

# Childhood exposure to the 1944–1945 Dutch famine and subsequent female reproductive function

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**BACKGROUND:** Childhood caloric restriction may lead to permanent changes in the hypothalamo–pituitary–gonadal axis, which could lead to impaired female reproductive ability. We assessed the effect of childhood exposure to the 1944–1945 Dutch famine on subsequent female reproductive function. **METHODS:** This was a population-based cohort study in Utrecht, The Netherlands. Between 1983 and 1985, 6030 women born between 1932–1941 were classified by questionnaire according to their famine exposure experiences. Dates of marriage, first and second childbirth, and information on a medical reason for having no children or fewer children than wanted were available from questionnaires, as well as ages and type of menopause. **RESULTS:** Severe famine exposure during childhood significantly decreased chances of first and second childbirth at any given time after marriage or first childbirth [adjusted hazard ratios (HR) 0.86, 95% confidence interval (CI) 0.76–0.96; and HR 0.87, 95% CI 0.78–0.97, respectively]. Risk of a medical reason for having no or fewer children than wanted was increased in the severely exposed (odds ratio 1.88; 95% CI 1.29–2.74), as was the risk of a surgical menopause (HR 1.53; 95% CI 1.27–1.84). **CONCLUSIONS:** Our findings support the presence of longstanding modest effects of childhood famine exposure on reproductive function in women.

*Key words:* caloric restriction/famine/human/reproduction/subfertility

## Introduction

During the 1944–1945 winter, a short but severe famine struck the occupied and densely populated western parts of The Netherlands. This famine evolved from an accumulation of circumstances. In support of an offensive in September 1944 to capture the Rhine bridge at Arnhem and hasten the end of World War II, a Dutch railroad strike was ordered by the Dutch government in exile to thwart German transport of troops and ammunition. As retaliation, the German occupiers responded with a food embargo, most effectively towards the western parts of the country, where the food situation deteriorated rapidly. The offensive failed and from October onwards, average daily rations per capita dropped from about 1500 kilocalories to below 700 kilocalories in January, whereas relative amounts of fats, carbohydrates and proteins remained essentially unchanged. With liberation in May, food supplies became abundant due to Allied intervention, ending the famine abruptly (Burger *et al.*, 1948). The female reproductive system is well known to be affected by undernutrition (Bongaarts, 1980; Warren, 1983; Harlow and Ephross, 1995) and it may not be surprising that the number of births in the Western Netherlands began to fall 9 months after onset of the famine (Stein and Susser, 1975).

Since this famine occurred in an otherwise well nourished population for a clearly demarcated period, it offers the opportunity to study its long-term effects and to pinpoint those effects to specific stages of human development. After birth, the hypothalamo–pituitary–gonadal axis continues to mature until menarche and the first years of menstruation, which tend to be irregular and anovulatory (Harlow and Ephross, 1995). This development is characterized by changes in amplitude and pulsatility of hypothalamic GnRH (Yen *et al.*, 1993; Apter and Hermanson, 2002). In order to establish regular ovulatory cycles, adequate hypothalamic and pituitary function is a prerequisite. Hypothalamic pulsatile secretion of GnRH results in a surge of LH being released from the pituitary. This surge of LH is necessary for ovulation (Filicori *et al.*, 1993). At reproductive ages, underfeeding can change the pattern of GnRH release towards a pre-pubertal state, resulting in menstrual disturbances or amenorrhoea (Warren, 1983). We therefore hypothesize that since GnRH secretion is sensitive to caloric restriction, the latter may also interfere with the maturation of the hypothalamo–pituitary–gonadal axis, leading to menstrual irregularities throughout life. Consequently, since irregular menses are less likely to be ovulatory (Harlow and Ephross, 1995),

the monthly chance of conception would be decreased, in severe cases to an extent of clinical subfertility. Moreover, menstrual disorders can be a reason for hysterectomy (van Hall, 1984), resulting in the premature end of reproductive life. We used data on women exposed at young ages to the 1944–1945 Dutch famine, a cohort in which we previously found the famine to be associated with a decrease in age at natural menopause (Elias *et al.*, 2003), to explore its effect on these parameters.

