The role of prenatal factors in cognitive decline and dementia

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CHAPTER 6

WOMEN EXPOSED TO FAMINE IN EARLY GESTATION HAVE INCREASED MORTALITY UP TO AGE 76 YEARS

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ABSTRACT

Introduction

We have previously shown that exposure to famine in early gestation was associated with poorer adult health and, in women, with reduced survival up to age 64. Our recent findings of accelerated aging in both men and women exposed to famine in early gestation, may, in addition to their increased disease risk, suggest an increased risk of mortality in both sexes at older ages. Here, we explore the association between prenatal famine exposure and mortality up to age 76 for men and women separately.

Methods

We studied adult mortality (>18 y) in men (n=989) and women (n=1002) born as term singletons around the time of the 1944-45 Dutch famine. We compared overall and cause-specific mortality among men and women exposed to famine in late, mid or early gestation to that among unexposed persons (born before or conceived after the famine) using Cox regression.

Results

In total 500 persons (25.1%) had died after age 18. Women exposed to famine in early gestation had higher overall (HR 1.49 [95%CI 1.00 to 2.23]), cancer (HR 2.17 [95%CI 1.32 to 3.58]) and cardiovascular mortality (HR 2.33 [95%CI 0.91 to 5.95]) compared to unexposed women. Mortality rates among men were not different between exposure groups.

Conclusion

This study shows that women, but not men, exposed to famine in early gestation had increased overall, cardiovascular and cancer mortality up to age 76. Although prenatal famine exposure affects adult health of both men and women, it seems to only lead to increased mortality among women.

Keywords: Prenatal famine, Prenatal undernutrition, Survival, Mortality

INTRODUCTION

Adverse conditions in utero, like prenatal undernutrition or fetal growth restriction, may result in poorer health throughout life which may subsequently reduce adult survival. This may be a direct consequence of hampered developmental processes, resulting in permanent changes in organ structure, cell number and gene expression.[1–3] In the short term, these changes may be beneficial for fetal survival. In the long-term, these changes may however have consequences for the physiology and function of key organs, which can eventually lead to the development of chronic diseases and reduced lifespan.[1–3] This phenomenon is known as fetal programming.[1–3]

One critical component for healthy fetal development is the availability of nutrients to the growing fetus. Undernutrition during pregnancy may cause an imbalance between fetal demands and the nutrient supply to the fetus, resulting in fetal undernutrition.[4] Studies in rodents, sheep and nonhuman primates have shown that undernutrition during pregnancy has long-term negative consequences for offspring health.[5–11] These may subsequently lead to increased mortality. In rodents, undernutrition during gestation indeed significantly reduced offspring lifespan.[8–11] A study in mice showed that prenatal undernutrition reduced lifespan by 25%.[11]

During the winter of 1944-45, the western part of the Netherlands was struck by an acute period of severe food scarcity. The circumstances of the 1944-45 Dutch famine were catastrophic, but provided the unique opportunity to study the long-term consequences of prenatal exposure to undernutrition on morbidity.[12] Men and women who were prenatally exposed to the Dutch famine had an increased risk for chronic diseases in later life, especially after exposure in early gestation.[12] Men and women exposed to famine in early gestation had a higher risk and an earlier onset of coronary heart disease in line with a more atherogenic lipid profile.[13–15] Women exposed to famine in early gestation were more centrally obese and had a higher risk for developing breast cancer compared to unexposed women.[16,17] In addition to morbidity, we have also studied mortality after prenatal exposure to the Dutch famine. Children born before or during the famine had higher mortality up to age 18, especially in the first year of life, which was mainly caused by nutritional factors and infection.[18] Up to age 57, we did not detect differences in adult survival between exposure groups.[18,19] However, in a study up to age 64, women exposed to famine in early gestation had higher overall, cardiovascular, cancer, and breast cancer mortality rates compared to women unexposed to the famine.[4] These differences in mortality rates were not observed in men.

