Prenatal Famine Exposure and Mortality in a National Birth cohort with follow-up through age 63 years

L.H. Lumey[a,1], P. Ekamper[b], Aryeh D. Stein[c], Frans van Poppel[b,d]

[a]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032;
[b]Netherlands Interdisciplinary Demographic Institute NIDI, 2502 AR the Hague, the Netherlands;
[c]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA 30322
[d]Department of Sociology, Utrecht University, 3508 TC Utrecht, the Netherlands

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[1]To whom correspondence should be addressed. E-mail: lumey@columbia.edu.

Abstract

The circumstances of the Dutch famine (Hunger Winter) of 1944-45, with civilian starvation caused by conditions of war, have been used in the past to examine the relation between nutrition in pregnancy, birth outcomes and morbidity later in life. This is an important question in view of the continuing and as yet unresolved debate on the contribution of early life factors to adult health and its policy implications (Ben-Shlomo Y & Kuh D (2002) Int J Epidemiol 31: 285-293). Little is known however about the effects of famine on mortality and life expectancy, especially in well defined populations.

Introduction

The Dutch famine occurred in a society with a well-developed administrative structure without food shortages. It resulted from an embargo on transport of food supplies imposed by the German occupying forces in early October 1944 in reprisal for a wave of partisan activity. The severity and widespread nature of the famine have been fully documented [1,2,3]. Before the embargo, the food situation in the Netherlands was generally satisfactory. Thereafter, official food rations dropped sharply and reached a low of 500 kcal per day by April 1945 in the large cities in the Western Netherlands [4]. The famine ceased soon after the German surrender in May 1945, when Allied food supplies were rapidly distributed across the country. (Figure 1)

Earlier studies of the Dutch famine following men and women from selected birth clinics have documented increases in weight and the risk of type 2 diabetes mellitus in men and women after prenatal famine exposure [5,6,7,8]. Taken together, the clinic studies on cardiovascular risk do not show a relation with famine [9,10]. Survival data from one of the clinic populations has recently become available [11] but those results are hard to interpret because of limited sample size. A comprehensive review of morbidity outcomes from prenatal famine studies world-wide is provided elsewhere [12].

The pioneering national cohort study of the Great Finnish Famine of 1866-68 [13] and a regional study of the Chinese Famine of 1959-61 [14] did not find differences in mortality or survival at older age for cohorts born during famine. Fertility or early mortality selection during the famine may have changed the characteristics of the survivors, masking possible negative long-term effects [14]. This is also suggested by a more recent analysis of the Finnish famine data, using frailty models to account for unobserved cohort heterogeneity [15]. Other discussions of the effects of early-life conditions on adult mortality have not included conditions during gestation [16].

We used the circumstances of the famine to examine if famine exposure during specific periods of or around gestation is associated with adult survival to age 63 years. In an earlier clinic study, two of the authors (L.H.L. and A.D.S.) found less DNA methylation of the imprinted *IGF2* gene among individuals with famine exposure in very early pregnancy, but no changes after exposure in late pregnancy [17]. Although this suggests that the early pregnancy period may be the crucial period for establishing epigenetic marks, the relation with long term health outcomes or survival is not known. We therefore examined in a national birth cohort if famine exposure in early gestation is associated with an increase in mortality. We then examined mortality in relation to famine exposure in late gestation as these births show lower birth weights [18,19] and low birth weight has been associated with increased morbidity later in life [20]. Finally, we examined mortality in relation to famine in adjacent exposure periods, including the first and second trimester of pregnancy, and the periods immediately after birth or before conception.

Results

Births in famine area. Military records were available for 408,015 Dutch recruits born between 1944-1947. A rapid decline was seen in the number of examinees from the West born between June 1945-January 1946, with a rebound in February 1946. Monthly birth counts from North and South cities showed no change (Figure 2).

Study population. We linked names to the military identification numbers of a) all men presenting for military examination and born between November 1944 and March 1946 in the six largest cities in the Western part of the country (cohorts exposed around birth, n=25,283)), of all men born in the same cities either before the famine (births between November 1944 and March 1945) or after the famine (births between April 1946 and December 1947) (unexposed time controls, n=10,667)), and of all 9,087 men sampled from among birth 1944-1947 in the non-Western region Names were successfully linked to military identification numbers in 99.6% of these men. 33% of the men had been born in Amsterdam, 25% in Rotterdam, 20% in the Hague, 10% in Utrecht, 7% in Leiden, and 5% in Haarlem. Combined, these cohorts provided 45,037 subjects for further tracing.