## Subjects and methods

From June 1983 until July 1985 a questionnaire regarding exposure to the 1944–1945 Dutch famine was sent to 8970 women born between 1932–1941 when they enrolled in the third cohort of the population-based DOM (Diagnostisch Onderzoek Mammacarcinoom) breast cancer screening project in Utrecht, The Netherlands (response 44%) (de Waard *et al.*, 1984).

Women who lived in the occupied parts of The Netherlands during the famine ( $n = 7941$ ) and could be classified according to their degree of famine exposure were eligible for analyses ( $n = 6037$ ). Individual famine exposure status was based on three separate questions on experiences of cold, hunger and weight loss during the famine period (ranked absent, moderate or severe). We considered women to be unexposed or severely exposed if they responded to at least two of these questions with absent or severe exposure, respectively. All remaining women were classified to moderate exposure (Elias *et al.*, 2002).

In this cohort, we determined the effects of famine exposure in childhood on several indicators of subsequent reproductive capability. Ideally, one would measure the probability of conceiving by asking women about the time when they tried to become pregnant. However, this information was unavailable as the data were not obtained specifically for this study, and we therefore chose to use both the time between marriage and first childbirth and the time between first and second childbirth as an alternative. We also assessed the risk of a medical reason for having no or fewer children than wanted. Because a large proportion of the women were premenopausal at recruitment (72%), we used additional questionnaires to assess the risk of surgical menopause. These questionnaires were sent biennially until 1995, at which time 82% of the total cohort had complete follow-up (de Vries *et al.*, 2001). Women reported the cause of menopause, but information on reason for surgery was not available.

### Potential confounders

Several variables differed between famine exposure categories and could be related to fertility: socio-economic status was based on type of health insurance: public health insurance (lower status), civil servants insurance (intermediate status) or private insurance (higher status). Information on highest educational attainment (primary school, vocational training, high school or MSc/BSc) and cigarette smoking habits (ever/never smoker) was available from questionnaires.

### Data analysis

From the study cohort ( $n = 6037$ ), we excluded seven women who had missing data on potential confounding variables. Thereafter, we selected appropriate subcohorts for the various analyses: (i) for time between marriage and first childbirth we selected all married women ( $n = 5762$ ) and excluded those who reported giving birth to their first child ( $n = 780$ ; 18%, 13% and 13% of the severely,

moderately and unexposed women, respectively) or recalled entering menopause ( $n = 6$ ) before marriage or within 32 weeks afterwards (the former were excluded because date of marriage was unlikely to coincide with the start of attempting to get pregnant, and including these women could thus lead to a dilution of any effects due to increased misclassification); (ii) for time between first and second childbirth we selected all parous women ( $n = 5395$ ); (iii) the question regarding a medical reason for having no or fewer children than wanted was asked conditional on wanting to have more children or being nulliparous, which was indicated by 2051 women, from whom we excluded 675 women who answered 'I don't know'; and (iv) the total study cohort could be used to assess the risk for surgical menopause.

To examine the effect of famine on interval between marriage and first childbirth, data were structured for time to event analyses with time coded in weeks from marriage onwards. Each woman contributed to the analysis the time until she either gave birth (event) or was not able to conceive a child due to entering the menopause (censoring event). Follow-up time ended at study recruitment for women who were at that time still premenopausal and nulliparous (censoring event). Data on interval between first and second childbirth were structured similarly. Hazard ratios (HRs) for first and second childbirth between famine exposure categories were estimated with Cox's proportional hazard analyses with 'unexposed' as the reference category. Adjustments were made for age during the famine, socio-economic status at recruitment, highest educational attainment, cigarette smoking habits and age at baseline (age at marriage or age at first childbirth, respectively).

Data on surgical menopause were also analysed with Cox's proportional hazard models as well as with analysis of covariance in order to report adjusted means of menopausal age. For Cox's proportional hazard models, follow-up time in years was coded from famine exposure onwards. Surgical menopause was considered to be an event and all other women were censored at the last reported menstrual cycle. Famine exposure estimates were adjusted for age during the famine and socio-economic status at recruitment. We evaluated the proportionality of the hazards assumption for all variables by log minus log plots, which we found to be justified.