In more recent clinical studies in the Dutch famine birth cohort we have found indications of accelerated aging of the brain, as well as more self-perceived cognitive problems in surviving men and women who had been exposed to famine in early gestation.[20–23] These brain and cognitive outcomes may be predictive for future cognitive decline and dementia risk and may suggest accelerated aging in those exposed to famine in early gestation.[24,25] Although increased mortality was previously (up to age 64) not observed in men, we hypothesized that, as a consequence of accelerated aging and elevated disease burden, increased mortality may be present in both men and women exposed to famine in early gestation at older ages. We therefore evaluated the association between prenatal famine exposure and overall and cause-specific adult mortality rate up to age 76 and performed these analyses for men and women separately.

METHODS

Participants

The Dutch famine birth cohort consists of 2414 term singletons born alive in the Wilhelmina Gasthuis (the main teaching hospital in Amsterdam, the Netherlands) between 1 November 1943 and 28 February 1947. We excluded 160 infants (6.6%) from the analysis because they were not registered as newborns in Amsterdam. Mortality up to the age of 18 years has been described elsewhere, therefore, we have reported on adult mortality only.[18] As 263 individuals died or emigrated before the age of 18, 1991 (88%) remaining persons were available for linkage after the age of 18 years.

Famine exposure

The Dutch famine was a 6-month period of severe food shortage that occurred in the western part of the Netherlands towards the end of the Second World War. The cascade of events leading up to the Dutch famine has been described in detail elsewhere.[12] During the Dutch famine food rations dropped steeply, reaching a level below 1000 calories per person on November 26, 1944. After the liberation of the Netherlands in May 1945, the food situation improved relatively quickly. In accordance with previous Dutch famine birth cohort studies, an individual was considered prenatally exposed to famine if the average daily food ration of the mother contained fewer than 1000 kilocalories for at least 13 weeks of gestation.[12] Based on this definition, children born between 7 January 1945 and 8 December 1945 were considered to be exposed to famine in utero. We considered three different 16-week exposure periods: individuals mainly exposed in late gestation (born between January 7 and April 28, 1945), mid-gestation (born between April 29 and August 18, 1945) or early gestation (born between August 19 and December 8, 1945).[12] As children younger than one year of age were

relatively protected against the famine, both individuals born before (born before January 7, 1945) and conceived after the famine (born after December 8, 1945) were considered unexposed and acted as a control group.[26]

Outcome ascertainment

Causes of death until 11 February 2022 were provided by linking the Dutch famine birth cohort with data from Statistics Netherlands. Causes of death were coded according to the International Classification of Diseases (ICD) coding system used at the time of death as previously described.[18] From 1996 onwards, the International Classification of Diseases, 10th Revision (ICD-10) was used. Corresponding to previous analyses[4,18,19], we categorized the primary cause of death into subgroups: infections (ICD-10 codes A00-B99), cardiovascular diseases (ICD-10 codes I10-I15, I20-I25, I30-I52, and I60-I69), cancer (ICD-10 codes C00-D48), and other or unknown cause of death. Due to the small number of deaths due to infection (n=5), we categorized these into the other and unknown cause of death category.

Statistical analysis

We compared general characteristics of those exposed to famine in late, mid or early gestation and those prenatally unexposed using linear and logistic regression. For the analyses, we calculated follow-up time as the time from birth until death or censoring (at the latest 11-02-2022). Age was used as the time variable in Cox regression, thereby accounting for age differences between the groups. Censoring occurred prior to the end of follow-up when participants had emigrated, did not consent to their address being made available, had unknown place of residence or could not be linked to the national deaths register. In these cases, the date at which the municipal registry had provided information about their status was used to construct the follow-up time. 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 y). The rate of overall, cardiovascular and cancer mortality among those born before the famine did not differ from the rate among those conceived after the famine. Therefore, we combined these groups into one control group in the analyses. We created Kaplan-Meier survival curves as a function of age for those exposed to famine in late, mid or early gestation and those unexposed. We used Cox regression to explore the effect of prenatal famine exposure on overall and cause-specific mortality (>18 y). We performed all analyses with STATA (16.1). As we have previously observed sex-specific effects of prenatal famine exposure on survival, we additionally performed all analyses separately for men and women.[4]