Demographic characteristics at age 18 years. Table 1 shows selected demographic characteristics at the time of medical examinations by famine exposure status. There were differences in categorical distributions of a few percentage points comparing famine exposed men and unexposed time controls with respect to father's occupation and subject's religion, family size (number of sibs), education, and the outcome of the military examination. Among the place controls, father's occupation is less likely to be non-manual (31.3% vs 46.6%) and more likely to be farming related (14.9% vs 1.6%). Religion is more likely to be Roman Catholic (45.5% vs 30.2%) and not 'Without religion' (11.7% vs 28.5%), and family size is more likely to be large (with the men having 6 or more sibs in 33.3% vs 17.6%).

Follow-up through age 63 years. Vital status at age 63 years was ascertained for 41,096 (91.2%) of men identified for tracing. 36,088 (80.1%) were alive in 2010 and

5,008 (11.1%) had died. Follow-up status was incomplete (because of emigration and other right-censoring events) for 1,316 (2.9%) and entirely unknown for 2,625 (5.8%) (Table 2), with minor variations in follow up status by exposure category or place of birth. The proportion of survivors among men exposed immediately post-natal, in the 3rd, 2nd or 1st trimester of pregnancy, prior to conception, or among unexposed time or place controls combining all months varied between 77.9% and 81.4%. The proportion who had died varied between 10.7% and 11.7%, and the proportion with unknown vital status varied between 5.7 and 6.8% for these same categories

Mortality by month of birth. Cumulative mortality for monthly birth cohorts in the Western cities relative to unexposed place controls is shown in Figure 3a. Whereas most risk estimates are not different from unity, births in the famine area in November 1944 (RR=1.20; 95% CI: 1.08 to 1.34) and in March 1945 (RR=1.20; 95% CI: 1.05 to 1.38), show a statistical increase in mortality compared to unexposed place controls.

Mortality by gestation period. Hazard ratios for the five pre-specified exposure categories in and around pregnancy are given in Table 3. Each exposure category represents a five month period, partially overlapping with the adjacent period(s). The models show the independent association of each exposure category to mortality 18-63 years. Overall, 5,008 deaths were observed after 1,853,023 person years of observation. The hazard ratio for men born after prenatal exposure in the first trimester of pregnancy adjusted for place of birth, education, and father's occupation is 1.10 (95% CI: 1.00 to 1.22) and after exposure in late pregnancy 1.03 (95% CI: 0.95 to 1.12). Estimates were not affected by further adjustments for family size, religion, or month of birth. Hazard ratios for each exposure category are shown in Fig 3b.

Discussion

This study uses a national birth cohort to quantify the relation between prenatal famine and adult survival through age 63 years.

As current mortality among tracked individuals is 12.2%, our findings only provide first estimates of the possible effect of prenatal famine in specific pregnancy periods on long-term mortality. Nevertheless, these estimates are already rather precise because of the size of the study population.

Hazard ratio estimates for mortality in specific famine exposure categories relative to unexposed individuals do not vary by more than 10% from unity. Confirming our a-priori hypotheses, we found an increase in mortality after famine exposure in the first trimester of pregnancy of 10% (95% CI: 1.00 to 1.22) but no increase after famine exposure in the third trimester (HR 1.03; 95% CI; 0.95 to 1.12). There were no mortality changes after exposures in the other categories.

Alternative statistical approaches to model frailty in the different exposure periods did not change risk estimates. Neither did statistical adjustment for established predictors at age 18 years of long-term survival in the Netherlands, including educational level [21].

Additional adjustments for month of birth in view of reported associations between month of birth and lifespan [22] had no effect on risk estimates. We reason that any effects related to month of birth are already covered by the included covariates.

Updated reports from age 63 years onwards based on progressively increasing numbers of deaths will provide even more precise and ultimately definitive risk measures of long-term mortality in relation to prenatal famine exposure.

