All that's mine I carry with me. Early life disease and adult health in Sweden during 250 years

Lindström, Martin

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To my wife Titti and my daugther Emma

In memory of my mother

Omnia mecum porto mea

Marcus Tullius Cicero 106-43 BC

(All that's mine I carry with me)

Contents

List of abbreviations

CI	Confidence interval
CRP	C reactive protein
CVD	Cardiovascular disease
GDP	Gross domestic product
ICD	International classification of diseases
IMR	Infant mortality rate
OR	Odds ratio
PENMR	Post-early neonatal mortality rate
PTCA	Percutaneous transluminal coronary angioplasty
RR	Relative risk
SEDD	Scanian Economic Demographic Database
SES	Socioeconomic status
SGA	Small for gestational age
SLI	Swedish Longitudinal Immigrant Database
SRH	Self-rated health

List of publications

This doctoral thesis is based on the following publications:

I. Lindström, M., & Davey Smith, G. (2007). A life course perspective to the modern secular mortality decline and socio-economic differences in morbidity and mortality in Sweden. In Bengtsson T (ed.). *Perspectives on Mortality Forecasting. V. Cohort factors: How conditions in early life influence mortality later in life*, pp.9-29. Stockholm: Social Insurance Agency.

II. Bengtsson, T., & Lindström, M. (2000). Childhood misery and disease in later life: The effects on mortality in old age of hazards experienced in early life, southern Sweden, 1760-1894. *Population Studies*, 54, 263-277.

III. Bengtsson, T., & Lindström, M. (2003). Airborne infectious diseases during infancy and mortality in later life in southern Sweden, 1766-1894. *International Journal of Epidemiology*, 32, 286-294.

IV. Klinthäll, M., & Lindström, M. (2011). Migration and health: a study effects early life experiences and current socio-economic situation on mortality of immigrants in Sweden. *Ethnicity and Health*, 16(6), 601-623.

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Malmö, October 2015

1.Introduction

1.1 The rationale and aim of the thesis

The past 200 hundred years have shown a global surge in life expectancy which started in some western countries including Sweden in the late 18th century and has generally, with wide variations in timing and a number of temporary setbacks, been ongoing since then. The mortality decline underlying this increase in life expectancy was eventually seen in all age strata in Sweden and most other countries. The mortality decline seems to have been correlated with an increase in stature and final adult height. Average adult height increased almost continuously already during the 19th century (Sandberg & Steckel, 1997; Öberg, 2014). According to Fogel (2004) and Floud et al. (2011), western populations have experienced a "technophysio evolution" during the past three hundred years by which increasing body height and work capacity has increased labour productivity, which in its turn has led to increased food and energy consumption, leading to even further increases in height and consequent work capacity in a virtuous cyclical development of events, although the causal relationships remain hard to confirm for both reasons of causal circularity and relative scarcity of empirical evidence. McKeown (1979) suggested an inverse correlation between improved nutrition (both better quality and increased energy content in the food) and the decrease in infectious disease mortality, and he implied a causal connection between increased nutrition and a decrease in infectious disease mortality which started and was mostly concluded before preventive measures and treatment with relevant antibiotics were introduced. Other authors also point to the fact that the massive mortality decline in most infectious diseases temporally preceded both the discovery and introduction of vaccination programs and antibiotics treatments in some western countries (Fridlizius 1984; Steckel, 2008; Floud et al. 2011), although Fridlizius asserts that changed virulence of some infectious diseases including smallpox may have caused the initial decline in infant mortality (Fridlizius, 1989).

The causal mechanisms involved in the modern secular mortality decline have historically varied over time both in essence and relative importance. In general terms changed virulence of some infectious diseases (see e.g. Fridlizius, 1989), and improved standards of living, nutrition and housing conditions, i.e. environmental factors (see e.g. McKeown, 1979), are likely to have been important in the earlier stages. On the other hand, factors such as improved health related behaviours, e.g. a substantial decline in tobacco smoking (see e.g. Jarvis & Wardle, 2006), and medical factors, e.g. the introduction and increased use of by-pass surgery in recent decades (see e.g. Persson, 2001; Danielsson, 2009), seem to have increased in importance during the recent stages of the decline. It seems that the increasing socioeconomic differences in mortality during the 20th century (see e.g. Bengtsson & Dribe, 2011), may to an important extent be explained by differences in health related behaviours (Danielsson, 2009), particularly in countries such as Sweden with at least formally equal access to health care, although the research regarding the long-term development remains scarce.

The causal mechanisms connected with the increase in life expectancy and corresponding decrease in age-specific mortality may be discussed in terms of period effects, i.e. effects in wide age groups with a restricted time lapse between exposure(s) to the factor(s) which trigger (cause) the disease and the disease itself. However, in recent decades the scientific debate concerning causal disease mechanisms have increasingly focused on life course epidemiology and the effects of exposure to health risk (and health protective) factors in early life on disease in later life, often several decades later (Kuh & Ben Schlomo, 2004). When such life course biological mechanisms stem from exposure in the very earliest part of life, i.e. during growth in utero or in the first year(s) of life, they are often referred to as cohort effects/mechanisms due to the fact that different birth cohorts in the same country or population may experience different exposures depending on the year of birth, i.e. which birth year cohort they belong to. Empirical evidence of such impact on mortality rates were reported already in the 1930s (Kermack, McKendrick, & McKinlay, 1934). This notion is also intuitively appealing, given the fact that the great mortality decline in e.g. Sweden started with a decrease in infant mortality rates, followed by age-specific mortality decline in childhood and early adult ages, finally starting more than half a century later with a decline in age-specific old age mortality.

The recent interest in cohort effects started with the physician D.J.P. Barker who initially adhered to the notion that infectious diseases particularly in

infancy (first year after birth), which he regarded as an indicator of standards of living, are associated with ischaemic heart disease incidence and mortality in later life (Barker & Osmond, 1986a), but soon he re-focused interest to effects of nutrition and consequent foetal growth retardation in utero on disease and particularly the metabolic syndrome in later life, i.e. "the Barker hypothesis" (Barker, 1995; Barker, 1997a), which will also be termed "the foetal origins hypothesis" in this thesis. "The Barker hypothesis" or "the foetal origins hypothesis" is one of the two early life hypotheses to be tested in the thesis. In this context nutrition is essential, and the concept "gross nutrition" designates the total dietary (nutrient) intake, while the concept "net nutrition" is defined as the balance between nutrient intake and the claims on that intake. Some other authors have expanded the notion that net nutrition in early life may affect disease incidence and mortality in later life to include not only the deficits in nutrition in the foetal stage, but also in the early parts of life after birth, particularly the parts of childhood with known growth spurts such as the first year of life and the entrance into adolescence (Floud et al., 2011).