In the current study, as prenatal exposure to famine is based on birthdate, age at the end of follow-up was dependent on the exposure group. At the end of the study

(February 2022), those born before the famine were the oldest and those conceived after the famine were the youngest, respectively. Therefore, at the final months of follow-up, those prenatally exposed to famine could only be compared to those born before the famine, as those conceived after the famine had not reached similar ages yet and had therefore been censored. To evaluate if this may have impacted our results, we compared if those born before the famine and those conceived after the famine had similar mortality by age before censoring of those conceived after the famine.

RESULTS

Of the 1,991 individuals available for follow-up, 500 (25.1%) individuals had died by the end of this period (11-02-22). A total of 444 (22.7%) individuals were lost to follow-up, and 1047 (52.6%) individuals were alive at the end of follow-up. In total, 683 (34.3%) participants were considered exposed to famine in utero of whom 251 were exposed to famine in late gestation, 248 in mid gestation and 184 in early gestation.

Individuals exposed to famine in late or mid gestation were lighter at birth and had smaller head circumference compared to those unexposed to famine, whereas those exposed to famine in early gestation had a slightly higher birth weight (Table 1).

In total, 223 individuals had died from cancer (44.6% of all deaths) and 97 individuals had died from cardiovascular causes (19.4% of all deaths), 180 individuals (36.0% of all deaths) had died from other or unknown causes (Table 2). The mortality rate was 24.4% (319 of 1,308) for those unexposed to famine in utero, 25.1% (63 of 251) for those exposed to famine in late gestation, 25.8% (64 of 248) for those exposed to famine in mid gestation and 29.3% (54 of 184) for those exposed to famine in early gestation. Men had higher overall adult mortality compared to women (28.8% compared to 21.5%).

When analyzing both sexes combined, there were no differences in overall mortality between those exposed to the famine in late (HR 0.85 [95%CI 0.65 to 1.12]), mid (HR 0.98 [95%CI 0.75 to 1.28) or early gestation (HR 1.17 [95%CI 0.88 to 1.56]) compared to those who had not been exposed (Figure 1). The rate of cancer and cardiovascular specific mortality did also not differ between exposure groups. Those exposed to famine in late gestation had died less often from other or unknown causes of death compared to unexposed individuals (HR 0.51 [95%CI 0.30 to 0.87]). The mortality rate did not differ between those born before and conceived after the famine.

Among men, we did not observe statistically significant differences in overall mortality after exposure to famine in late (HR 0.85 [95%CI 0.58 to 1.23]), mid (HR 1.12 [95%CI 0.78 to 1.61]) or early gestation (HR 0.95 [95%CI 0.62 to 1.46]) compared to unexposed men, nor any differences for cause-specific mortality (Figure 3). Women exposed to famine in early gestation had higher overall adult mortality (HR 1.49 [95%CI 1.00 to 2.23]; Figure 2), cancer (HR 2.17 [95%CI 1.32 to 3.58]) and cardiovascular mortality rates (HR 2.33 [95%CI 0.91 to 5.95]) compared to unexposed women. There were no significant differences in overall and cause-specific mortality rates of women exposed to famine in mid or late gestation compared to those in unexposed women.

Table 1. Characteristics by prenatal exposure to the Dutch famine.

		Exposure to famine					
	n	**Born before**	**In late gestation**	**In mid gestation**	**In early gestation**	**Conceived after**	**Total**
General characteristics							
N at risk at age 18 y (%)	1991	626	251	248	184	682	1991
Total accumulated observation time	1991	41427	17330	16473	12132	43748	131111
N Women (%)	1991	305 (48.7)	138 (55.0)	132 (53.2)	99 (53.8)	328 (48.1)	1002 (50.3)
Maternal age at birth (SD)	1991	28.7 (6.3)	30.4 (6.8) ***	28.3 (6.3)	27.6 (6.1)	28.0 (6.4) *	28.5 (6.4)
Birth weight (SD)	1991	3382 (457)	3163 (446) ***	3234 (435) ***	3492 (474) *	3425 (486)	3361 (475)
Head circumference (SD)	1976	32.9 (1.6)	32.3 (1.7) ***	32.1 (1.4) ***	32.9 (1.4)	33.2 (1.6) **	32.8 (1.6)