Our results provide crucial refinements to studies from the national Finnish famine cohort study by Kannisto, Christensen and Vaupel [13] and the regional study of the Chinese Famine [14] that did not find differences in survival for cohorts born during famine. Our study shows that the relation between mortality and well-defined specific periods before, during and after gestation can be evaluated with a high degree of accuracy and points to the early pregnancy period as being critically sensitive to the nutrition environment. Such inferences are not possible with small studies of clinic populations. Follow-up is currently limited to age 63 years and the study findings are therefore not strictly comparable to increased mortality patterns seen among individuals age 60 years and over in recent frailty analyses in the Finnish famine cohort [15]. Although these findings appear to be consistent with our results, it will take some time to assess later age mortality in the Dutch cohort as the population ages.

Famine exposure in defined periods of gestation was defined by distributed food rations in relation to date of birth, assuming a gestation period of 40 weeks for each individual. Gestation estimates could potentially be biased if gestation were differentially affected by famine at any time during pregnancy. We do not think such bias is likely as the birth clinic records from this period in famine and non-famine cities show no consistent relation between the degree of famine and duration of pregnancy and only small variations (3-4 days) in the duration of pregnancy over time [19]. In addition, gestation periods based on mother's last menstrual period in famine cities show broad agreement with categories based on date of birth [18]. As expected, there is a sharp decline in monthly birth counts corresponding to a decreased fertility at the time of the lowest food rations in the famine cities (Table 2 and Figure 2).

While some additional official rations were provided to pregnant women, re-allocation of rations within the family may have taken place. From hospital records in the affected cities of Amsterdam, Rotterdam, the Hague, and Leiden it is clear however that the additional rations did not protect pregnant women from severe under-nutrition, leading to weight loss in pregnancy and a decrease in offspring birth weights [18,19,23,24,25,26].

We have full confidence that all targeted births in the famine and control cities in the time period of study are adequately accounted for by a) tracings from birth to age 18 years when the men are examined for service, and b) the completeness of the military induction file, and c) tracings between the ages 18-63 years.

For tracings 0-18 years, Stein et al. [2], showed with national samples of stillbirths, infant deaths, and deaths between 1-18 years of age for births 1944-1947 in the Netherlands that first trimester famine exposure was associated with stillbirths and an increase in preterm delivery; first and third trimester exposure with first week deaths, and third trimester exposure with deaths in weeks 2-12 after birth. Deaths from 1-18 years were not related to prenatal famine exposure. There was also an increase in mortality in the first year of life due to infectious disease epidemics immediately following the war. Overall mortality for births in the Western cities between birth and age 18 years was 6.3% after first trimester famine exposure, 7.6% after second trimester exposure, 10.7% after third trimester exposure, and 11.1% after immediate postnatal exposure [2].

In view of these differences, survival in the different exposure period was not only modeled with Cox proportional hazard models but also with Gompertz models with or without frailty (gamma) parameter. All models gave the same results to the second decimal place, and our models failed to detect frailty within defined clusters. We therefore do not think it is likely that differences in survival from birth to 18 years between exposure categories could have biased the study results.

On the completeness of the military induction file, previous studies confirm that in essence every young man of Dutch nationality born between 1943 and 1947 and resident in the Netherlands was examined or accounted for at the age of examination for military service. The available files are therefore essentially complete for all surviving males who reside in the Netherlands [2].

Overall mortality between 18-63 years in the study population was 12.2%, in close agreement with estimates based on national cohort life tables. From the latter, cumulative mortality through 2010 of birth cohorts born 1944-1947 and alive at age 18 years can be estimated as 12.7 %. In spite of this agreement, there is still some potential for biased results because of the incomplete or missing follow-up of some study subjects. For 5.8% of men it has not yet been possible to ascertain vital status in any form. These men could have died or could still be living in the Netherlands and have escaped linkage due to variations in spellings of names and other imperfect linkage procedures. Also, men who migrated have been lost to follow-up unless they later returned to the Netherlands. We do not think however that the study outcomes could have been biased in any substantive way by selective loss to follow-up as the numbers are proportionally small and are evenly distributed across exposure categories. Nevertheless, further searches will continue for men who are still lost to follow-up.

Considering the overall pattern of tracings from birth to 63 years, it was reassuring to see that traced and untraced men did not differ with respect to demographic and examination characteristics collected at age 18 years, including date and place of birth, religion, education, (father's) occupation and fitness for military service.