Whether famine exposure is related to the risk of a medical reason for having no or fewer children than wanted was analysed by means of logistic regression. First we assessed the crude odds ratios (ORs) of reporting such a medical reason between famine exposure categories with 'unexposed' as the reference category. Adjustments were made for age during the famine and socio-economic status at recruitment. All models fitted well to the data according to the Hosmer–Lemeshow goodness-of-fit test.

To explore the possibility of modification of the famine exposure effects by age during the famine, we included in the fully adjusted models interaction terms for famine exposure status and subgroups according to age at start of the famine (1 October 1944). These subgroups are based on stages in female development: 2–6 years (early childhood), 7–9 years (middle childhood) and 10–12 years (later childhood) (Bogin, 1999).

Statistical analyses were performed with SPSS 11. Point estimates are given with corresponding 95% confidence intervals (CIs).

## Results

Table I shows the baseline characteristics of the study cohort. In total, 8% reported being severely and 37% being

**Table I.** Selected baseline characteristics according to famine exposure in the total cohort

	Famine exposure [ <i>n</i> (%)]		
	Unexposed	Moderately exposed	Severely exposed
Number of participants <sup>a</sup>	3357 (56)	2216 (37)	457 (8)
Age at time of questionnaire (years) <sup>b</sup>	46 (41–53)	47 (41–53)	48 (42–52)
Age during the famine (years) <sup>b</sup>	7 (2–12)	8 (2–12)	9 (2–12)
Marital status			
Unmarried	143 (4)	103 (5)	22 (5)
Married	3214 (96)	2113 (95)	435 (95)
Socio-economic status			
Lower status	1882 (56)	1330 (60)	287 (63)
Intermediate status	391 (12)	244 (11)	68 (15)
Higher status	1084 (32)	642 (29)	102 (22)
Highest educational attainment			
Primary school	887 (26)	659 (30)	142 (31)
Vocational training	1611 (48)	998 (45)	210 (46)
High school	550 (16)	367 (17)	80 (18)
MSc/BSc	309 (9)	192 (9)	25 (5)
Cigarette smoking status			
Never	1952 (58)	1,229 (55)	223 (49)
Ever	1405 (42)	987 (46)	234 (51)

<sup>a</sup>Percentages may not total 100% due to rounding.

<sup>b</sup>Median (range).

moderately exposed to the famine. Almost all women were married (95%), which did not differ between categories of famine exposure. However, the severely exposed tended to be older during the famine and at study recruitment, and had a lower socio-economic status and educational attainment. Frequency of ever smoking cigarettes was highest in the severely exposed.

Reproductive milestones according to famine exposure status are shown in Table II. Severely famine-exposed women were similar to the unexposed for mean age at menarche, mean age at second childbirth and proportion of childlessness. They generally married younger and gave birth to their first child at younger ages as well, although these differences are very small. After marriage, 93% of women gave birth after an overall median time of 78 weeks. With increasing severity of famine exposure, the chance of first childbirth decreased. At any given time after marriage, severely exposed women were 14% (HR 0.86; 95% CI 0.76–0.96) less likely to give birth to a first child compared with the unexposed women (Table III). Similar effects of famine exposure were found for second childbirth (92% gave birth to a second child after an overall median time of 121 weeks since first childbirth). At any given time, severely famine-exposed women were 13% (HR 0.87; 95% CI 0.78–0.97) less likely to give birth to a second child compared with the unexposed women. We found no indications that the relationship between the famine and time to second childbirth depended on age during the famine. On the other hand, it seemed that

