Independent and additive association of prenatal famine exposure and intermediary life conditions with adult mortality between age 18-63 years

Ekamper, P.; van Poppel, F.W.A.; Stein, A.D.; Lumey, L.H.

published in
Social Science & Medicine
2014

DOI (link to publisher)
10.1016/j.socscimed.2013.10.027

document version
Peer reviewed version

Accepted Manuscript

Independent and additive association of prenatal famine exposure and intermediary life conditions with adult mortality age 18-63 years

P. Ekamper, F. van Poppel, A.D. Stein, L.H. Lumey

PII: S0277-9536(13)00575-3

DOI: 10.1016/j.socscimed.2013.10.027

Reference: SSM 9154

To appear in: *Social Science & Medicine*

Received Date: 9 March 2013

Revised Date: 1 July 2013

Accepted Date: 23 October 2013

Please cite this article as: Ekamper, P., van Poppel, F., Stein, A.D., Lumey, L.H., Independent and additive association of prenatal famine exposure and intermediary life conditions with adult mortality age 18-63 years, *Social Science & Medicine* (2013), doi: 10.1016/j.socscimed.2013.10.027.

Research Highlights

- Prenatal famine is associated with an increased mortality from age 18-63 years.
- This is not explained by socio-economic and health characteristics at age 18.
- Increased mortality is related to exposure in early but not in late pregnancy.
- Findings are from national military conscription records and linked death files.
- Military conscriptions in the Netherlands included all men but not women.

ACCEPTED MANUSCRIPT

Independent and additive association of prenatal famine exposure and intermediary life conditions with adult mortality age 18-63 years

P. Ekamper[a], F. van Poppel[a,b], A.D. Stein[c], L.H. Lumey[d*]

[a]Netherlands Interdisciplinary Demographic Institute NIDI, PO Box 11650, 2502 AR The Hague, Netherlands. ekamper@nidi.nl

[b]Department of Sociology, Utrecht University, PO Box 80140, 3508 TC Utrecht, Netherlands. poppel@nidi.nl

[c]Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322, USA. aryeh.stein@emory.edu

[d]Mailman School of Public Health, Columbia University, 722 West 168 Street, New York, NY 10032, USA. lumey@columbia.edu

*Corresponding author
phone +1 212 305-9222

Acknowledgements We thank Drs Diana Kuh, George Davey Smith and Mervyn Susser for study advice; Ingeborg Deerenberg (Netherlands Central Bureau of Statistics), Dr F. Willekens (Director, NIDI), Mr Gerard van der Horst (Chief, Administration Personnel Office, Ministry of Defense), Dr Bert Lever (Director, Central Bureau of Genealogy) and Mr Jan Groenewegen (Office of Registration and Information on Discharged Personnel (BRIOP), Ministry of Defence) for their cooperation on the execution of study.

ABSTRACT

Objectives To quantify the relation between prenatal famine exposure and adult mortality, taking into account mediating effects of intermediary life conditions.

Design Historical follow-up study.

Setting The Dutch famine (Hunger Winter) of 1944-1945 which occurred towards the end of WWII in occupied Netherlands.

Study population From 408,015 Dutch male births born 1944-1947, examined for military service at age 18, we selected for follow-up all men born at the time of the famine in six affected cities in the Western Netherlands (n=25,283), and a sample of unexposed time (n=10,667) and place (n=9,087) controls. These men were traced and followed for mortality through the national population and death record systems.

Outcome measure All-cause mortality between ages 18 and 63 years using Cox proportional hazards models adjusted for intermediary life conditions.

Results An increase in mortality was seen after famine exposure in early gestation (HR 1.12; 95% confidence interval (CI): 1.01 to 1.24) but not late gestation (HR 1.04; 95% CI: 0.96 to 1.13). Among intermediary life conditions at age 18 years, educational level was inversely associated with mortality and mortality was elevated in men with fathers with a manual versus non-manual occupations (HR 1.08; CI: 1.02 to 1.16) and in men who were declared unfit for military service (HR 1.44; CI: 1.31 to 1.58). Associations of intermediate factors with mortality were independent of famine exposure in early life and associations between prenatal famine exposure and adult mortality were independent of social class and education at age 18.

Conclusions Timing of exposure in relation to the stage of pregnancy may be of critical importance for later health outcomes independent of intermediary life conditions.

INTRODUCTION

The circumstances of the Dutch famine (Hunger Winter) of 1944-1945 at the end of WWII with civilian starvation caused by conditions of war have been used to examine the relation between nutrition in pregnancy, birth outcomes and morbidity later in life.(Lumey & Van Poppel, 2013) (Stein, Susser, Saenger, & Marolla, 1975) This is an important question in view of the continuing and as yet unresolved debate on the contribution of early life factors and possibly mediating intermediary life conditions to the various ways in which adult health risks may accumulate over the life course and its policy implications.(Ben-Shlomo & Kuh, 2002) Little is known however about the effects of prenatal famine exposure and intermediary life conditions as possible mediators or modifiers on adult mortality.