In a follow-up study through age 50 years of Dutch military recruits born in 1932, a strong inverse relation was seen between education at age 18 years and survival [21]. In the current study, statistical adjustment for education had no effect on the mortality risk estimates for the specific pregnancy cohorts. This suggests that education is neither a confounder of the relation between famine exposure and mortality nor an intermediary factor. Risk estimates were also unaffected by adjustment for father's occupation, itself highly correlated with subject's education.

The military examination files do not include information on smoking habits. At the time of assessment, 90% of men in the Netherlands smoked. In 1958, men on average started smoking at age 16 years and only 5% had started smoking in adulthood [27]. This suggests that nearly all examinees must have been smokers. Study outcomes could be biased in the event of systematic differences in smoking habits by date of birth in the period 1944-1947 but this seems unlikely. Study results were not affected by statistical adjustment for reported demographic correlates of smoking (occupation, education, religion) [27]. Between 1958-1982, smoking levels in the Netherlands dropped significantly and the proportion of male former smokers increased from 6% to

31% [28]. This would have mitigated any differences in smoking related deaths associated with unmeasured cohort characteristics at age 18 years. We therefore think it is highly unlikely that systematic and unknown differences in smoking patterns by place or date of birth could have biased the study results. In future studies it will be possible to examine this question in more detail by comparing smoking related vs. non-smoking related deaths by place and date of birth, as cigarette smokers on average die about 10 years younger than non-smokers and from different causes of death [29].

In summary, we report an increase in mortality in a national birth cohort of men with prenatal exposure to the Dutch famine of 1944-1945 and followed between ages 18-63 years. Confirming a-priori formulated study hypotheses, a small increase in mortality was seen after famine exposure in early gestation but not after exposure in late gestation. Our findings provide further evidence that the timing of exposure in relation to the stage of pregnancy may be of critical importance for determining later health outcomes. Further follow-up of the study cohort will provide more accurate and ultimately definitive risk measures of long-term mortality in relation to extreme nutrition changes in early life.

Methods

Study population. We sampled for follow-up men from the national birth cohorts 1944-1947, who were examined at age 18 years for military service in the Netherlands (n=408,015). Military examinations were based on yearly listings of all male Netherlands citizens aged 18 years in the national population registers. These men were called to a military service induction exam, except those living in psychiatric institutions or in nursing institutes for the blind or for the deaf-mute. Exemptions (0.6%) were based on a communication from the institution's medical officer that the individual was unfit for military service for specific reasons, but still provide a military record with full demographic information and relevant medical diagnoses from the institution. We sampled all men who were born between January 1944 and December 1947 in any of the six most affected cities in the Western Netherlands (Amsterdam, Haarlem, Rotterdam, The Hague, Leiden, and Utrecht) as likely to have had famine exposure. As non-exposed time controls we sampled prefamine and postfamine births in these same cities. As unexposed place-controls, we randomly sampled births in 1944-1947 in the North/Eastern and Southern parts of the country. We excluded from study all men born in the rural and smaller urbanized areas in the West as access to food was only partially limited in this group [4].

Famine exposure. Famine exposure during specific trimesters of pregnancy was defined by a mean caloric ration of 900 kcal or less in that trimester, based on date of birth in relation to distributed weekly food rations in the Western Netherlands and assuming a gestation period of nine months. Accordingly, births between November 1, 1944 and March 31, 1945 are defined as being famine exposed in the immediate post-natal period (PN), births between February 1 and June 30, 1945 as exposed in the third trimester of pregnancy (T3), births between May 1 and September 30, 1945 in the second trimester (T2), births between August 1 and December 31, 1945 in the first trimester (T1), and births between November 1, 1945 and March 31, 1946 around the estimated date of conception (T0). Each category spans 5 months, and adjacent categories have a 2 month overlap.

Individual characteristics at military examination. The military records provide a unique identification number and place and date of birth for each individual. In addition, they provide demographic characteristics including father’s occupation, religion, family size, education, height and weight, and fitness status for military service.

Father’s occupation was classified as non-manual or manual as per a previous study in this cohort [30]. The non-manual group includes upper professional, lower professional, managerial and clerical occupations, and the manual group includes self-employed proprietors, craftsmen and foremen, shop assistants, operatives, process workers, domestic and other service workers, mine workers, and laborers. Farm workers and farm owners were classified separately in view of their likely easier access to food supplies during the famine. Unknown father’s occupations were also classified separately.