In contrast, other authors have further developed the notion that particularly infectious diseases experienced in early childhood affect disease incidence and mortality rates of certain diseases in adulthood and later life. Fridlizius (1989) suggested as one of several plausible hypotheses that a decrease in infectious disease mortality in childhood (0-5 year) may lead to better health for a cohort even in adulthood, resulting in decreased mortality. This notion was investigated in two empirical and historical longitudinal studies including individual level data which demonstrated that higher infant mortality rate (IMR) (age 0-1 year) experienced by a specific birth cohort was positively associated with old age (55-80 year) mortality for the same birth cohort during the late 18th and 19th centuries (Bengtsson & Lindström, 2000), and that these IMR effects on later life mortality may have been caused by infectious diseases and particularly airborne infectious diseases during the first year of life after birth (Bengtsson & Lindström, 2003). The Bengtsson and Lindström (2000) and Bengtsson and Lindström (2003) articles are among the five articles of this thesis, but they are presented here because somewhat later Finch and Crimmins (2004), citing Bengtsson and Lindström (2003), presented and further developed the notion that inflammatory exposure in early life may affect human life-spans particularly if the exposure to inflammation becomes chronic. Later studies on Swedish data have also empirically demonstrated effects of post-neonatal mortality rates (PENMR)

on adult mortality (Quaranta, 2014) and effects of infant mortality rates on sickness absence during adulthood among children to parents with low socioeconomic status (Helgertz & Persson, 2014). The concepts "selection" and "scarring" have been introduced to denote different effects of adverse conditions in early life. "Selection" is defined as the selection of individuals who survive or resist adverse exposures and living conditions for genetic, congenital or other reasons. "Scarring" is defined as permanent damaging effects on the human body resulting in increasing death rates later in life (Preston et al., 1998; Quaranta, 2013). Recent studies on historical British data also suggest that infant mortality have "scarring" rather than "selecting" effects on survivors in the sense that birth cohorts exposed to high infant mortality rates have poorer health later in life ("scarring") rather than the survivors becoming stronger and selected to better health and a longer life ("selection") (Hatton, 2011). This notion is now highly viable and applied to clinical practise for diseases, including a number of modern chronic diseases, with the inclusion of the inflammation marker CRP as a risk factor in clinical risk assessment of cardiovascular diseases in the USA as one of the most recent examples (Goff et al., 2014). Still, the persistence of "the Barker hypothesis" and the work by Floud et al. (2011) indicates that the debate concerning diet/net nutrition versus disease exposure in early life is still ongoing, and consequently both "the foetal origins hypothesis" and "the inflammation hypothesis" will be investigated in this thesis.

The overall aim of this thesis is to investigate whether associations between early life risk exposures and adult health may have existed during different parts of the secular mortality decline. The idea that early life experiences and exposures may eventually become clinically apparent in adult and even late adult life may be captured by the quotation by Marcus Tullius Cicero (106-43 BC) saying "all that's mine I carry with me" (Omnia mecum porto mea) which is the title of this thesis. This proverb has been used in different meanings partly or wholly deviating from the original meaning which concerns the independence of intellectuals and philosophers in relation to material goods. In the title of this thesis it alludes to the fact that effects of early life experiences and exposures may be carried in subclinical stages through the life course by those exposed until the effects become clinically apparent in adulthood, but it may of course just as well reversely allude to decreased risk due to the lack of risk-inducing early life exposures.

One specific aim is to discuss early life mechanisms in the secular mortality decline in historical and modern settings in Sweden and other countries. The

second specific aim is to investigate the importance of early life conditions such as disease load on infants and their mothers during the preceding pregnancy, nutrition load during the foetal stage and first year of life and disease load during the first year of life, and current (adult) conditions for mortality including causes of death in later life in four parishes in Scania during the 18th and 19th centuries. The third specific aim is to investigate the importance of early life and current (adult) conditions for mortality in later life (55-80 years) in Scania in the 18th and 19th centuries, taking the causes of death during infancy (0-1 year) of a particular cohort into consideration. Early life exposures include disease load during the year of birth, food prices during pregnancy, birth season, and disease load on mothers during pregnancy. The fourth aim is to investigate associations between early life conditions, measured as IMR and GDP per capita in the year of birth in the country of birth as well as current socioeconomic conditions in adult life and mortality in cardiovascular diseases, all cancers, all other causes of death and total mortality in Sweden in the late 20th century for men and women born in eleven different countries in the inter-war period. The fifth aim is to investigate associations between IMR in the year of birth as well as individual socioeconomic stress in childhood, and self-rated health in adulthood in a sample of adult men and women aged 47-81 living in Scania in 2008. It should be noted that the aim of this thesis is not to investigate the relative impact of early life or cohort exposures on the total secular mortality decline that started in the late 18th century.

The following introduction will first present essential aspects of the secular mortality decline and the discussion in the literature concerning its causes. The introduction will then present and discuss the cohort mechanisms, "the foetal origins hypothesis" and "the inflammatory hypothesis", to be investigated in the thesis. Finally, the introduction will present the historical, geographic and social backgrounds for each of the empirical studies presented in the thesis.