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.(Burger, Drummond, & Sandstead, 1948; Lumey & Van Poppel, 1994; Stein et al., 1975) 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.(Trienekens, 2000) 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.(Lumey, Stein, & Kahn, 2009; A. C. Ravelli et al., 1998; Ravelli, van der Meulen, Osmond, Barker, & Bleker, 1999; Stein et al., 2007) Taken together, clinic-based studies on cardiovascular risk do not show a relation with famine.(Lumey, Martini, Myerson, Stein, & Prineas, 2012; Roseboom et al., 2000) Survival data from one clinic population was recently become published (Van Abeelen et al., 2012) but those results are hard to interpret because of limited sample size. Increases in weight and diabetes prevalence have been confirmed in a comprehensive review of morbidity outcomes from prenatal famine studies world-wide as discussed elsewhere. (Lumey, Stein, & Susser, 2011)

The pioneering national cohort study of the Great Finnish Famine of 1866-68(Kannisto, Christensen, & Vaupel, 1997) and a regional study of the Chinese Famine of 1959-61 (Song, 2009) did not find differences in mortality for cohorts born during famine but did not examine specific pregnancy periods. Fertility or early mortality selection during the famine may have changed the characteristics of the survivors, masking possible negative long-term effects.(Song, 2009) This is also suggested by a more recent analysis of the Finnish famine data, using frailty models to account for unobserved cohort heterogeneity.(Doblhammer, Van den Berg, & Lumey, In press) Other discussions of the effects of early-life conditions on adult mortality have not included conditions during specific gestation periods.(Elo & Preston, 1992; Montez & Hayward, 2011)

Several studies have shown that early life family characteristics and socioeconomic conditions, like father’s occupation, (parental) education, housing characteristics and family income are important predictors of adult health and mortality.(Hayward & Gorman, 2004; Preston, Hill, & Drevenstedt, 1998; Strand & Kunst, 2007) Doornbos and Kromhout (1990) observed a significant association between educational level at age 18 and mortality in later life in a 32-year follow-up study of 18-year old men in the Netherlands. Confounding factors such as height and health score at age 18 years had little effect on the estimated risks. Using the same cohort, Hoffmans et al.(Hoffmans, Kromhout, & de Lezenne Coulander, 1988) concluded that BMI at young adult age is an independent predictor for mortality.

We use 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 earlier studies of men and women born around the time of the famine an increase in diabetes mellitus and in body size was seen among middle-aged men and women after famine exposure during gestation, but these studies were too small to accurately identify which period of gestation was the most important.(Lumey et al., 2009; Ravelli et al., 1998; Stein et al., 2007) We also 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.(Heijmans et al., 2008) . We therefore examine in a large national sample of male births if famine exposure in the early gestation period or any other gestation period is associated with an increase in overall mortality. We specifically examine mortality in relation to famine exposure in late gestation as these births show lower birth weights (Stein, Zybert, van de Bor, & Lumey, 2004; Stein & Susser, 1975) and low birth weight has been associated with increased morbidity later in life.(Barker, 1998) We examine 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. We also examine whether intermediary life conditions at age 18 are possible mediators or independent of the relation between prenatal famine and adult mortality.

METHODS

Study population

We sampled for follow-up men from the national birth cohorts 1944-1947 examined at age 18 years for military service in the Netherlands (n=408,015). Military examinations were based on yearly listings of all Dutch male citizens aged 18 years in the national population registers. All 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. These 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 November 1944 and March 1946 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 gestational famine exposure (n=25,283). As unexposed time-controls we randomly sampled prefamine and postfamine births (born before November 1944 or born after March 1946) in these same cities (n=10,667). As unexposed place-controls, we randomly sampled births in 1944-1947 in the rest of the country (n=9,087). Combined, these cohorts provided 45,037 subjects for further tracing.

Under approved confidentiality procedures, all sampled 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, by which time the youngest (those born December 1947) would have been 63 years of age.

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 uniform gestation period of nine months. Accordingly, births between November 1, 1944 and March 31, 1945 are defined as being famine exposed in the immediate postnatal 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 (PC). Each category spans 5 months, and adjacent categories have a 2 months overlap. (Figure 2)

Individual characteristics at military examination

The military records provide place and date of birth for each individual. In addition, they provide demographic and socioeconomic characteristics including education, father's occupation, religion, family size, fitness for military service, height, and weight.

Education was classified in four levels (Doornbos & Kromhout, 1990): primary school (age 6-12 years); lower vocational education (two years post primary school); lower secondary education (four years post primary school); and intermediate vocational education, general secondary education, higher non-university or university education (at least six years post primary school). Men who did not complete primary school or in education for the physically or mentally handicapped were classified in a special category.

Father's occupation was classified as non-manual or manual as per a previous study in this cohort.(Ravelli, Stein, & Susser, 1976) The non-manual group includes upper professional, lower professional, managerial and clerical occupations, and the manual group includes selfemployed 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, or none, based on self-report. For family size, the number of siblings as reported by the examinee was taken. Examination results were summarized by a determination of status of fitness for military service (fit, almost fit, fairly fit, or unfit). Body Mass Index was calculated from weight and height.