Religion was classified as Roman-Catholic, Dutch Reformed, Other religion, or Without religion, based on self-report at examination. For family size, the number of siblings as reported by the examinee was taken.

Education was classified in four levels, based on schooling at age 18 years [21]. The first level includes men who completed primary school (age 6-12 years), the second men with lower vocational education (primary school and two years of additional education); the third men with lower secondary education (primary school and four years of additional education); and the fourth, men with intermediate vocational education, general secondary education, higher non-university and university education (primary school and at least six years of additional education). Men who did not complete primary school or who had been in special education for the physically or mentally handicapped were classified in a separate category.

Examination results were summarized by a determination of fitness status for military service.

Follow-up. Under approved confidentiality procedures, examination records were linked by military identification number to individuals at the Office of Registration and Information on Discharged Personnel (BRIOP) at the Netherlands Ministry of Defence in Kerkrade, the Netherlands. These individuals were linked at the Netherlands Central Bureau of Statistics (CBS) to population records and recent national death records. In the event of a failed linkage, matching to older national death records was carried out by the Central Bureau of Genealogy (CBG) in The Hague (Netherlands) with computer assistance and by hand matching where needed. Follow-up was through 2010 for all individuals. The study was reviewed by the IRB at Columbia University, New York, NY who made the determination that the study does not classify as human subjects research and does not require IRB review.

Statistical Analysis. We created binary predictor variables (coded 1 if exposed, 0 otherwise) for each of the five famine exposure categories (periconceptional, 1^{st}, 2^{nd}, or 3^{rd} trimester of pregnancy, immediate post-natal). In our first models, we included all the five predictor variables so as to evaluate the independent effects of individual exposure periods relative to unexposed time and place controls. In later models, we evaluated each of the five predictor variables in turn, excluding subjects from any of the other four exposure categories relative to all time and place controls. Results from these later models are not reported as they did not differ from the mutually adjusted results. As study outcome we modeled mortality from all causes between ages 19 and 63 years, comparing subjects in selected exposure categories with unexposed controls. Two-sided tests were used throughout, even though some of the hypotheses of interest are uni-directional. Time to death was evaluated in Cox proportional hazard models [31] with an age-time scale, using the stcox procedure in the STATA statistical package (v.11, College Station, TX) setting age at study entry at 18 years and age at follow-up to age of event (death, emigration, loss to follow-up from other causes). The current age of the youngest study subject (63 years in 2010) was taken as the endpoint for all analyses. The adequacy of the proportional hazards assumption was confirmed by examining plots of Schoenfeld residuals [32]. Additional analyses included adjustments for relevant covariate information from the medical examination data file. Time to death was also evaluated with Gompertz models, with or without frailty (gamma) parameter. Results from these models are not further reported as they did not show detectable frailty within defined clusters (with frailty variance components θ equal to zero and associated p-values equal to one) and the effect estimates did not differ from the reported Cox models.

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Table 1
Demographics and baseline characteristics by famine exposure status

		Total	Total	Exposed around pregnancy	Time controls	Place controls	p-value
Number			45,037	25,283	10,667	9,087	
		N	%	%	%	%	
Father's Occupation							
	Non-manual	19,494	43.3	46.6	45.7	31.3	<0.001
	Manual	20,153	44.7	43.8	44.7	47.3	
	Farming	1,933	4.3	1.6	1.6	14.9	
	Unknown	3,457	7.7	8.0	8.0	6.5	
Religion							
	Roman Catholic	14,805	32.9	30.2	28.5	45.5	<0.001
	Dutch Reformed	13,592	30.2	29.9	29.3	31.8	
	Other	3,787	8.4	7.8	7.6	11.0	
	Without religion	12,853	28.5	32.1	34.5	11.7	
Family size							
	1	3,220	7.1	7.7	8.4	4.1	<0.001
	2	9,639	21.4	22.8	24.5	13.9	
	3	9,715	21.6	22.6	22.5	17.8	
	4	7,448	16.5	16.6	16.6	16.2	
	5	4,960	11.0	10.9	9.9	12.6	
	6+	9,190	20.4	17.6	16.0	33.3	
	Unknown	865	1.9	1.8	2.1	2.1	
Education							
	Special (less than primary school)	2,734	6.1	5.5	6.2	7.4	<0.001
	Primary school (6 years)	6,020	13.4	12.9	13.7	14.4	
	Primary school and 2 more years	15,386	34.2	32.4	32.5	40.9	
	Primary school and 4 more years	14,017	31.1	33.1	31.4	25.4	
	Primary school and 6+ more years	6,880	15.3	16.1	16.2	11.9	
Military examination outcome							
	Suitable for service	33,388	74.1	75.3	72.3	72.9	<0.001
	Unsuitable/other	11,649	25.9	24.7	27.7	27.1	