Numbers represent frequencies (%) or means (SD). Asterisks represent *p*-values of linear and logistic regression analyses comparing individuals exposed to famine in early, mid or late gestation to either those unexposed to famine in gestation, or, for individuals born before the famine, compared to individuals conceived after the famine. *<0.05, **<0.01, ***<0.001.

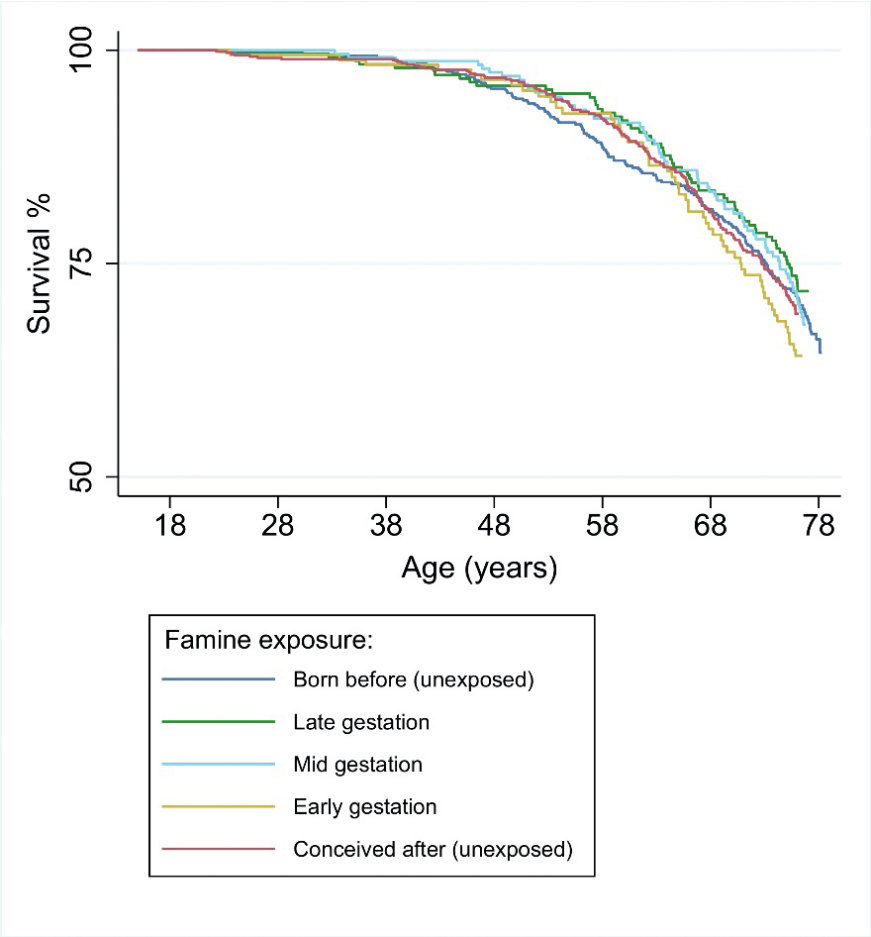

Figure 1. Kaplan-Meier survival curves for individuals born before the famine, exposed mainly in late, mid or early gestation and those conceived after the famine.