**Table II.** Reproductive milestones according to famine exposure

	Famine exposure		
	Unexposed	Moderately exposed	Severely exposed
Age at menarche (years) <sup>a</sup>	13.6 ± 1.5 <sup>a</sup>	13.6 ± 1.5	13.6 ± 1.6
Age at marriage (years) <sup>a</sup>	24.5 ± 3.7	24.3 ± 3.8	24.1 ± 3.7
Age at first childbirth (years) <sup>a</sup>	26.0 ± 3.6	25.8 ± 3.8	25.5 ± 3.5
Age at second childbirth (years) <sup>a</sup>	28.3 ± 3.5	28.3 ± 3.7	28.2 ± 3.6
Number of live-born children [ <i>n</i> (%)]			
0	335 (10)	244 (11)	52 (11)
1	247 (7)	144 (7)	41 (9)
≥ 2	2775 (83)	1828 (82)	364 (80)

<sup>a</sup>Values are means ± standard deviation.

the relationship between the famine and time to first childbirth became stronger with increasing age during the famine (Table III). These differences in effect between the age groups were, however, small, and accordingly interaction terms were not significant.

Among women who expressed the wish to have more children or who were nulliparous, 35% reported having a medical reason for this. Women with severe famine exposure during childhood were at higher risk of reporting a medical reason compared with the unexposed (OR 1.88; 95% CI 1.29–2.74). Risk for women with moderate famine exposure was also elevated (OR 1.31; 95% CI 1.03–1.66), reflecting a dose–response relationship. Adjustment for socio-economic status and age during the famine did not change these risk estimates.

Previously, we have shown that the famine was associated with a decrease in subsequent age at natural menopause (Elias *et al.*, 2003). Here we find that famine exposure was related to a higher occurrence of surgical menopause. From the total study cohort, 1369 (23%) women reported a surgical menopause. Mean age at surgical menopause, adjusted for age during the famine and socio-economic status, decreased with severity of famine exposure: 43.8 years (95% CI 43.4–44.1) in the unexposed group, 43.1 years (95% CI 42.6–43.5) in the moderately exposed group and 42.6 years (95% CI 41.7–43.6) in the severely exposed group (test of between-subjects effects  $P = 0.022$ ). Compared with the unexposed women, severely exposed women were at increased risk for surgical menopause (HR 1.53; 95% CI 1.27–1.84). Moderate famine exposure was also related to the risk of surgical menopause, but to a lesser extent (HR 1.11; 95% CI 0.99–1.24). These estimates did not change after adjustment for socio-economic status and age during the famine.

We did not find specific time-windows in female prepubertal development in which caloric restriction has a larger impact on the risk for surgical menopause or for having a medical reason for having no or fewer children than wanted (interaction terms non-significant).

**Table III.** Famine and likelihood of conceiving a child after marriage or after birth first child – overall and according to age during the famine

Famine exposure	After marriage <sup>a</sup>		After birth first child <sup>b</sup>	
	Unadjusted HR (95% CI)	Adjusted <sup>c</sup> HR (95% CI)	Unadjusted HR (95% CI)	Adjusted <sup>c</sup> HR (95% CI)
Overall				
Unexposed	1	1	1	1
Moderately exposed	0.94 (0.88–1.00)	0.93 (0.88–0.99)	0.96 (0.91–1.02)	0.97 (0.91–1.03)
Severely exposed	0.87 (0.77–0.98)	0.86 (0.76–0.96)	0.86 (0.77–0.96)	0.87 (0.78–0.97)
Women aged 2–6 years during the famine				
Unexposed	1	1	1	1
Moderately exposed	1.02 (0.92–1.12)	1.00 (0.91–1.10)	1.02 (0.93–1.11)	1.02 (0.93–1.11)
Severely exposed	0.98 (0.79–1.23)	0.94 (0.75–1.17)	0.84 (0.68–1.04)	0.86 (0.69–1.07)
Women aged 7–9 years during the famine				
Unexposed	1	1	1	1
Moderately exposed	0.90 (0.80–1.01)	0.92 (0.81–1.03)	0.95 (0.85–1.06)	0.95 (0.85–1.06)
Severely exposed	0.83 (0.68–1.01)	0.83 (0.68–1.01)	0.84 (0.70–1.01)	0.85 (0.71–1.02)
Women aged 10–12 years during the famine				
Unexposed	1	1	1	1
Moderately exposed	0.87 (0.77–0.97)	0.87 (0.77–0.97)	0.92 (0.82–1.03)	0.93 (0.83–1.04)
Severely exposed	0.80 (0.66–0.96)	0.80 (0.66–0.97)	0.89 (0.74–1.06)	0.87 (0.72–1.04)

<sup>a</sup>Overall: 4603 events, 373 censored data; 2–9 years: 1917 events, 151 censored data; 7–9 years: 1360 events, 117 censored data; 10–12 years: 1326 events, 105 censored data.