Table 2

Follow-up status at age 63 years by month and year of birth, Jan 1944-Dec 1947, for military recruits examined at age 18 years in the Netherlands, by exposure to famine in pregnancy

Month and year of birth	Exposure period*	In military records	Alive	Deaths	Partial or no follow up**	In military records	Alive	Deaths	Partial or no follow up**
		Famine cities				Non-famine areas			
		n	%	%	%	n	%	%	%
Jan 1944-Oct 1944	Born before famine	2565	78.5	11.5	9.9	1863	79.3	12.1	8.6
Nov 1944	PN (Post-natal)	1628	79.7	13.1	7.1	168	82.1	10.7	7.1
Dec 1944	PN	1588	81.5	10.2	8.3	160	78.8	8.8	12.5
Jan 1945	PN	1718	79.9	10.9	9.3	144	83.3	9.0	7.6
Feb 1945	PN/T3	1591	80.4	10.9	8.7	186	81.7	11.3	7.0
Mar 1945	PN/T3	1675	76.9	13.2	9.9	210	82.9	11.0	6.2
Apr 1945	T3	1780	79.9	11.1	9.0	195	83.1	8.7	8.2
May 1945	T3/T2	1704	79.1	11.6	9.3	176	81.3	9.7	9.1
Jun 1945	T3/T2	1430	80.8	10.1	9.0	176	80.7	13.1	6.2
Jul 1945	T2	1444	81.2	10.2	8.6	154	78.6	14.9	6.5
Aug 1945	T2/T1	1223	76.9	12.5	10.6	169	75.7	16.6	7.7
Sep 1945	T2/T1	999	77.9	12.8	9.3	150	86.0	8.0	6.0
Oct 1945	T1	803	77.8	10.7	11.5	139	86.3	6.5	7.2
Nov 1945	T1/PC	744	77.7	10.9	11.4	128	86.7	7.8	5.5
Dec 1945	T1/PC	891	79.7	10.3	10.0	164	79.9	14.0	6.1
Jan 1946	PC	1181	79.8	11.2	9.1	184	84.2	8.7	7.1
Feb 1946	PC	1803	79.8	10.3	9.9	216	84.7	10.2	5.1
Mar 1946	PC (PreConception)	3081	80.5	10.7	8.8	270	85.6	11.1	3.3
Apr 1946-Dec 1947	Conceived a fter famine	8102	80.9	10.9	8.2	4235	81.7	10.7	7.6

* Exposure periods abbreviated as follows: PN: exposed in the immediate post-natal period; T3: exposed in the third trimester of pregnancy; T2: in the second trimester; T1: in the first trimester; PC: just before the estimated date of conception. Each category spans 5 months, and adjacent categories have a 2 month overlap.

** Partial follow up includes individuals who after some follow-up emigrated from the Netherlands (1.9%) and individuals with partial follow-up for other reasons (1.0%). There was no follow-up information for 5.8% of individuals. These categories cannot be further differentiated by month of birth to preserve confidentiality.

Table 3

Death rates in specific famine exposure groups compared to unexposed controls; Hazard Ratios (95% confidence intervals) from Cox regression models

	Famine exposure in each of five periods in/around pregnancy*				
Model	Postnatal	3rd Trim	2nd Trim	1st Trim	Preconception
Adjusted for place of birth	1.06 0.97 to 1.15	1.02 0.94 to 1.11	1.00 0.91 to 1.10	1.09 0.99 to 1.21	0.95 0.87 to 1.04
Adjusted for place of birth, education and father's occupation	1.07 0.98 to 1.16	1.03 0.95 to 1.12	0.99 0.90 to 1.09	1.10 1.00 to 1.22	0.96 0.88 to 1.05

*Adjusting for all other periods in same model. Estimates for any of five birth cohorts alone vs. unexposed baseline give same results to 2nd decimal point. Number of deaths/ person years of follow-up after post-natal exposure: 957/337,755; third trimester exposure: 933/336,073; second trimester exposure: 770/278,660; first trimester exposure: 540/189,325; periconceptional exposure: 821/317, 117; and without exposure to any of the above: 2,177/813,755. Deaths/person years of follow-up in the entire study population: 5,008/1,853,023.