Statistical Analysis

We created binary predictor variables (1 if exposed, 0 otherwise) for each of the five famine exposure categories (periconceptional, 1st, 2nd, or 3rd trimester of pregnancy, immediate postnatal). First, we included each of the five predictor variables in our model separately so as to evaluate the effects of specific exposure periods relative to unexposed time- and place-controls. Then we included all the five famine exposure categories together in the model. Next we added the set of intermediary life conditions (education, father's occupation, religion, family size, fitness for military service, and BMI). Finally, we ran the same models without famine exposure. The study outcome was mortality from all causes between ages 18 and 63 years. Two-sided tests were used throughout, even though some of the hypotheses of interest are uni-directional. Age at death was evaluated in Cox proportional hazard models(Cox, 1972) with an age-time scale, using the stcox procedure in STATA (StataCorp, 2009) 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 at the end of 2010) was taken as the endpoint for all analyses. The adequacy of the proportional hazards assumption was confirmed by examining plots of Schoenfeld residuals.(Schoenfeld, 1980)

RESULTS

Comparing recruits born in the famine cities in the West in the period 1944-1947 (n=93,176) with births from selected unexposed cities in the North and the South of the country (n=41,408), 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, while monthly birth counts from North and South cities showed no change. (Figure 3)

Of all men in our sample identified for tracing (n=45,037), vital status in 2010 was ascertained for 41,096 (91.2%). 36,088 (80.1%) were alive at age 63 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%). Follow-up status by month and place of birth is given in Table 1. Only minor variations are seen in follow-up status by exposure category or place of birth. The proportion of surviving men exposed immediately postnatal, 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 between 5.7 and 6.8%. (percentages calculated from Table 1)

Table 2 shows selected demographic and socioeconomic characteristics at the time of medical examinations by famine exposure status. The time-controls and place-controls have different characteristics. There were small differences comparing famine exposed men and unexposed time-controls with respect to father's occupation and subject's religion, family size (number of siblings), education, and fitness for military service. By contrast, among place-controls, comprising men from the less-urbanized and more rural areas, 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%).

Hazard ratios for the five pre-specified exposure categories considered as a group and ignoring intermediary life conditions are given in Table 3, column B. 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 is 1.09 (95% confidence interval (CI): 0.99 to 1.21) and after exposure in late pregnancy 1.02 (95% CI: 0.94 to 1.11).

The results of adding intermediary life conditions at age 18 years to the model with famine exposure categories are shown in Table 3, column D. The hazard ratio for men born after prenatal exposure in the first trimester of pregnancy is 1.12 (95% CI: 1.01 to 1.24) after exposure in late pregnancy 1.04 (95% CI: 0.96 to 1.13), and for men with postnatal exposure is 1.08 (95% CI: 0.99 to 1.13). Educational level was inversely associated with mortality. We found strong relations of low education, low father's occupation and low fitness for military service at age 18 with mortality through age 63. Family size was not related to subsequent mortality.

Applying the same models for educational level, father's occupation, religion, family size, fitness status, and BMI but without famine exposure status gave the same results to the 2nd decimal point (Table 3, column C).

Time to death was also evaluated with Gompertz models, with or without a frailty (gamma) parameter. Results from these models 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. (Results not shown)

DISCUSSION

This study is the first to quantify in a national birth cohort the relation between prenatal famine and survival through age 63 years, taking into account possible mediating effects of characteristics measured at age 18 years. Hazard ratio estimates for mortality in specific famine exposure periods relative to unexposed individuals do not vary by more than 12% from unity. We found a 12% (95% CI: 1 to 24%) increase in mortality after famine exposure in the first trimester of pregnancy but no increase after famine exposure in the third trimester. We found a 8% (95% CI: 0 to 18%) increase after postnatal famine exposure. There were no mortality changes after exposures in any of the other exposure periods before, during, or after pregnancy.

As current mortality was tracked through age 63 years, our findings provide estimates of the possible effect of prenatal famine in specific pregnancy periods on mortality only through early middle age. Nevertheless, these estimates are relatively precise because of the size of the study population. Updated reports from age 63 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.

Alternative statistical approaches to model frailty in the different exposure periods did not change risk estimates. Statistical adjustment for established predictors at age 18 of long-term survival in the Netherlands, including educational level (Doornbos & Kromhout, 1990), hardly changed risk estimates.

Our results provide crucial refinements to studies from the national Finnish famine cohort study by Kannisto, Christensen and Vaupel(1997) and the regional study of the Chinese Famine

(Song, 2009) 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. 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.(Doblhammer et al., In press) Although these findings seem 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 uniform gestation period of 40 weeks. Exposure 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.(Stein & Susser, 1975) In addition, gestation periods based on mother's last menstrual period in famine cities show broad agreement with categories based on date of birth.(Stein, Zybert, Van de Bor, & Lumey, 2004)

Some additional official rations were provided to pregnant women and some re-allocation of rations within the family may have taken place, although the direction of such re-allocation is not known. From hospital records in the affected cities of Amsterdam, Rotterdam, the Hague, and Leiden it is clear that any additional rations did not protect pregnant women from severe under-nutrition, leading to weight loss in pregnancy and a decrease in offspring birth weights.(Sindram, 1953; Smith, 1947a, 1947b; Stein, Ravelli, & Lumey, 1995; Stein et al., 2004; Stein & Susser, 1975)

We believe that all targeted births in the famine and control cities in the time period of study are adequately accounted for by tracings from birth to age 18 years when the men are examined for service, and by tracings between the ages 18-63 years. For tracings 0-18 years, Stein et al. (Z. A. Stein et al., 1975), showed with national samples of live and stillbirths, infant deaths, and deaths between 1-18 years of age for births 1944-1947 in the Netherlands that there was some variation in survival depending on the timing of the famine exposure. In view of these differences, survival in the different exposure period was modeled not only with Cox proportional hazard models but also with Gompertz models with or without a 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.