1.2 The secular decline in overall and infant mortality

During the past 200 years most countries in the world have experienced a dramatic increase in life expectancy. The general mortality decline started in Sweden and some other countries in Western Europe in the second part of

the 18th century. In 1751 life expectancy at birth was 36.8 years for men, 39.9 years for women and 38.4 years for the entire population (men and women) in Sweden (Human Mortality Database, www.mortality.org, Figure 1). In 1945 it had increased to more than 67 years for men and almost 70 years for women, and in 2013 life expectancy at birth was 80.1 years for men and 83.7 years for women (Danielsson, 2009; Heimersson, 2014). The timing of the onset of this mortality decline and corresponding increase in life expectancy has vastly differed between countries. Interestingly, only eight countries- Australia, Iceland, Japan, The Netherlands, New Zealand (non-Maori), Norway, Sweden and Switzerland- have been leaders in the sense of having had the highest life expectancy in the world in a given year over the past almost 200 years (Oeppen & Vaupel, 2002), although many other countries followed them in the same trend of rising life expectancy. The pace of the development has also varied considerably. Some countries in the world have still not achieved the life expectancy levels experienced by the most developed countries already more than one hundred years ago. Some countries have even experienced a temporary backlash in the form of declining life expectancy in the 1990s due to for instance increased unemployment and alcohol consumption in some Eastern European countries, and the HIV/AIDS epidemic and civil war in some African countries. Still, the general picture of improvement in life expectancy remains massively impressive.

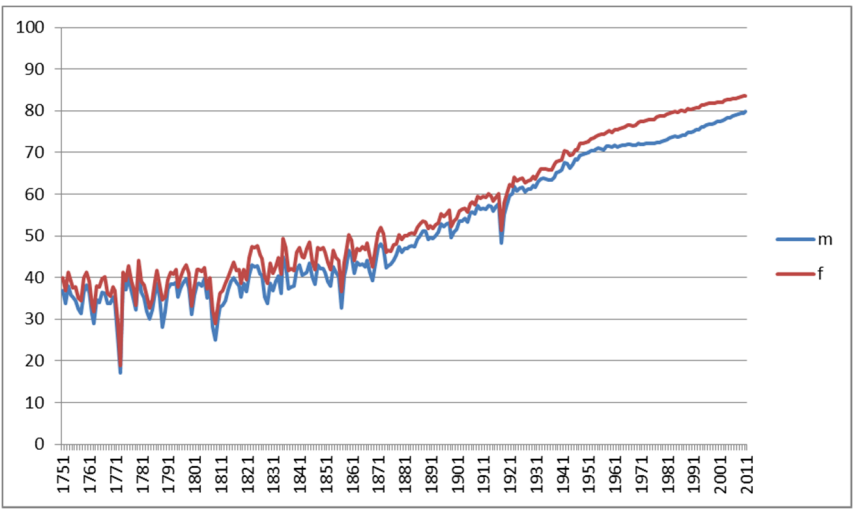

Figure 1. Life expectancy among men and women in Sweden 1751-2011. (Human Mortality Database, www.mortality.org)

The pre-modern mortality regime was characterized even in normal, non-catastrophic years by higher levels of age-specific mortality in all age intervals compared to corresponding age intervals today. In comparison with current age-specific mortality rates, the age-specific mortality rates were comparatively high for children, and the age-specific mortality rate was particularly high among infants (0-1 years). The pre-modern mortality regime was also characterised by intermittently recurring mortality catastrophes mostly due to recurring epidemics of infectious diseases (McNeill, 1976). Another feature of the pre-modern mortality regime was that there were secular trends or, more specifically, secular cyclical patterns in the comparatively high levels of age-specific mortality (Wrigley & Schofield, 1981).

The mortality decline that started in Sweden in the 18th century included a secular decline in the normal-year age specific mortality rates, but also the disappearance of the intermittently recurring epidemic catastrophes. The normal-year age specific mortality rates first started to decline in Sweden among infants (0-1 year) in the late 18th century. In the beginning of the 19th century the mortality decline also started in other age groups among children and young adults. In the mid-19th century, the decline in old-age mortality slowly commenced (Fridlizius, 1984; Perrenoud, 1984).

An important factor in the secular mortality decline has until relatively recently been the decline in infant mortality rate (IMR), i.e. the mortality rate in the 0-1 year age interval. The decline in IMR has been an ongoing trend since the late 18th century, but it has also been characterized by a reduction in the between-year variation in IMR (Figure 2). In 1801-1810 IMR was still approximately 200 per 1000 in the age interval 0-1. In 1901-1910 it had declined over a century to approximately 85 per 1000 (Hofsten, 1986). The decline in IMR has continued in modern Sweden from somewhat more than 60/1000 in the late 1920s to approximately 6/1000 in 1990 and 2.06/1000 in 2011 (Danielsson, 2009; see also Human Mortality Database, www.mortality.org). The historically and internationally low IMR as well as child mortality above age 1 year in present-day Sweden and other developed countries implies that the decline in IMR and child mortality above age 1 year can no longer be a major (or even minor) driving force in the still ongoing secular mortality decline. Predictions that life expectancy will continue to increase (see e.g. Oeppen & Vaupel, 2002) will thus inevitably have to rely on decreases in age specific mortality in the middle-age and older segments of the population(s) in developed countries (Deaton, 2013; Oeppen & Vaupel, 2002).

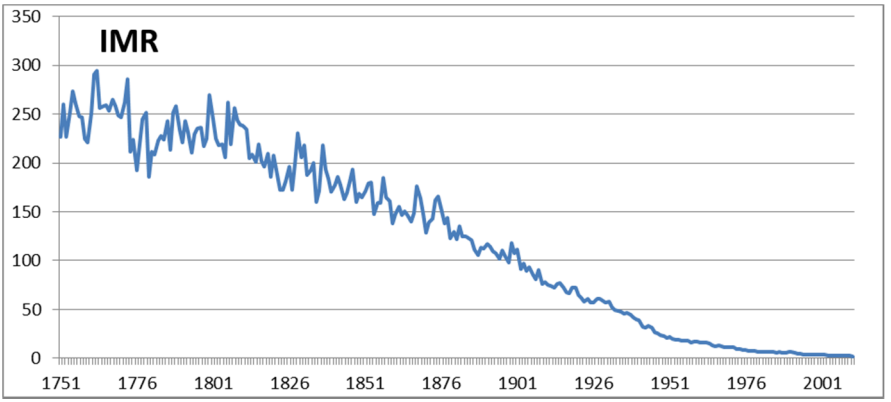

Figure 2. Infant Mortality Rate (IMR), defined as deaths per 1000, in Sweden 1751-2011. (Human Mortality Database, www.mortality.org)

1.3 The influence of disease patterns, prevention, medical treatment, nutrition and other factors on the mortality decline

The literature concerning the changing preconditions for health in the general mortality decline contains a number of causal factors including economic, social, institutional, behavioural, nutritional and medical/disease-related factors. The nutritional and medical/disease-related factors seem to be the most prominent in the literature, probably because they are proximal in the chain of causality.