Gompertz models with or without frailty (gamma) parameter give same results to second decimal place; models show no detectable frailty within defined clusters (frailty variance θ is zero and p-value equal one)

Figure 1

Food rations (calories/day) in Western Netherlands, September 1944 to October 1945

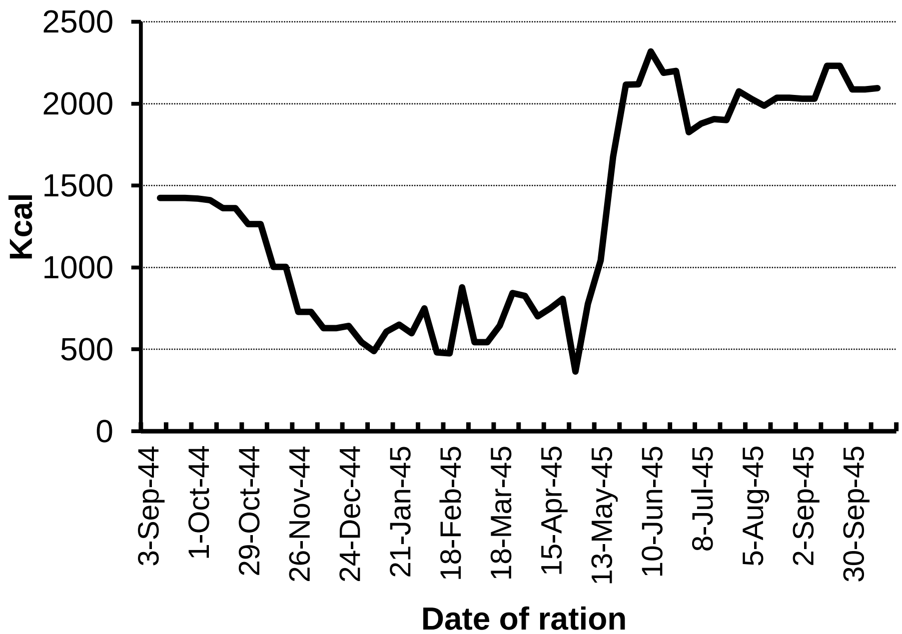


Figure 2

Examinations of Dutch recruits
born in North, South, and Western cities
by year and month of birth

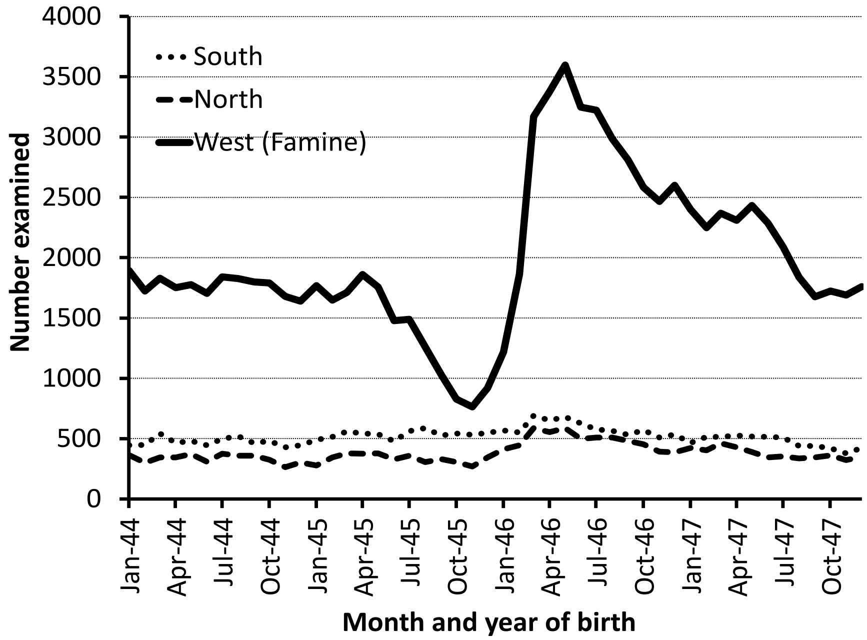


Figure 3a

Mortality between 18-63 years among Dutch recruits born in Western cities 1944-1946, by month and year of birth Risk ratio's relative to unexposed controls