<sup>b</sup>Overall: 4932 events, 463 censored data; 2–9 years: 2063 events, 207 censored data; 7–9 years: 1481 events, 111 censored data; 10–12 years: 1388 events, 145 censored data.

<sup>c</sup>Adjusted for age during the famine, socio-economic status at recruitment, highest educational attainment, cigarette smoking habits and age at baseline (age at marriage or age at first childbirth, respectively).

Censored data are due to entering menopause or reaching end of follow-up prior to giving birth.

## Discussion

The results of this study show some moderate impairments of reproductive function in a large population of women who were exposed in childhood to caloric restriction during the 1944–1945 Dutch famine. Chances of first and second childbirth decreased modestly with severity of famine exposure in a dose–response-like manner. Furthermore, women who were severely exposed to the famine in childhood were at higher risk of a medical reason for having no or fewer children than wanted, and of surgical menopause.

As a result of the Dutch famine at the end of World War II, which struck an otherwise well-nourished population, we can now study the impact of short but severe starvation. We collected individual data on famine exposure for a large group of women. Although this famine exposure classification is based on recollection and thus prone to misclassification, we believe that it is more accurate than ecological comparisons. We found a good correlation between place of residence during the war and recalled famine exposure severity (Elias *et al.*, 2002), reflecting differences in exposure between people living in rural versus urbanized areas at time of the famine (de Jong, 1981). Also, the finding that the young were less exposed than the old is historically accurate (Burger *et al.*, 1948). From these circumstantial data, the individual famine exposure score seems valid. Misclassification owing to recall would most likely have underestimated the observed effects, since we believe that recall of famine exposure is not related to fertility experiences.

With regard to the analyses on time to childbirth, some issues on the validity of our findings need to be discussed. First of all, the participation rate in our study was 44%, which may have caused selection bias. Yet, in order to explain the observed results by selection bias, non-participation of

women with a short waiting time should be higher among women who were severely exposed to the famine as compared with the unexposed. Or, *vice versa*, non-participation of women with a long waiting time should be higher among women who were unexposed to the famine as compared with the severely exposed. It is unlikely that such a bias due to selection has occurred.

Secondly, time to pregnancy is widely used as a measure for subfertility (Baird *et al.*, 1986; Greenhall and Vessey, 1990). As we were not able to directly determine time to pregnancy, we used the surrogate measures of time to childbirth after marriage or after birth of a first child. This should yield adequate estimation of fertility in cultures with a close link between marriage and procreation, as the Dutch culture was before the widespread use of oral contraceptives. In The Netherlands, oral contraceptives were introduced in 1962 (lynestrenol), mainly to treat abnormalities of the menstrual cycle. Within our analyses on time to first and second childbirth we did not control for oral contraceptive use, although we adjusted for socio-economic status, which did not change the results. Since we hypothesize that childhood caloric restriction leads to disturbances of the menstrual cycle and therefore to decreased chances of childbirth, it would be inappropriate to control for oral contraceptive use. However, analyses restricted to women who gave birth before 1962, 36% and 21% of the population on time to first and second childbirth, respectively, yielded similar results.

