed to famine in early gestation. Our results suggest that the increased morbidity in people exposed to famine in early gestation only leads to a concomitant increased mortality among women; this may not be the case in men. Previously, we reported that the number of boys born during the famine decreased in relation to the number of girls\textsuperscript{20}. This might explain the lower overall adult mortality among famine exposed men, because the surviving boys may represent a more robust population with a better prognosis of disease. Furthermore, similar associations between adverse intrauterine conditions and decreased cancer mortality in men have been observed in other studies\textsuperscript{15,14}. Lower birth weight, as a marker of adverse intrauterine conditions, was found to be associated with decreased cancer mortality among men, but not among women\textsuperscript{15,14}.
The association between maternal undernutrition and lifespan has also been studied in animal experiments. These studies have shown that intrauterine exposure to a maternal low protein diet can reduce longevity, especially in animals with a rapid catch-up growth in early postnatal life\textsuperscript{7-10}. These experiments were inconclusive about whether this association is limited to female or male animals\textsuperscript{6-10}.

A few studies in humans have examined the effects of prenatal famine exposure on adult mortality. In contrast with the results of our study, a Finnish and Chinese study found no effects of famine exposure in early life on mortality in later life\textsuperscript{14,33}. Studies among Bangladeshi and Senegalese populations were unable to show effects of prenatal famine exposure on adult mortality\textsuperscript{12,13}. However, those studies examined the effects of prenatal undernutrition superimposed on chronic malnutrition. In contrast, the Dutch famine was a relatively short (six months) period of acute and severe undernutrition, which occurred in a previously and subsequently well-nourished population. Therefore, some of our findings may be due to catch-up growth in early postnatal life, which might be absent in chronically malnourished populations. Food rations returned to adequate levels within weeks after the famine, which made an early postnatal catch-up growth effect likely. Animal studies have shown that maternal undernutrition reduces the lifespan of the offspring, especially in animals that experienced early postnatal catch-up growth\textsuperscript{7-10}. In a Gambian study, adult mortality was mainly due to infectious diseases, whereas adult mortality in the Netherlands was mainly due to cardiovascular diseases and cancer\textsuperscript{11}.

In summary, this study provides the first direct evidence that famine exposure in early gestation in women results in increased overall adult, cardiovascular, cancer, and breast cancer mortality compared with mortality in unexposed women. These results agree with the findings of animal studies and with our previous findings among people exposed to famine in utero. These findings also confirm our previous observation\textsuperscript{32} that the balance in phenotypic traits underpinning life history regulation may be set by the environmental conditions during fetal development, at least in women.

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