First, one mechanism may be a change in the patterns of exposure to infectious diseases in particular. The plague for instance intermittently returned to Europe from the mid-14th century until the beginning of the 18th century in recurring waves of epidemics. These waves of plague epidemics disappeared in the first part of the 18th century in Western Europe, although the disease remained almost endemic in Eastern Europe, the Middle East and Asia Minor (McNeill, 1976). The causes behind this transformation are not known.

A second mechanism could be a change not in the exposure but in the virulence of some infectious diseases, i.e. a change in the severity of the disease

caused by the agent once it has established itself in the host. Fridlizius (1984) made the interpretation that the earliest demographic signs of increasing life expectancy, observed as a decrease in infant mortality in Sweden in the late 18th century, were caused by decreasing virulence of some infectious diseases, i.e. a changed relationship between micro-organisms and the human host in favour of the human host. This change in virulence is particularly obvious for smallpox, a disease which started to decline in the middle of the 18th century even prior to the introduction of inoculation and vaccination (Helleiner, 1957; McKeown & Record, 1962; Sköld, 1996a, 1996b). Older historical records also suggest that smallpox was recognised before 1500 without having been considered a particularly virulent infection (Carmichael & Silverstein, 1987). There thus seems to have been rather dramatic and idiopathic, i.e. unexplained, changes in the virulence of smallpox both around 1550 and 1750 without any known or even plausible medical or hygienic explanations, a fact which supports the virulence theory.

A third mechanism is the advancement of medicine during the past 200 years. In some regards the impact of the development of medical treatments on health and disease outcomes, e.g. penicillin and other antibiotics in the field of infectious diseases, seems to be unquestionable though mostly late. McKeown (1979) investigated the relationship between the cause specific mortality decline in a vast number of infectious diseases and the invention of preventive measures such as vaccinations and active treatments such as antibiotics. He found in most cases, including smallpox in England and Wales, that prevention such as vaccination and active treatments such as antibiotics or other pharmaceutical drugs were implemented long after the initiation of cause specific mortality decline in many infectious diseases or, in the most extreme case, even after the extinction of the disease. Most vaccinations as well as active treatments of infectious diseases were introduced well into the 20th century, e.g. penicillin in the early 1940s, long after the start of the corresponding mortality decline. McKeown found similar lags in other aspects of the relationship between the development of medical science as well as medical institutions, and cause specific mortality in infectious diseases as well as non-infectious diseases (McKeown, 1979). McKeown also discussed the relationship between the early development of public health and the situation of hygiene during the early period of the modern mortality decline. The effects of the development of public health reforms on mortality were late and did not encompass the first period of the modern mortality decline, due to for instance the poor quality of the available water which made

it relatively advantageous not to wash hands or to use the water for cleaning (McKeown, 1979). Still, the total effects on life expectancy of screening and active treatment of medical conditions was estimated to an additional approximately five years in the 2001 national public health report in Sweden, of which coronary artery surgery and PTCA alone were estimated to account for 1.2 years (Persson, 2001). It is thus possible that the role of medicine has increased in the later phases of the modern secular mortality decline (Bunker, Frazier & Mosteller, 1994).

McKeown indirectly, by exclusion of other factors, concluded that other factors such as the general social development and economic growth during the late 18th, 19th and early 20th centuries must have contributed significantly to the mortality decline. The most important causal pathway, according to McKeown, was improved nutrition (as a consequence of the economic improvements), which for instance might have reduced the mortality rates in infectious diseases (McKeown, 1979.; McKeown, 1988). The nutrition hypothesis suggested by McKeown thus constitutes a fourth mechanism in the secular mortality decline.

The nutrition hypothesis suggested by McKeown has been supported to some extent by findings from empirical investigations from England and Wales 1750-1914 (Harris, 2004). The association between nutrition and health is certainly obvious because certain amounts of energy and nutrients are required in order to stay alive. The World Health Organization provides formulas to calculate the "basal metabolic rate" (BMR), i.e. the lowest amount of energy required to maintain essential body functions even without energy expenditure in the form of physical activity (World Health Organization, 1985). The Body Mass Index (BMI) (measured as body weight in kilograms divided by the square of body height in metres) is also related to body function and survival. Obesity (BMI>30) and overweight (BMI>25) are causally related to cardiovascular diseases and diabetes mellitus type II (Wickelgren, 1998). However, underweight is also still a public health problem even in economically highly developed countries. The recommended cut-off levels between underweight and normal weight have long revolved around BMI 18.5-19.0 with reference to increased risk of long-term development of cardiovascular diseases (James & Francois, 1994).

Specific nutrients are also essential in adequate doses for preventing the occurrence of diseases as well as stunting. Samuel Preston has suggested not only a health production function, relating life expectancy to GDP per capita,

but also an upward "shift" in the function caused by "technological change" and the increased ability, made possible by increased education and caloric intake per capita, to use given resources more productively in order to control disease and lengthen life (Preston, 1975). Other authors also suggest that important segments of the pre-modern populations in some countries in Europe, e.g. France, were stunted and consequently, due to this fact, prone to higher morbidity and mortality and decreased work capacity (Fogel, 1994). According to Fogel (Fogel, 2004) and Floud et al. (Floud et al., 2011), humans and human societies have during the past 300 years in a historically unprecedented way been able to create economic and technological innovations in order to control their environment, which have resulted in physiological development and improvement of the human body, e.g. increased height, resulting in increased capacity to work and increased life expectancy, in its turn followed by further improvements in the physiological properties of the human body such as height, and further increased capacity to work in the next generation, in a virtuous cycle that commenced in the 18th century in the western world. This theory and the empirical findings which support it also point to the life course and trans-generational approach to epidemiology which will be more thoroughly discussed in the cohort explanations section. The theory and the empirical findings which support it also suggest that Malthus' notion that human populations were limited in number by the access to nutrition and energy (Malthus, 2007(1798)) should be modified, because data suggest that the human body and human populations probably could also adapt to varying access to nutrition and energy by changing body height and body size (Floud et al., 2011).