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 % (calculations not shown). In spite of this agreement, there is still some potential for biased results because of incomplete follow-up. For 5.8% of men it was not possible to ascertain vital status. 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 are lost to follow-up unless they later returned to the Netherlands. The study results are not likely to have been biased in any substantive way by selective loss to follow-up however as the numbers involved are proportionally small and are evenly distributed across exposure categories. Furthermore, 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. (data not shown)

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 (Doornbos & Kromhout, 1990) and BMI at young adult age was found to be an independent predictor for mortality .(Hoffmans et al., 1988) We recognize that mortality patterns may change with age (Horiuchi, 1983), but the focus of our study is on relative contributions of prenatal and intermediary life conditions.

The choice of potential confounders and mediators was dictated by their established relation with prenatal famine exposure (e.g. body size) or their established relation with adult mortality (education and BMI). Other characteristics such as father's occupation, religion, and fitness for military service were included for exploratory purposes. In the current study, statistical adjustment for intermediary life conditions, including education and BMI, had no effect on the mortality risk estimates for the specific pregnancy periods. Social and medical characteristics at age 18 show a significant association with mortality in later life but were unrelated to the early life environment. This suggests that intermediary life conditions are neither confounders of the relation between prenatal famine exposure and mortality nor intermediary factors. The relation between prenatal famine and mortality as estimated in Table 3 (model B) was not changed by the additional adjustment for any one of the intermediary life conditions. Any such change might have highlighted a potential pathway to better understand the relation. Such pathways will be further explored in future analyses of specific causes of death (including from cardiovascular, cancer, or from other causes such as diabetes mellitus) that contributed to overall mortality in the study population.

The military examination files do not include information on smoking habits. At the time of assessment, 82% of men in the Netherlands smoked.(Van Reek, 1984) In 1958, men on average started smoking at age 16 years and only 5% had started smoking in adulthood.(Gadourek, 1963) This suggests that the majority of examinees would 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. Study results were not affected by statistical adjustment for reported demographic correlates of smoking (occupation, education, religion)(Gadourek, 1963). Between 1958-1982, smoking levels in the Netherlands dropped significantly and the proportion of male former smokers increased from 6% to 31%.(Van Reek & Adriaanse, 1987) This would have mitigated any differences in smoking related deaths associated with unmeasured cohort characteristics at age 18 years. We therefore think it is unlikely that systematic differences in smoking patterns by place or date of birth or other characteristics would have biased the study results. In future studies it may 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.(Doll, Peto, Boreham, & Sutherland, 2004)

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 our expectation, an increase in mortality was seen after famine exposure in early gestation but not after exposure in late gestation. In our analyses, early postnatal exposure to famine may also be associated with an increase in mortality but the effect estimate was smaller than for early gestation exposure. 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. Our findings also show that intermediary life conditions do not modify or mediate the relation between famine exposure and mortality. Further follow-up of the study cohort will provide more accurate and ultimately definitive risk measures of long-term mortality and possible mediating intermediary life conditions in relation to extreme nutrition changes in early life.

References

Barker, D. J. P. (1998). *Mothers, babies, and health in later life. 2nd ed*. Edinburgh, New York: Churchill Livingstone.

Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol, 31*(2), 285-293.

Burger, G. C. E., Drummond, J. C., & Sandstead, H. R. (1948). *Malnutrition and Starvation in Western Netherlands, September 1944 to July 1945. Pt 1 & 2*. 's-Gravenhage: Staatsuitgeverij.

Cox, D. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society Series B, 34*, 187-220.

Doblhammer, G., Van den Berg, G. J., & Lumey, L. H. (In press). How Long-term Effects of Famine on Mortality can be underestimated. Unravelling the interplay between Selection and Debilitation. *Population Studies*.

Doll, R., Peto, R., Boreham, J., & Sutherland, I. (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ, 328*(7455), 1519.

Doornbos, G., & Kromhout, D. (1990). Educational level and mortality in a 32-year follow-up study of 18-year-old men in The Netherlands. *Int J Epidemiol, 19*(2), 374-379.

Elo, I. T., & Preston, S. H. (1992). Effects of early-life conditions on adult mortality: a review. *Popul Index, 58*(2), 186-212.

Gadourek, I. (1963). *Riskante Gewoonten en Zorg voor Eigen Welzijn (Risky Habits and Concern about Individual Wellbeing)*. Groningen: J.B.Wolters.