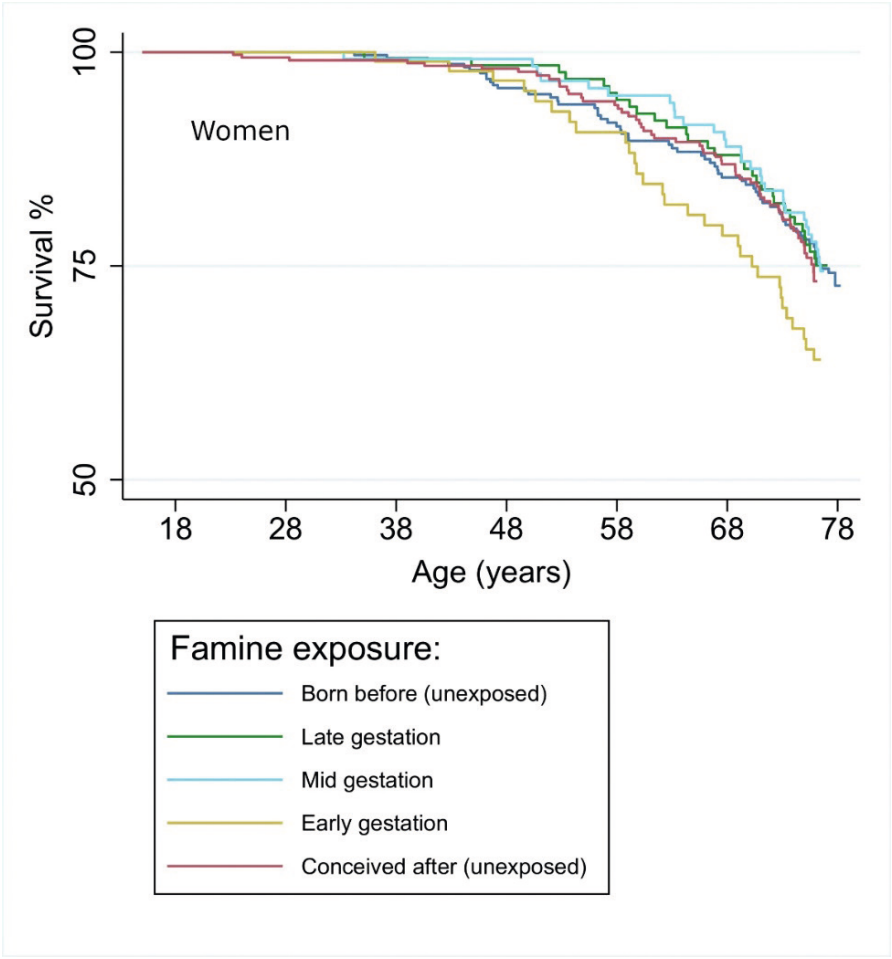

Figure 2. Kaplan-Meier survival curves for women born before the famine, exposed mainly in late, mid or early gestation and those conceived after the famine.