Famine and under-nutrition also remain serious problems in many present underdeveloped countries, and under-nourishment is still a very commonplace problem in different segments of the population, e.g. old people in highly developed countries. Under-nourishment affects children particularly hard (Riley, 2001), and the natural course of some infectious diseases such as measles, diarrhoeas, tuberculosis, most respiratory infections, pertussis, most intestinal parasites, cholera, leprosy and herpes are definitely influenced by nutrition (Rotberg & Rabb, 1985; Terris, 1948).

Livi-Bacci (1991) has pointed to the fact that socio-economic differences in mortality seem to have appeared as late as in the later part of the eighteenth century in England and even later in many other countries in Europe. Other authors supported by empirical studies with a wide geographic coverage (individual-level data from Western and Southern Europe, the USA and

Canada) and a long time horizon (mainly the 19th and early 20th centuries) conclude that mostly weak socio-economic differences in mortality existed in some locations before the industrial revolution and not in others. The same authors also conclude that socioeconomic differences in mortality appeared both before and after the industrial revolution, but also that the more consistent associations between income (and other indicators of socioeconomic status) and mortality observed in recent decades is a relatively new phenomenon (Bengtsson & van Poppel, 2011). The pre-modern comparatively weak socioeconomic differences in mortality or lack of socioeconomic differences in mortality could be explained by factors such as the high incidence of deaths in infectious diseases in which the outcomes death/non-death do not depend on either nutritional factors such as current nutritional status and stature, or death in combat (which seems to have increased the mortality of the male population of particularly the nobility) (Livi-Bacci, 1991). In combinations cereals and vegetables can provide an adequate diet, even in the absence of animal proteins (Wing & Brown, 1979). Traditional Mediterranean and Mesoamerican diets, rich in leguminous vegetables and cereals, are quite adequate in terms of proteins. Some populations living on strictly vegetarian diets show no evidence of protein deficiency (Livi-Bacci, 1991). According to Livi-Bacci, there are no or very scarce data available indicating improvements in nutrition in the late 18th or early 19th centuries at the point in time when the modern decline in mortality began in some European countries. Some data even indicate that the stature (body height) of young male military conscripts in the Habsburg Empire was lower at the beginning of the 19th century than they had been earlier in the 18th century, while other data from Sweden show no increase in stature (body height) from the 18th to the early 19th century. These findings suggest the lack of explanatory power in the nutrition (and indirectly economic growth) hypothesis regarding the mortality decline (Livi-Bacci, 1991). A recent study from five parishes in southern Sweden suggests that the linear increase in stature started in the 1830s and 1840s, which is the same pattern as the national pattern and also precedes the start of the industrial revolution in Sweden which commenced in approximately 1870. Results from this study also show that there were no or very small socioeconomic differences in height between sons of farmers and farm labourers among male conscripts (mostly aged 21) in the 19th and early 20th centuries in the five parishes, although some consistent differences in height were observed between some non-manual and manual workers (Öberg, 2014).

Rotberg and Rabb (1985) have also critisised McKeown for being too unidirectional in his conclusions concerning the relationship between nutritional status and infectious diseases. Rotberg and Rabb argued that infectious diseases *per se* may also lead to undernutrition and poor nutritional status. Not only gross nutrition but also net nutrition, i.e. the balance between the energy and nutrients required to maintain essential body functions and the energy and nutrients consumed, is of importance. Infectious diseases increase the demand for energy and nutrients to uphold basal body functions (Bengtsson et al., 1998).

Szreter has critisised McKeown for using a very narrow definition of medicine, i.e. "medicine" defined as either scientific discovery or the effects of clinical and hospital practises only. According to Szreter this definition in a misleading way tends to understate the importance of medical men, public health policy and human agency in general in bringing about the 19th century mortality decline (Szreter, 1988).

New methods to prevent diseases (starting in mid-18th century), new vaccines (programs starting to be implemented in the 1890s, with the exception of smallpox which was implemented earlier and had distinct earlier effects), new medicines and antibiotics as treatments against infectious diseases (starting in the 1930s) and the sanitary revolution (starting in England in the 1840s and implemented in most other Western countries in the late 19th century) contributed to the mortality decline (Preston & van de Walle, 1978; Easterlin, 1996; Easterlin, 1999).

The literature so far suggests that much of the debate is centred on the task of trying to find mono-causal disease mechanisms. Disease exposure, changing virulence and nutritional mechanisms are sharply contrasted against institutional or medical human agency mechanisms. In contrast, Abdel Omran (1971) outlined a more dynamic and multi-causal perspective on the secular mortality decline and the subsequent shifts in disease patterns and disease mechanisms. Omran emphasised that a long-term shift in mortality and disease patterns occurred. As a result, pandemics of infectious diseases were gradually replaced by degenerative and man-made diseases as the chief cause of morbidity and primary cause of death. Omran also stressed the importance of complex patterns of ecobiologic, socioeconomic, political, cultural, medical and public health determinants (Omran, 1971). These shifts in health and disease patterns that characterise the epidemiologic transition are closely associated with the general demographic and socioeconomic

transition which constitutes the modernisation complex, according to Omran (Omran, 1971).

The complex patterns of disease mechanisms have also been stressed by Riley (2001) who emphasised the varying relative importance of public health policy, medicine (e.g. early smallpox vaccination), wealth and income, nutrition and diet, health related behaviours and literacy/education in the web of causal factors resulting in rising life expectancy during a long time period, i.e, a multifactorial model or web of causation. Public health measures helped suppress water borne diseases in much of Western Europe. Public health inaugurated the study of the disease problems of poverty. It also added new and effective means of disease surveillance and control, it produced mass vaccination, and it launched insect control. Public health also pioneered the purposeful application of medical, social and scientific insight into health and survival. Medicine provided useful therapies and spectacular remedies for some diseases, especially infectious diseases. Medicine also provided new knowledge concerning disease avoidance. Furthermore, techno-medicine added the promise of replacing defective, diseased, or worn-out body parts. Income and wealth are enabling factors, which, however, may have both beneficial and detrimental effects on health. The beneficial effects include more money for spending on public health programs, medical treatments and healthcare in general as well as improved living conditions, housing, nutrition and sanitation. Detrimental effects caused by high income and wealth stem from factors such as sedentary lifestyles, over-consumption of food and environmental effects of rising living standards. Education and literacy have become increasingly important in promoting health during the past century. Education also strengthens the mother's role in advocating the child's rights and interests (Riley, 2001).