Hayward, M. D., & Gorman, B. K. (2004). The long arm of childhood: The influence of early-life conditions on men's mortality. *Demography, 41*(1), 87-107.

Heijmans, B. T., Tobi, E. W., Stein, A. D., Putter, H., Blauw, G. J., Susser, E. S., et al. (2008). Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A, 105*(44), 17046-17049.

Hoffmans, M. D., Kromhout, D., & de Lezenne Coulander, C. (1988). The impact of body mass index of 78,612 18-year old Dutch men on 32-year mortality from all causes. *J Clin Epidemiol, 41*(8), 749-756.

Horiuchi, S. (1983). The long-term impact of war on mortality: old age mortality of the first world war survivors in the Federal Republic of Germany. *Population Bulletin of the United Nations, 15*, 80-92.

Kannisto, V., Christensen, K., & Vaupel, J. W. (1997). No increased mortality in later life for cohorts born during famine. *Am J Epidemiol, 145*(11), 987-994.

Lumey, L., Martini, L., Myerson, M., Stein, A. D., & Prineas, R. J. (2012). No relation between coronary artery disease or electrocardiographic markers of disease in middle-age and prenatal exposure to the Dutch famine of 1944-1945. *Heart, 98*(22), 1653-1659.

Lumey, L. H., Stein, A. D., & Kahn, H. S. (2009). Food restriction during gestation and impaired fasting glucose or glucose tolerance and type 2 diabetes mellitus in adulthood: evidence from the Dutch Hunger Winter Families Study. *Journal of Developmental Origins of Health and Disease, 1*(S1), S164.

Lumey, L. H., Stein, A. D., & Susser, E. (2011). Prenatal famine and adult health. *Annu Rev Public Health, 32*, 237-262.

Lumey, L. H., & Van Poppel, F. (2013). The Dutch famine of 1944-45 as a human laboratory. In L. H. Lumey & A. Vaiserman (Eds.), *Early Life Nutrition, Adult Health, and Development: Lessons from Changing Diets, Famines, and Experimental Studies*. Hauppauge, NY: Nova Science Publishers, Inc.

Lumey, L. H., & Van Poppel, F. W. (1994). The Dutch famine of 1944-45: mortality and morbidity in past and present generations. *Soc Hist Med, 7*(2), 229-246.
Montez, J. K., & Hayward, M. D. (2011). Early Life Conditions and Later Life Mortality. In R. M. Rogers & E. M. Crimmins (Eds.), *International Handbook of Adult Mortality* (Vol. 2, pp. 187-206). New York, Heidelberg: Springer Science+Business Media.
Preston, S. H., Hill, M. E., & Drevenstedt, G. L. (1998). Childhood conditions that predict survival to advanced ages among African-Americans. *Social Science and Medicine, 47*(9), 1231-1246.
Ravelli, A. C., van der Meulen, J. H., Michels, R. P., Osmond, C., Barker, D. J., Hales, C. N., et al. (1998). Glucose tolerance in adults after prenatal exposure to famine. *Lancet, 351*(9097), 173-177.
Ravelli, A. C., van der Meulen, J. H., Osmond, C., Barker, D. J., & Bleker, O. P. (1999). Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr, 70*(5), 811-816.
Ravelli, G. P., Stein, Z. A., & Susser, M. W. (1976). Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med, 295*(7), 349-353.
Roseboom, T. J., van der Meulen, J. H., Osmond, C., Barker, D. J., Ravelli, A. C., Schroeder-Tanka, J. M., et al. (2000). Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart, 84*(6), 595-598.
Schoenfeld, D. (1980). Chi-squared goodness of fit tests for the proportional hazards regression model. *Biometrika*(67), 145-153.
Sindram, I. S. (1953). [Undernutrition and fetal growth] De invloed van ondervoeding op de groei van de vrucht. *Nederlands Tijdschrift voor Verloskunde en Gynaecologie, 53*, 30-.
Smith, C. (1947a). The Effect of Wartime Starvation in Holland upon Pregnancy and its Product. *Am J Obstet Gynecol, 53*, 10.
Smith, C. (1947b). Effects of Maternal Undernutrition upon the Newborn Infact in Holland (1944-1945). *Journal of Pediatrics, 30*(3), 14.
Song, S. (2009). Does famine have a long-term effect on cohort mortality? Evidence from the 1959-1961 great leap forward famine in China. *J Biosoc Sci, 41*(4), 469-491.
StataCorp. (2009). *Stata: Release 11. Statistical Software*. College Station, TX: StataCorp LP.
Stein, A. D., Kahn, H. S., Rundle, A., Zybert, P. A., van der Pal-de Bruin, K., & Lumey, L. H. (2007). Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine. *Am J Clin Nutr, 85*(3), 869-876.
Stein, A. D., Ravelli, A. C., & Lumey, L. H. (1995). Famine, third-trimester pregnancy weight gain, and intrauterine growth: the Dutch Famine Birth Cohort Study. *Hum Biol, 67*(1), 135-150.
Stein, A. D., Zybert, P. A., Van de Bor, M., & Lumey, L. (2004). Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter. *International Journal of Epidemiology, 33*(4), 831-836.
Stein, A. D., Zybert, P. A., van de Bor, M., & Lumey, L. H. (2004). Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter. *Int J Epidemiol, 33*(4), 831-836.
Stein, Z., & Susser, M. (1975). The Dutch famine, 1944-1945, and the reproductive process. I. Effects or six indices at birth. *Pediatr Res, 9*(2), 70-76.
Stein, Z. A., Susser, M., Saenger, G., & Marolla, F. (1975). *Famine and Human Development: The Dutch Hunger Winter of 1944-1945*. New York: Oxford University Press.
Strand, B. H., & Kunst, A. E. (2007). Childhood socioeconomic position and cause-specific mortality in early adulthood. *American Journal of Epidemiology, 165*(1), 85-93.
Trienekens, G. (2000). The food supply in the Netherlands during the Second World War. In D. F. Smith & J. Phillips (Eds.), *Food, science, policy and regulation in the twentieth century. International and comparative perspectives*. Routledge: London.