Thirdly, time to childbirth was taken as a proxy of female fertility. Of all cases of subfertility, ~20% can be accounted for by a male factor only, and ~27% by both male and female factors (Wong *et al.*, 2000). Male infertility may be related to lifestyle habits such as smoking and alcohol use (Wong *et al.*, 2000), and therefore to low

socio-economic status. Since people tend to marry within their peer-group and women with a low socio-economic status were more often severely famine-exposed, a male cause of subfertility could have confounded the effect of famine exposure. Consequently, we adjusted for socio-economic status, which did not change our results. Still, this misclassification by male factors may have diluted the observed effects. Additionally, the measures of subfertility we used in our analyses are rather crude compared with a proper time-to-pregnancy analysis, where one would ideally ask women about the time they tried to become pregnant. Unfortunately, this information was unavailable in our cohort. It is very likely that the crudeness of our subfertility measures have led to considerable underestimation of contrasts and we therefore expect the true association between famine and subfertility to be of a larger magnitude. In order to minimize misclassification as much as possible, we excluded all women whose date of marriage could not possibly coincide with the date of trying to get pregnant. By making use of data on a comparable cohort of women we decided to exclude all women who gave birth within 32 weeks after marriage, representing the 5th percentile of gestation, and thereby limiting loss of valuable information and minimizing misclassification (Kloosterman, 1970). Reanalysis of the data with all women included indeed yielded similar, albeit diluted, results (adjusted HR of first childbirth after marriage 0.93, 95% CI 0.88–0.99 for moderate exposure; and HR 0.90, 95% CI 0.81–1.01 for severe exposure).

Adjustment for potential confounders had remarkably little impact on the results (Table III), potentially partly because we adjusted rather crudely for cigarette smoking habits, which could have led to residual confounding. However, reanalysis of our data in only women who reported to have never smoked (57%) did not change the results. We could also not control for body mass index at conception, since these data were not available. Adjustment for body mass index at study recruitment did not change the results.

Data on age at menopause were obtained mostly in a prospective fashion until 82% complete follow-up (de Vries *et al.*, 2001). The reproducibility and validity of recalled type and age of menopause is fairly high (Colditz *et al.*, 1987; den Tonkelaar, 1997). Unfortunately, we did not have data on reason for surgery and therefore can only speculate on the underlying mechanisms that may have resulted in the higher risk of surgical menopause in the severely famine-exposed women. In line with our other findings, an effect on disorders of menstruation seems plausible, which was a medical indication in 23% of all, including postmenopausal, hysterectomies performed in The Netherlands around 1980 (van Hall, 1984). Involvement of other indications, such as leiomyomata, can, however, not be ruled out. Similarly, we did not have information on the type of diagnosis when evaluating the risk of a medical reason for having no or fewer children than wanted. In a Western population, female subfertility is reported to be caused in 24% of cases by ovulatory disorders. Other causes include a male factor, as discussed above, and endometriosis (Evers, 2002).

Literature on decreased female reproduction during periods of starvation is abundant (Bongaarts, 1980; Warren, 1983; Harlow and Ephross, 1995), in contrast to literature on childhood caloric restriction and subsequent fertility. Women exposed *in utero* to the 1944–1945 Dutch famine showed no differences in proportion childlessness, age at first delivery or family size (Lumey *et al.*, 1995). We also could not detect such effects. Data on Gainj women from highland Papua New Guinea show that the mean time to pregnancy is 1 month longer compared with a Western population. These women are frequently exposed to low-level undernutrition, which may play a role in these differences and is in line with our findings (Johnson *et al.*, 1990). One study specifically examined childhood nutrition and subsequent fertility milestones in Guatemala. Researchers randomly allocated two pairs of villages to low-energy or high-energy nutritional supplements. Women were exposed to these supplements already *in utero* and up to 3 years of age. High-energy supplementation led to increased chance of childbirth after first intercourse (HR 1.12; 95% CI 1.01–1.23) (Ramakrishnan *et al.*, 1999).

In conclusion, our findings support the view that childhood famine exposure impairs subsequent female reproductive function. These effects appear not to be related to specific time-windows in female prepubertal development, although the relationship between the famine and time to first childbirth after marriage seemed to be strongest in those aged 10–12 years during the famine.

### Acknowledgements

The authors are grateful to Bernard Slotboom and Bep Verkerk for processing and handling of data. This work was supported by a Dutch Cancer Society grant KWF UU-2000-2314 to P.A.H.v.N.

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*Submitted on August 4, 2003; resubmitted on November 15, 2004; accepted on April 25, 2005*