Social Science & Medicine xxx (2013) 1–8

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

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

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Nutrition
famine
Mortality
Prenatal exposure
Delayed effects
Netherlands
World war II

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 ($n = 9087$) 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): 1.01–1.24) but not late gestation (HR 1.04; 95% CI: 0.96–1.13). Among intermediary life conditions at age 18 years, educational level was inversely associated with mortality and mortality was elevated in men with fathers with manual versus non-manual occupations (HR 1.08; CI: 1.02–1.16) and in men who were declared unfit for military service (HR 1.44; CI: 1.31–1.58). 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

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http://dx.doi.org/10.1016/j.socscimed.2013.10.027

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 (Fig. 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; 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 were recently 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 1866–1868 (Kannisto, Christensen, & Vaupel, 1997) and a regional study of the Chinese Famine of 1959–1961 (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, 2013). 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, Kromhout, and de Lezenne Coulander (1988) concluded that BMI at young adult age is an independent predictor for mortality.

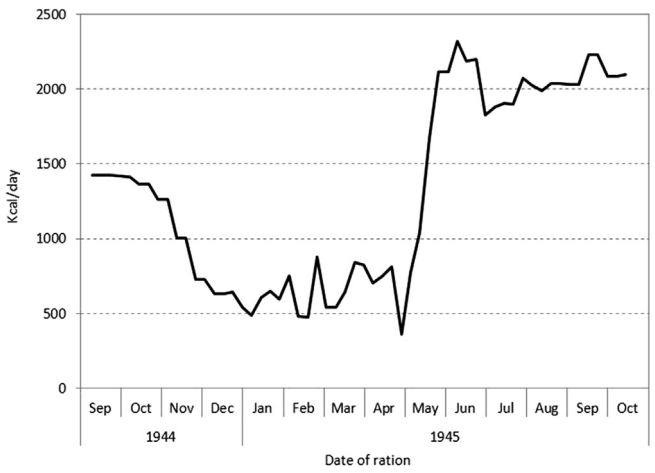

Fig. 1. Food rations in Western Netherlands, Sep 1944–Oct 1945. Source: Departement van Landbouw en Visserij, Rijksbureau voor de Voedselvoorziening in oorlogstijd, afdeling Voedingsvraagstukken, Onderafd. Statistiek, West-Nederland. Overzicht van het verloop der rantsoenen in West-Nederland per product, 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.

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 & Susser, 1975; Stein, Zybert, Van de Bor, & Lumey, 2004) 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 = 9087). 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

Please cite this article in press as: Ekamper, P., et al., Independent and additive association of prenatal famine exposure and intermediary life conditions with adult mortality between age 18–63 years, *Social Science & Medicine* (2013), http://dx.doi.org/10.1016/j.socscimed.2013.10.027