Van Abeelen, A. F., Veenendaal, M. V., Painter, R. C., De Rooij, S. R., Dijkgraaf, M. G., Bossuyt, P. M., et al. (2012). Survival effects of prenatal famine exposure. *Am J Clin Nutr, 95*(1), 179-183.

Van Reek, J. (1984). Smoking behaviour in the Netherlands and the United Kingdom: 1958-1982. *Revue d'Epidémiologie et de Santé Publique, 32*(6), 383-390.

Van Reek, J., & Adriaanse, H. (1987). Smoking policy in the Netherlands since the fifties: one factor in the social dynamics of changes in smoking behaviour. *Health Policy, 7*, 361-368.

Table 1. Follow-up status at age 63 by month and year of birth, Jan 1944-Dec 1947, for men examined for military service at age 18 in the Netherlands, by exposure to famine in pregnancy

Month and year of birth	Exposure period*	Famine cities: In military records	Famine cities: Alive	Famine cities: Deaths	Famine cities: Partial or no follow-up**	Non-famine areas: In military records	Non-famine areas: Alive	Non-famine areas: Deaths	Non-famine areas: Partial or no follow-up**
		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 (Postnatal)	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 after 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 postnatal 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.

Table 2. Characteristics at age 18 years, by famine exposure status

	Total	Exposed around pregnancy	Time-controls	Place-controls
Educational level (%)				
Special (less than primary school)	6.1	5.5	6.2	7.4
Primary school (6 years)	13.4	12.9	13.7	14.4
Primary school and 2 more years	34.2	32.4	32.5	40.9
Primary school and 4 more years	31.1	33.1	31.4	25.4
Primary school and 6+ more years	15.3	16.1	16.2	11.9
Father's Occupation (%)				
Non-manual	43.3	46.6	45.7	31.3
Manual	44.7	43.8	44.7	47.3
Farming	4.3	1.6	1.6	14.9
Unknown	7.7	8.0	8.0	6.5
Religion (%)				
Roman Catholic	32.9	30.2	28.5	45.5
Dutch Reformed	30.2	29.9	29.3	31.8
Other	8.4	7.8	7.6	11.0
Without	28.5	32.1	34.5	11.7
Family size (number of siblings) (%)				
1	7.1	7.7	8.4	4.1
2	21.4	22.8	24.5	13.9
3	21.6	22.6	22.5	17.8
4	16.5	16.6	16.6	16.2
5	11.0	10.9	9.9	12.6
6+	20.4	17.6	16.0	33.3
Unknown	1.9	1.8	2.1	2.1
Fitness for military service (%)				
Fit	80.3	81.4	77.9	80.2
Almost fit	6.4	6.0	7.4	6.4
Fairly fit	2.0	2.2	2.1	1.5
Unfit	8.0	7.5	9.0	7.9
Unknown	3.3	2.9	3.6	4.0
Body Mass Index (wt/ht^2) (%)				
<19	2.2	2.1	2.4	2.2
19-20	22.4	21.9	23.9	22.3
20-25	68.5	69.0	66.8	69.1
25+	6.9	7.0	6.9	6.4
Total number	45,037	25,283	10,667	9,087

Table 3. Risk of death in selected famine exposure groups compared to unexposed controls; Hazard Ratios (95% confidence intervals) from Cox regression models