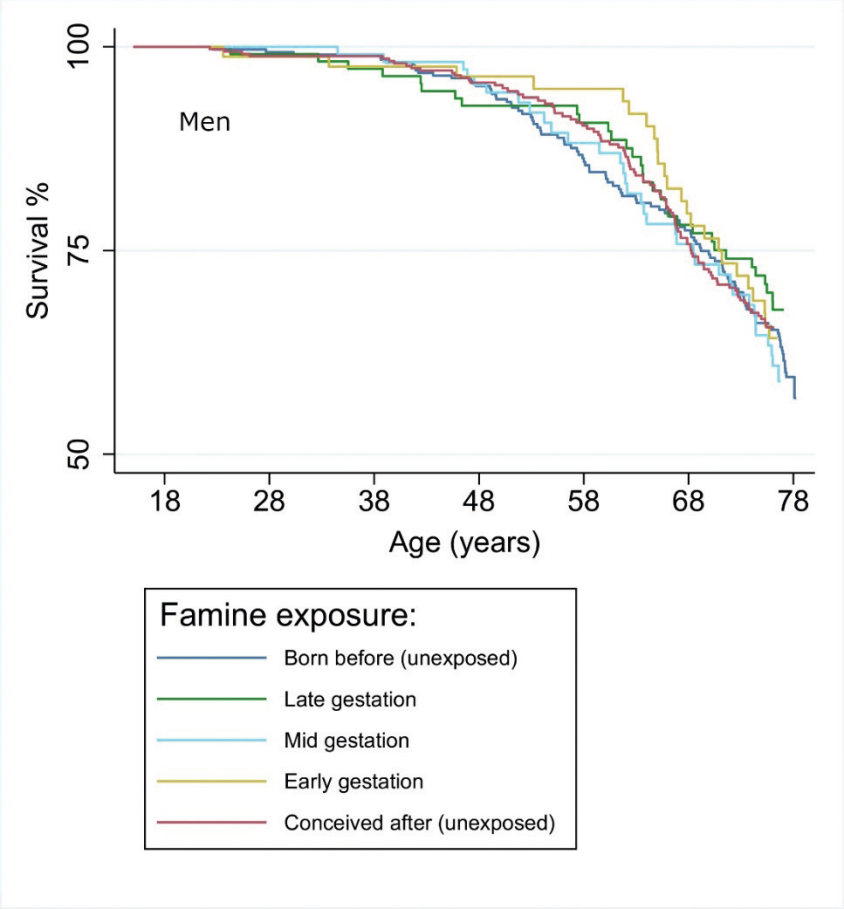

Figure 3. Kaplan-Meier survival curves for men born before the famine, exposed mainly in late, mid or early gestation and those conceived after the famine.

Table 2. Overall, cardiovascular and cancer mortality expressed as HRs (95%CI), for women and men between 18 and 76 years for those exposed to famine in late, mid or early gestation compared to those unexposed (born before and conceived after the famine).

		Prenatal famine exposure				
Cause of mortality	**n**	**Born before**	**Late gestation**	**Mid gestation**	**Early gestation**	**Conceived after**
Overall adult						
N (%)	500 (25.1)	166 (26.5)	63 (25.1)	64 (25.8)	54 (29.3)	153 (22.4)
Hazard ratio (95%CI)		Reference	0.85 (0.65-1.12)	0.98 (0.75-1.28)	1.17 (0.88-1.56)	Reference
Cardiovascular						
N (%)	97 (4.9)	28 (4.5)	12 (4.8)	13 (5.2)	13 (7.1)	31 (4.5)
Hazard ratio (95%CI)		Reference	0.85 (0.46-1.59)	1.05 (0.57-1.91)	1.50 (0.82-2.74)	Reference
Cancer						
N (%)	223 (11.2)	73 (11.7)	36 (14.3)	24 (9.7)	29 (15.8)	61 (8.9)
Hazard ratio (95%CI)		Reference	1.17 (0.81-1.70)	0.87 (0.56-1.35)	1.48 (0.99-2.21)	Reference
Other or unknown cause						
N (%)	180 (9.0)	65 (10.4)	15 (6.0)	27 (10.9)	12 (6.5)	61 (8.9)
Hazard ratio (95%CI)		Reference	0.51 (0.30-0.87)	1.07 (0.70-1.62)	0.67 (0.37-1.22)	Reference
Women						
Overall adult						
N (%)	215 (21.5)	64 (21.0)	31 (22.5)	30 (22.7)	30 (30.3)	60 (18.3)
Hazard ratio (95%CI)		Reference	0.92 (0.62-1.36)	0.93 (0.62-1.39)	1.49 (1.00-2.23)	Reference
Cardiovascular						
N (%)	31 (3.1)	12 (3.9)	3 (2.2)	6 (4.6)	6 (6.1)	4 (1.2)
Hazard ratio (95%CI)		Reference	0.68 (0.20-2.32)	1.41 (0.55-3.62)	2.33 (0.91-5.95)	Reference
Cancer						
N (%)	114 (11.4)	29 (9.5)	21 (15.2)	12 (9.1)	21 (21.2)	31 (9.5)
Hazard ratio (95%CI)		Reference	1.30 (0.79-2.14)	0.78 (0.42-1.45)	2.17 (1.32-3.58)	Reference
Other or unknown cause						
N (%)	70 (7.0)	23 (7.5)	7 (5.1)	12 (9.1)	3 (3.0)	25 (7.6)
Hazard ratio (95%CI)		Reference	0.53 (0.24-1.17)	0.95 (0.50-1.79)	0.38 (0.12-1.22)	Reference