In connection with the complex patterns of health determinants and their interaction, not only socioeconomic status (SES) differences but also socioeconomic status gradients in health have been identified and studied since the 1970s (Marmot et al., 1978; Marmot & Wilkinson, 2006). Socioeconomic status (SES) is commonly defined according to education, income and occupation (Lynch & Kaplan, 2000). Socioeconomic determinants of health as well as socioeconomic differences in health are of high importance for modern disease and mortality patterns (Marmot et al., 1978; Marmot & Wilkinson, 2006), but results of empirical studies suggest that socioeconomic differences in health were less prominent or, as observed in a few studies, even absent in pre-modern times (Bengtsson, 2000;

Bengtsson, 2004; Bengtsson & van Poppel, 2011; Bengtsson & Dribe, 2011; Schenk & van Poppel, 2011; Haines & Ferrie, 2011; see also Wrigley & Schofield, 1981). Socioeconomic status according to occupation is often defined in historical data according to level of skills, degree of supervision, employment status and occupational category (van de Putte & Miles, 2005), but socioeconomic conditions of pre-industrial agrarian society such as owner conditions and farm size are also relevant (Bengtsson & Lindström, 2003). The epidemiologic transition theory presented and described by Omran (1971) may thus imply an increasing importance of varying aspects of SES as determinants of morbidity, mortality and life expectancy as the age of pestilence and famine and the age of receding pandemics, both dominated by infectious disease morbidity and mortality, progress into the age of degenerative and man-made diseases, dominated by chronic diseases such as cardiovascular diseases and cancers which for decades have been the two major causes of death in the Western world as well as two of the major causes of chronic disease.

The growing interest in a life course perspective on epidemiology considers long-term effects of early life exposure on later life chronic disease pathogenesis, subclinical progress, incidence, symptoms and mortality. Barker (1995, 1997a, 1998) has suggested a causal connection between foetal nutrition and cardiovascular disease in later life, preceded and mediated by the pathogenesis and progression of subclinical atheroschlerosis in a long symptom free latent stage, which spurred an exponentially growing research interest in life course approaches to chronic disease epidemiology (Kuh & Ben-Schlomo, 2004). Although infectious diseases were initially mainly considered to have a mono-causal one-to-one relationship between exposure (bacteria) and disease by their discoverers in the 1870s, Jakob Henle and Robert Koch (Carter, 1985), infectious diseases may also have long-term effects on health mediated by chronic inflammatory processes consistent with a life course perspective in epidemiology. The "foetal origins" hypothesis and the infancy "inflammation" hypothesis will both be discussed in greater depth in the following section concerning early life and life course disease mechanisms where they rightly belong.

1.4 Early life and life course/ cohort mechanisms

The secular mortality decline can plausibly only be discussed in terms of multi-causality rather than mono-causality. However, this multitude of causes and their plausible interactions does not only include direct, periodic effects on mortality and survival such as for instance the immediate effects of epidemics, starvation or access to health care and treatment. Instead, the multitude of causes also includes long-term, sometimes very long-term, effects. Such causal mechanisms referred to as cohort mechanisms will be discussed in more detail in this section.

The literature referred to so far, with the exception of Fogel (2004) and Floud et al. (2011) and their notion the "technophysio evolution", generally discusses temporally direct or period effects on mortality and trends in mortality caused by factors such as changes in the exposure to epidemics, the virulence of infectious diseases, public health, medicine, income, nutrition, health related behaviours and education/literacy. The term period effect denotes effects on health and survival caused by health determinants (see above) with a short time period between exposure and health/disease outcome. Most infectious diseases for instance give rise to symptoms in very short time (hours-days-weeks) after the initial exposure to infection. However, for some infectious diseases such as tuberculosis (caused by *mycobacterium tuberculosis*) and lepra (caused by *mycobacterium leprae*) the time interval from exposure to disease/symptoms may be much longer (months-years) due to the slow pace of multiplication of the pathogen in the infected human host. Other exposures and diseases, especially non-infectious chronic diseases such as many specific cancers and cardiovascular diseases and their lifestyle risk factors, may have much longer latency periods, i.e. time intervals from exposure of determinant risk factors to disease, amounting to several decades. Tobacco smoking is a prevalent, potent and thus very important example of exposures leading to symptomatic disease decades later.

For some diseases, the time lag between exposure and disease may even range from early-life (intra-uterine or first year/years of life) exposure resulting in later life or old-age morbidity and mortality. This notion seems plausible already given the fact that the general mortality decline started with a decrease in infant (0-1 year) mortality, then continued with a start in the decrease in child mortality, later followed by a start in the decrease in adult mortality and, eventually, a decrease in old-age mortality approximately 60-70 years later

than the initial decrease started in infant mortality (see section 1.2 above). The idea that exposure in early life to risk factors or protective factors may affect disease and health in later life had been proposed earlier (for details in the history of such ideas see Bengtsson et al., 1998), but the cohort or early life effects in relation to the great mortality decline was first proposed and empirically investigated by Kermack, McKendrick and McKinley in 1934. They studied age-specific mortality in England, Wales, Scotland and Sweden in the late eighteenth century and onwards. Their conclusion was that reductions attained at any particular time in the death rates of various age groups depended primarily on the date of birth of the individuals, i.e. it depended on birth cohort, and only secondarily on the actual year of death. The essential beneficial effects on health and survival among adults and older persons were mainly caused by a decrease in disease load, particularly a decrease in tuberculosis, achieved in these birth cohorts during early childhood several decades earlier (Kermack, McKendrick, & McKinley, 1934). The general idea behind the term cohort effect is thus that events such as stress or heavy disease load on the different organs or organ systems in the human body experienced during certain periods in early life, most importantly during pregnancy and the first year(s) of life after birth when the body is most susceptible to permanent damage, may "program" the organs to increased susceptibility to various diseases much later in life. Such periods of increased susceptibility are often referred to as "critical periods". The concept critical period broadly refers to any stage in the development of an individual in which a heightened sensitivity to risk may have effects on health in later life (Hallqvist et al., 2004).