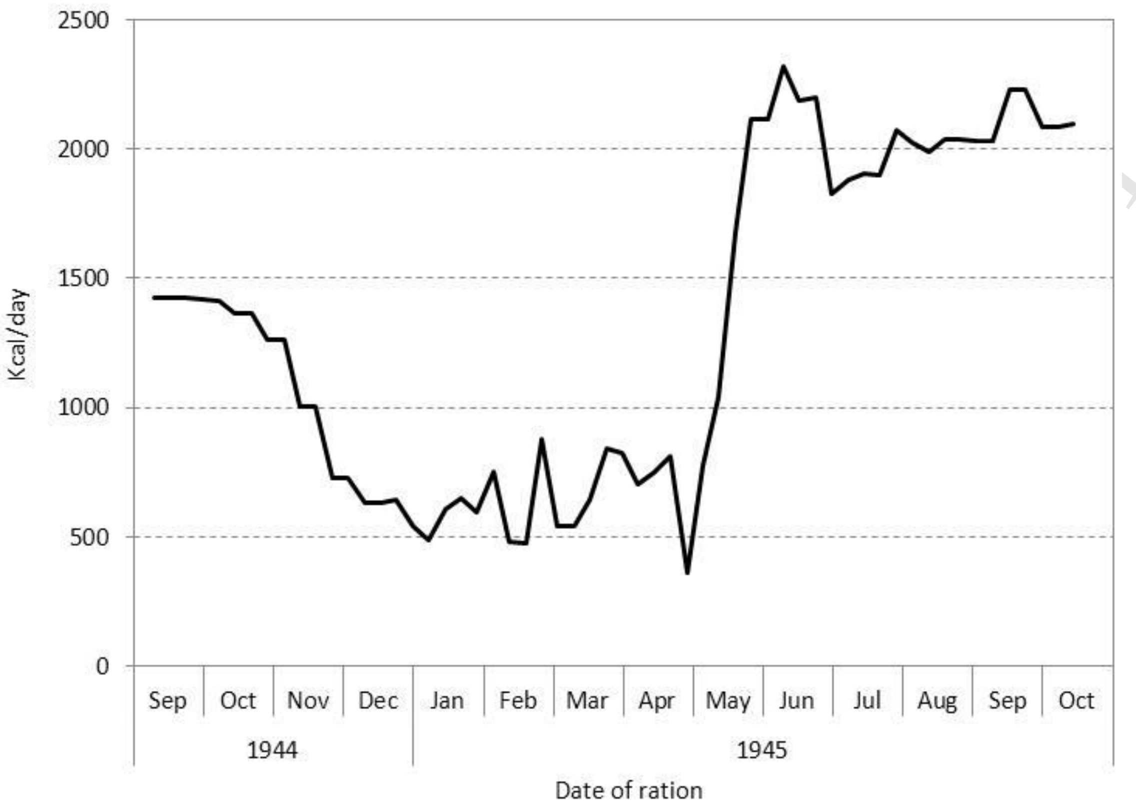
	A			B			C			D		
	HR	p	CI	HR	p	CI	HR	p	CI	HR	p	CI
Famine exposure periods												
Postnatal (PN)	1.06		(0.99-1.14)	1.06		(0.97-1.15)				1.08	*	(0.99-1.18)
3rd trimester (T3)	1.03		(0.96-1.11)	1.02		(0.94-1.11)				1.04		(0.96-1.13)
2nd trimester (T2)	1.02		(0.95-1.11)	1.00		(0.91-1.10)				0.99		(0.90-1.09)
1st trimester (T1)	1.06		(0.97-1.16)	1.09	*	(0.99-1.21)				1.12	**	(1.01-1.24)
Preconception (PC)	0.94		(0.87-1.01)	0.95		(0.87-1.04)				0.96		(0.88-1.04)
Educational level												
Special (less than primary school)	1.35	***	(1.21-1.50)				1.20	***	(1.06-1.37)	1.20	***	(1.06-1.36)
Primary school (6 years)	1.00						1.00			1.00		
Primary school and 2 more years	0.73	***	(0.67-0.79)				0.75	***	(0.69-0.82)	0.75	***	(0.69-0.82)
Primary school and 4 more years	0.70	***	(0.64-0.76)				0.74	***	(0.68-0.80)	0.74	***	(0.67-0.80)
Primary school and 6+ more years	0.57	***	(0.51-0.63)				0.61	***	(0.55-0.69)	0.61	***	(0.55-0.68)
Father's occupation												
Non-manual	1.00						1.00			1.00		
Manual	1.22	***	(1.15-1.30)				1.09	**	(1.02-1.16)	1.08	**	(1.02-1.16)
Farming	1.08		(0.93-1.26)				1.02		(0.87-1.18)	1.01		(0.87-1.18)
Unknown	1.66	***	(1.51-1.83)				1.26	***	(1.13-1.42)	1.26	***	(1.12-1.41)
Religion												
Roman Catholic	0.97		(0.90-1.04)				0.97		(0.90-1.04)	0.97		(0.90-1.04)
Dutch Reformed	0.94		(0.88-1.02)				0.96		(0.88-1.03)	0.96		(0.89-1.03)
Other	0.81	***	(0.72-0.91)				0.83	***	(0.74-0.94)	0.83	***	(0.74-0.94)
Without	1.00						1.00			1.00		
Fitness for military service												
Fit	1.00						1.00			1.00		
Almost fit	1.06		(0.94-1.19)				1.06		(0.94-1.19)	1.07		(0.95-1.20)
Fairly fit	1.03		(0.85-1.26)				1.03		(0.84-1.26)	1.03		(0.84-1.26)
Unfit	1.52	***	(1.39-1.66)				1.43	***	(1.31-1.57)	1.44	***	(1.31-1.58)
Unknown	1.75	***	(1.54-1.99)				1.26	***	(1.06-1.48)	1.27	***	(1.08-1.50)
Body Mass Index (wt/ht^2)												
<19	2.16	***	(1.86-2.50)				1.01		(0.81-1.26)	1.01		(0.81-1.26)
19-20	1.00						1.00			1.00		
20-25	1.00		(0.94-1.08)				1.01		(0.94-1.09)	1.01		(0.94-1.09)
25+	1.38	***	(1.23-1.54)				1.30	***	(1.17-1.47)	1.32	***	(1.18-1.48)