Table 2. (Continued)

		Prenatal famine exposure				
Cause of mortality	**n**	**Born before**	**Late gestation**	**Mid gestation**	**Early gestation**	**Conceived after**
Men						
Overall adult						
N (%)	285 (28.8)	102 (31.8)	32 (28.3)	34 (29.3)	24 (28.2)	93 (26.3)
Hazard ratio (95%CI)		Reference	0.85 (0.58-1.23)	1.12 (0.78-1.61)	0.95 (0.62-1.46)	Reference
Cardiovascular						
N (%)	66 (6.7)	16 (5.0)	9 (8.0)	7 (6.0)	7 (8.2)	27 (7.6)
Hazard ratio (95%CI)		Reference	1.05 (0.51-2.15)	1.00 (0.45-2.22)	1.22 (0.55-2.72)	Reference
Cancer						
N (%)	109 (11.0)	44 (13.7)	15 (13.3)	12 (10.3)	8 (9.4)	30 (8.5)
Hazard ratio (95%CI)		Reference	1.07 (0.61-1.87)	1.04 (0.56-1.91)	0.82 (0.39-1.70)	Reference
Other or unknown cause						
N (%)	110 (11.1)	42 (13.1)	8 (7.1)	15 (12.9)	9 (10.6)	36 (10.2)
Hazard ratio (95%CI)		Reference	0.53 (0.25-1.09)	1.27 (0.73-2.22)	0.94 (0.47-1.88)	Reference

DISCUSSION

Although both men and women exposed to the Dutch famine in early gestation had higher rates of chronic disease and increased rates of aging, we observed increased overall and cardiovascular and cancer mortality among exposed women but not among exposed men. Our findings are in line with our previous observations on mortality up to age 64 and suggest lasting negative consequences of prenatal undernutrition on lifespan in women.

Even though overall mortality was higher in men than in women, which is in line with the general Dutch population, in our current analyses women exposed to famine in early gestation had the highest mortality rates of all male and female groups. Cancer was the largest cause of mortality in the current study and also the largest contributor to excess mortality in women exposed to famine in early gestation. The increased cancer mortality among women exposed to famine in early gestation was not explained by an increase in mortality by any specific cancer type, suggesting an overall increase in mortality from cancer of all types. These findings are in line with the overall greater risk for developing cancer as well as higher cancer mortality observed in both men and women exposed

to the 1959-61 Great Chinese famine during gestation.[27–29] Prenatal undernutrition has been shown to result in epigenetic changes, such as hypomethylation of specific gene promotors.[30] Changes in the epigenetic regulation of genes, for instance genes related to cell division and apoptosis, have been implicated as a causal mechanism in the development of cancer and could be a pathway via which prenatal undernutrition may increase the risk for cancer.[30–32]

In contrast to women, men exposed to famine in early gestation did not have increased mortality compared to unexposed men up to age 76. This was surprising as, similar to women in the Dutch famine birth cohort, men exposed to famine in early gestation did have increased rates of chronic diseases and more signs of accelerated aging compared to unexposed men.[12–15] Although unexpected based on our previous finding in the Dutch famine birth cohort, our findings in men are in line with the results from another study conducted in men who were born in six different cities in the Netherlands that were struck by the Dutch famine, which showed that men who were prenatally exposed to the Dutch famine did not have increased cancer and cardiovascular mortality up to age 63.[33]