Long-term life course health effects may also be caused by exposures later in life. However, later-acting biological exposures acting after the developmental period in early life can only affect the timing and rate of health decline, while, in contrast, biological exposures acting early in life may adversely affect for instance lung function but sometimes not the later life rate of decline (Kuh & Ben-Schlomo, 2004).

Two approaches to life course epidemiology other than the "critical period" approach have also been hypothesized and investigated in recent decades. The accumulation of risk hypothesis is based on the notion that exposures may accumulate over the life course and cumulatively increase the risk of chronic disease morbidity and mortality in a graded manner (Hallqvist et al., 2004; Mann, Wadsworth & Colley, 1992; Wunsch et al., 1996). The social mobility approach suggests that intra- and inter-generational social mobility,

often defined in terms of one or more aspects of socioeconomic status (SES), will affect health in later life (Lynch et al. 1994). Few studies have tested all three hypotheses (Lindström, Hansen & Rosvall, 2012).

In addition, it should also be noted that the notion of cohort or early life causes of disease in later life is not restricted to only biological mechanisms. Early life events of psychological and psychosocial significance experienced in early life may also affect poor psychological health (Lindström, Fridh & Rosvall, 2014), health locus of control (Lindström & Rosvall 2014) and health related behaviours (Lindström, Modén & Rosvall, 2013).

The main focus of this thesis concerns early life exposures in the forms of foetal growth retardation ("the foetal origins hypothesis") and infectious diseases in the first year of life ("the inflammation hypothesis"), i.e. two defined critical periods which may affect different birth cohorts to varying extent depending on the nutritional exposure in utero and the infectious disease exposure (epidemics) mainly in the first year of life (infancy), and their influence on health in later life.

1.4.1 The foetal origins hypothesis

The past decades have witnessed a renewed interest in the cohort or early life approach to disease and particularly chronic disease epidemiology (Kuh & Ben-Schlomo, 1997, 2004). This approach has been supported by particularly the work of Barker and colleagues, who have both hypothesised and investigated the early life preconditions for later life development of cardiovascular diseases and the metabolic syndrome, i.e. coronary/ischaemic heart disease, hypertension, deranged blood cholesterol and lipids, stroke, type II diabetes mellitus, and overweight/obesity, as well as chronic thyreoiditis. The causal mechanism behind these diseases induced in early life is suggested to be inadequate cellular development in utero due to lack of sufficient nutrition, also termed down regulation (Barker, 1995, 1997a, 1998, 2001), a notion which has also been supported by Fogel (1994). The concept of down regulation of foetal growth has been developed further into the nutritional programming (or foetal origins) hypothesis. According to this hypothesis the development of cardiovascular and other diseases in later life depends on whether foetal growth retardation due to insufficient nutrition is "proportionate" or "disproportionate". The "disproportionate" growth retardation induced by insufficient nutrition during the mid and late trimesters of pregnancy seems to be responsible for cardiovascular diseases

later in life, while the "proportionate" growth retardation of the first trimester is not (Barker, 1995). Not all evidence suggests an exclusive role of malnutrition in the foetal-origins hypothesis. The famine in rural Finland from 1866 to 1868, for instance, tripled death rates but did not alter the survivors' life-spans (Kannisto, Christensen & Vaupel, 1997). Still, the results of a study of the 1866-1868 famine in Finland suggest a lower life expectancy at age 60 for male cohorts in Finland born during the famine while the results for the corresponding female cohorts are less conclusive (Doblhammer, van den Berg, & Lumey, 2013). The association between extreme nutritional deprivation among pregnant women in the Dutch famine in the winter of 1944-1945 at the end of the Second World War and the development of the metabolic syndrome, type II diabetes and cardiovascular diseases among their offspring in later life is another natural experiment, i.e. a documented event which may secondarily be used for research. However, the results have been inconsistent due to the fact that they are based on small numbers of disease events (Roseboom et al., 1999; Roseboom et al., 2000a; Ravelli et al., 1998; Roseboom et al., 2000b; Roseboom et al., 2001; see also Lawlor, Ben-Schlomo & Leon 2004). Individuals born in Leningrad during the 1941 siege of Leningrad had similar lipid, blood pressure, as well as fasting and post-challenge glucose and insulin levels as those born outside the area under siege (Stanner et al., 1997). In fact, the scarce data on severe nutritional deprivation in the form of documented natural experiments has resulted in few empirical investigations on the original "foetal origins" hypothesis.

The components in the metabolic syndrome stem from a complex set of gene-environment interactions. The exact causal mechanisms of these interactions remain under debate. Many diabetics have genetic variations which make them "exceptionally efficient in the intake and/or utilization of food" (Neel, 1962), a notion supported by the fact that type 2 diabetes has a strong hereditary component. The "thrifty phenotype hypothesis" by Hales and Barker (1992) suggests that during gestation in utero and in early post-natal life the individual is programmed to adapt and survive in a particular nutritional environment, which implies that early life malnutrition may trigger pathways leading to a higher risk of chronic conditions and diseases such as hypertension, CVD and type 2 diabetes during the life course (Hales & Barker, 2001).

Barker's ideas concerning in utero exposure in the form of the risk factor malnutrition has led to other early life hypotheses and stimulated the life course epidemiology research area. This research includes partly other "critical

periods" and children born small for gestational age (SGA) for other reasons and due to other specific causes than malnutrition in utero (Dejin-Karlsson, Hanson & Östergren, 1997, Dejin-Karlsson et al., 2000). We aim to test the original Barker "foetal origins" hypothesis in the first two empirical investigations in this thesis (studies II and III). In the historical empirical studies II and III rye prices will be used as proxies for economic and nutritional prenatal stress in the 18th and 19th centuries. Grain prices, and rye prices in particular, may be regarded as an exogenous measure of short-term economic stress and nutrition level until 1870. It should also be noted that rye prices and infant mortality rate (IMR) are two statistically independent types of early life exposures in the Scanian Economic Demographic Database (SEDD) analysed in the two historical studies II and III (Quaranta, 2013).