Column A reports estimates for all exposure periods separately and for all intermediary life conditions separately; column B all exposure periods in the same model; column C all intermediary life conditions in the same model; column D all exposure periods and intermediary life conditions in the same model . All models adjusted for place-controls. Number of deaths/person years of follow-up after postnatal exposure: 957/337,755; third trimester exposure: 933/336,073; second trimester exposure: 770/278,660; first trimester exposure: 540/189,325; peri conceptional 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 point; models show no detectable frailty within defined clusters (frailty variance θ is zero and p-value equal one)

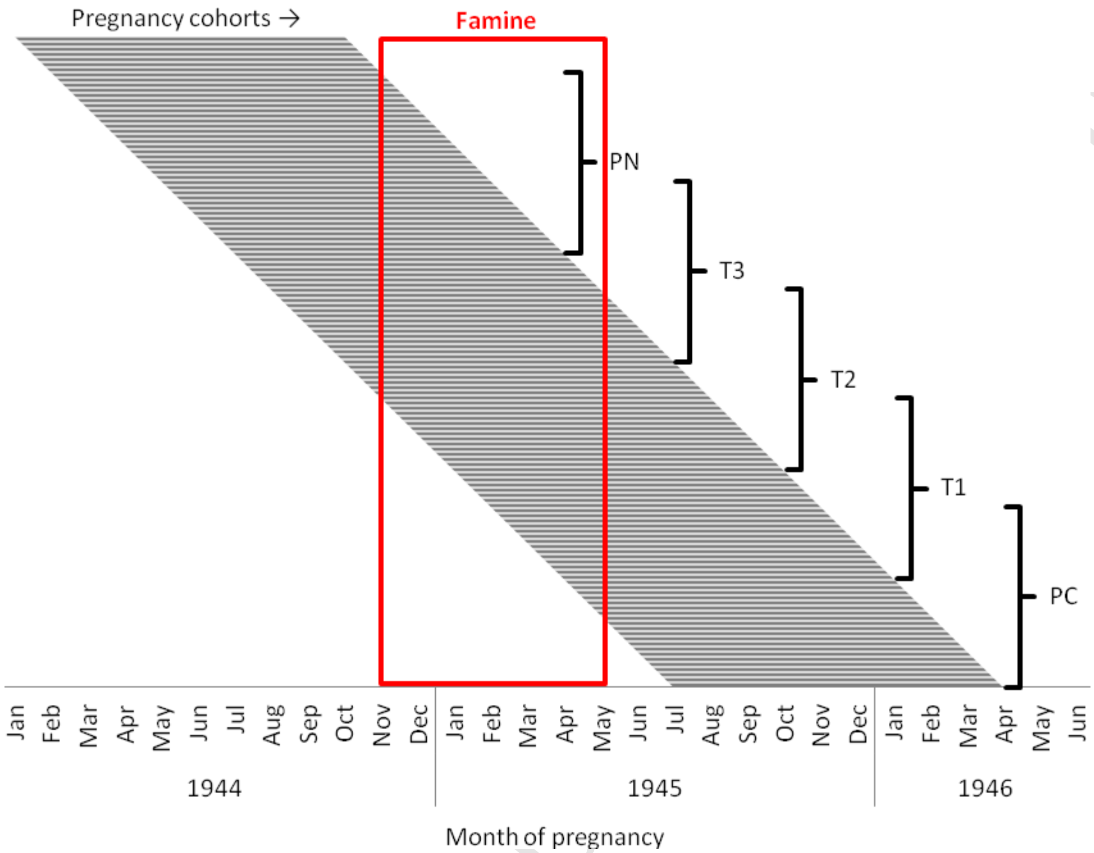
***p < 0.01, **p < 0.05, , *p < 0.10

Figure 1. Food rations in Western Netherlands, Sep 1944 – Oct 1945



Source: Departement van Landbouw en Visserij, Rijksbureau voor de Voedselvoorziening in oorlogstijd, afdeling Voedingsvraagstukken, Onderafd. Statistiek, *West-Nederland. Overzicht van het verloop der rantsoenen in West-Nederland per product, per verbruikers- en arbeidersgroep. A. In grammen per week. B. In aantal calorieen en grammen koolhydraten, eiwitten en vetten, gemiddeld per dag. Over het tijdvak 1 Oct. 1944 – 5 Jan 1946*. Onderafd Statistiek, vL/A1/H. 6 Mei 1946. Daily average from weekly rations.

Figure 2. Classification of famine exposure categories* by pregnancy cohorts



* PN: exposed in the immediate postnatal period; T3: exposed in the third trimester of pregnancy; T2: in the second trimester; T1: in the first trimester; PC:prior to the estimated date of conception.

Figure 3. Military service examinations in early 1960s by region and year and month of birth, Jan 1944 – Dec 1947