Different factors may explain why we did not find indications that prenatal famine exposure in early gestation has not resulted in increased mortality in men (yet). First, there are sex differences in prenatal development.[34,35] Boys grow faster in the womb and are known to have increased risks of perinatal mortality and complications compared to girls. During the famine, slightly fewer boys were born alive compared to before or after the famine, possibly due to better survival chances of female fetuses.[36,37] Due to selective mortality of potentially weaker male fetuses after famine exposure, men born alive after prenatal famine exposure may represent a relatively healthy population and, although they experience negative health consequences of prenatal famine they may have a relatively better prognosis which may explain why we do not observe increased mortality rates in these men (yet). In addition, due to the differences in the prenatal development of men and women, the consequences of prenatal undernutrition may differ between the sexes. We have indeed observed that although men and women both experience negative health consequences of prenatal famine exposure, the precise consequences often differed between the sexes. In men, exposure to famine in early gestation was for instance associated with increased symptoms of depression and anxiety and decreased physical performance scores.[38,39] Furthermore, signs of accelerated brain aging, such as smaller brain size, worse brain perfusion and more self-perceived cognitive problems were mostly found in men.[20–23] On the other hand, women exposed to famine in early gestation had higher body mass index (BMI) and larger waist circumference at age 50 years compared to unexposed women.[34,40] Furthermore, women exposed to famine in early gestation had a higher risk for developing breast

cancer compared to unexposed women.[16,17] Although the precise mechanisms remain unclear, differences in prenatal development as well as differences in adult physiology between men and women may explain the current sex-specific findings. Finally, cardiovascular diseases manifest themselves differently in men and women and due to the gender bias in research the effectiveness of treatments is generally better for men.[41] Women have not been sufficiently represented in clinical trials and continue to experience delays in diagnosis and treatment of cardiovascular diseases. As a consequence, women suffer worse outcomes.[41] Symptoms of myocardial infarction are for instance less well recognized in women, leading to delays in treatment and a worse prognosis.[42] We have previously observed that both men and women had more cardiovascular disease after famine exposure in early gestation, suggesting that the observed sex-differences in cardiovascular mortality are not explained by differences in disease prevalence alone.[13–15] Gender inequities in diagnosis and treatment may have resulted in relatively lower survival of women with cardiovascular disease and this may have amplified the effects of prenatal famine exposure on cardiovascular mortality in women.

To summarize, our findings suggest that although prenatal famine exposure negatively affects health in both men and women, the consequences on morbidity and mortality seem to differ between the sexes. These differences may be due to sex differences in prenatal development, adult physiological differences as well as gender inequities that may exist in society and health care.

Strengths and limitations

Strengths of the current study include the long follow-up time and the use of national registry data to study mortality in the cohort. We were able to follow-up a large proportion of the Dutch famine birth cohort, thereby limiting the risk of selection bias. We made use of a unique cohort based on men and women born around the time of the Dutch famine, which can be classified as a "natural experiment". The Dutch famine was severe, relatively brief and exposure was relatively independent from other factors, thereby limiting the risk of bias and confounding in the current study.

The current study has limitations. First, we were not able to follow 22.3% of included individuals until the end of follow-up due to emigration, unknown place of residence or not being matched to the national deaths register. However, as matching to the national death register occurred around age 50 (and we were able to update these at older ages), these censoring events typically occurred before age 50, therefore we do not expect most of these events to be associated with mortality risk. Therefore, we do not assume censoring to have caused bias. Secondly, we did not have individual data

on famine exposure but based exposure on date of birth. Therefore, misclassification may have occurred. However, Amsterdam was severely struck by the famine and as most people were affected, misclassification of famine exposure was most likely limited. In addition, misclassification would likely result in an underestimation rather than an overestimation of any true associations as those not or only mildly exposed to famine would have been included in the exposed groups as well. Lastly, as described in the methods section, the exposed groups were only compared to those born before the famine at the final stages of follow-up. As mortality incidence did not differ between those born before the famine or conceived after the famine we do not expect this to have introduced bias.

CONCLUSION

This study shows that women – but not men - exposed to famine in early gestation had increased overall, cardiovascular and cancer mortality up to age 76. Although prenatal famine exposure affects health of both men and women in adulthood, it seems to only lead to increased mortality among women.

DECLARATIONS

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Competing interests
The authors have no relevant financial or non-financial interests to disclose.

Author contributions
All authors designed the study. Results are based on calculations by AMW using non-public microdata from Statistics Netherlands. AMW drafted the manuscript and all authors critically reviewed and revised the manuscript.

Ethics approval
The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of the Academic Medical Center.

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