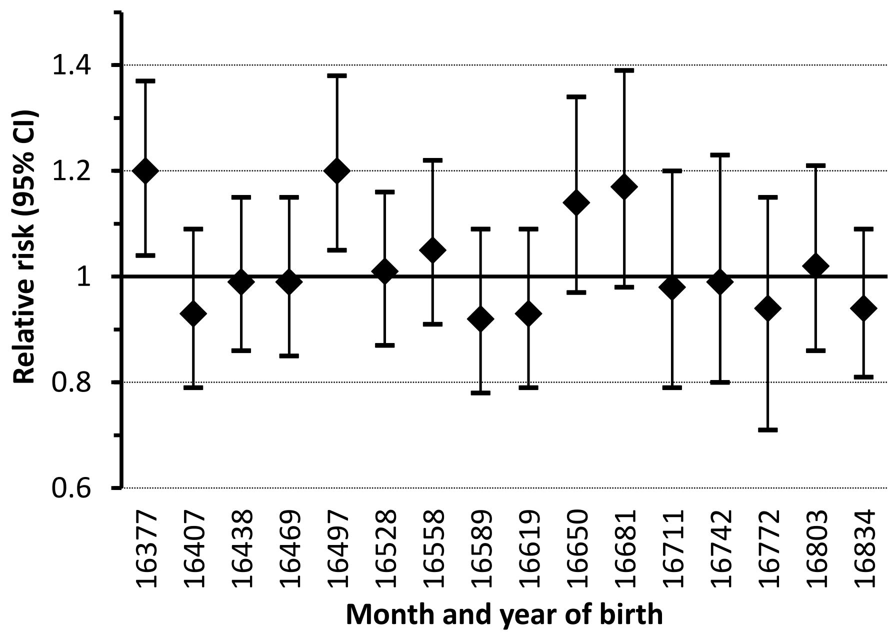
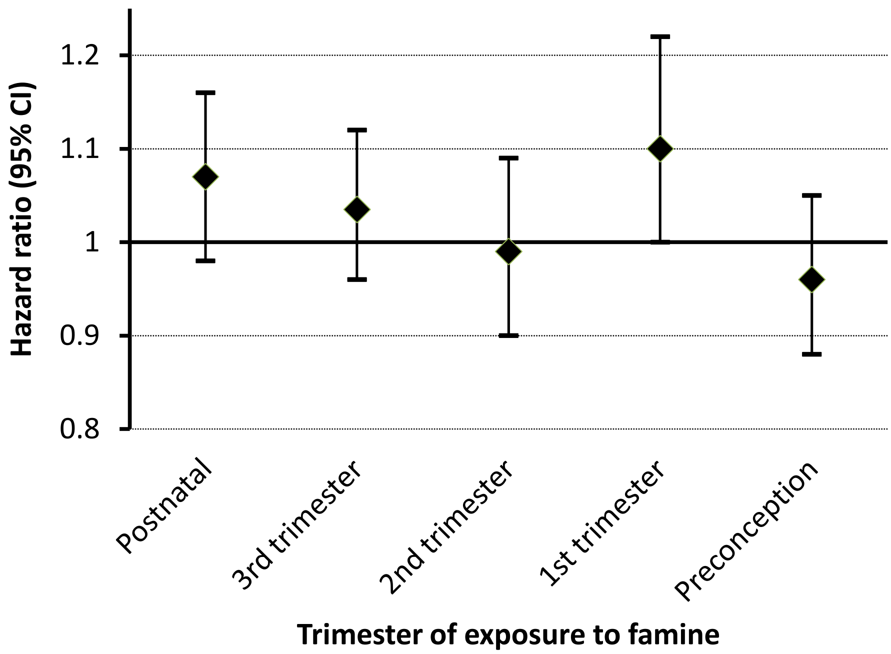


Figure 3b

Mortality between 18-63 years among Dutch recruits born in Western cities 1944-1946, by pregnancy exposure period Hazard ratio's relative to unexposed controls



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