1.4.2 The inflammation hypothesis

The original disease load *cohort* mechanism proposed by Kermack, McKendrick and McKinley has also been developed and further investigated in other directions than Barker's foetal origins hypothesis and its followers by other authors. Fridlizius suggested that the development of diseases in later life may be due to exposure to certain infectious diseases, i.e. exposure to smallpox in the late 18th century and exposure to scarlet fever in the mid-19th century, in the first five years after birth, resulting in reduced immunity against other diseases throughout life, and thus a higher general susceptibility of getting other infectious diseases in later life. In neither case did susceptibility to disease in adulthood seem to have been connected with nutrition in early life (Fridlizius, 1989), because the risks of being infected with for instance smallpox and scarlet fever are to a high extent independent of nutrition (Rotberg and Rabb 1985), although some findings of empirical investigations have suggested an association between nutrition and morbidity and mortality of scarlet fever epidemics in the Sundsvall region in northern Sweden (Curtis, 2004). In contrast to nutrition, Fridlizius suggests that deranged immunological balance between infectious agents and the human host may have implications for later life disease experiences (Fridlizius, 1989). These and other early life causes of disease in later life are discussed by Lindström and Davey Smith (2007) in relation to the historical development of socio-economic differences in morbidity and mortality.

In recent years the causal connections between exposure to infections in infancy and childhood, chronic inflammatory processes and disease in later life have been more thoroughly discussed. Finch and Crimmins (Finch & Crimmins, 2004, Crimmins & Finch, 2006) have suggested that early growth and cardiovascular disease as well as other chronic diseases in old age may have infectious and inflammatory causes stemming from the external environment as common causes. In a doctoral thesis based on rural five parishes in western Scania, individuals born in 1813-1898 were demonstrated to have experienced severe long-term effects on survival following exposure to whooping cough epidemics in infancy. In this study, the effects of whooping cough in infancy were more severe and uniform across the entire population than the effects of measles and scarlet fever in infancy. Females exposed to whooping cough also experienced decreased ability to attain high socioeconomic status in adulthood and worse reproductive health (Quaranta, 2013). Epidemic infectious diseases that historically commonly recurred as epidemics display a number of long-term health effects. Scarlet fever, caused by beta-hemolytic streptococci, causes acute rheumatic fever which is an inflammatory disease following autoimmune responses to the streptococcus infection. Rheumatic fever includes carditis (inflammation) of the mitral and aortic valves of the heart leading to rheumatic heart disease in a substantial proportion of patients (Guilherme & Kalil, 2004). Scarlet fever may also cause glomerulonephritis (Bisno, 1991). Some studies on whooping cough, caused by Bordetella pertussis, have shown higher incidence of respiratory problems, but other studies have not (Britten & Wadsworth, 1986, Krantz et al., 1990; Shaheen et al., 1994, 1998; Tennant, Gibson & Pearce, 2008; see also Quaranta, 2013). Early life (in utero and during infancy) exposure to the 1918 influenza pandemic was in the USA associated with increases in old-age mortality from non-cancer causes including cardiovascular and respiratory diseases (Myrskylä, Mehta & Chand, 2013), although the study may be biased by the fact that there was a social gradient in conscription to military service in the US Army in the First World War whereby young men in poor families were enrolled to a lesser extent, resulting in proportionately more children being born in poor families under adverse socioeconomic circumstances during this particular period (Bengtsson & Helgertz, 2015). These are examples of (often causally unclear) associations between exposure to epidemic infectious diseases in infancy which may affect cohorts differently and disease in adulthood/ later life, but the causal mechanisms linking exposure to infectious diseases in infancy to chronic diseases in adulthood are not fully known, and neither are any plausible common biological traits.

Since growing organisms adapt to early signals in the environment, profound adaptations in early life that differ from the normal or usual environment in later life may be harmful (Stearns, 1989). One example is that exposure to malnutrition/ nutritional deficit may result in alterations in the glucose-insulin metabolism (Hales & Barker, 1992; Barker, 1997b; Hales & Barker, 2001), a notion already briefly discussed above in relation to the "foetal origins" hypothesis. Due to malnutrition the foetus adapts to a limited supply of nutrients in the environment, resulting in the pathogenesis of subclinical chronic disorders which ultimately lead to coronary heart disease, stroke, diabetes and hypertension. However, such adaptations may also be relevant as responses to the early exposure to infectious diseases. Early exposure to infectious diseases, particularly in infancy, may set the immune system to be chronically alert, leading to chronic inflammation which increases the risk of for example later life cardiovascular disease (Finch & Crimmins, 2004, Crimmins & Finch, 2006; Roivainen et al., 2000; see also Myrskylä, Mehta & Chand, 2013). A few examples of such causal mechanisms linking early life exposure to infectious diseases and a group of chronic diseases, i.e. cardiovascular diseases, in adulthood/ later life will be discussed in more detail in the following.

There are pathways linking exposure to infectious diseases in early life to infectious diseases in later life which have been previously discussed in the literature, and they mainly concern the respiratory tract. Respiratory infections, atopy, reversible airway obstruction, chronic mucus hyper-secretion and irreversible airflow obstruction are interconnected through a complex web of causality (Kuh & Ben-Schlomo, 1997, 2004; see also Bengtsson & Lindström, 2003). Respiratory infectious diseases in infancy (0-1 year) have been proposed to be one cause or, alternatively, a component cause of chronic wheezing tendency (Samet & Tager, 1983; McKonnochie & Roghmann, 1984), chronic cough and phlegm (Samet & Tager, 1983; Colley, Douglas & Reid., 1973), irreversible impaired ventilator function (Samet & Tager, 1983; Britten & Wadsworth, 1987), and their related mortality (Barker & Osmond, 1986b).

The bacterium Helicobacter pylori (H. pylori) can rest inactive in the human body for decades until disturbance in the bacteria-host equilibrium occurs. It is a major determinant of peptic ulcer as well as gastric cancer, but may also be involved in the pathogenesis of stroke and ischaemic heart disease by hypothesised pathways of chronic inflammation, changes in lipid patterns, and endothelial dysfunction (Manolakis, Kapsoritakis & Potamianos, 2007;

see also Dowd, Zajacova & Aiello, 2009). It may also be involved in growth impairment in children (Mohammad et al., 2008; see also Dowd, Zajacova & Aiello, 2009).

Probably the most investigated pathway between life course effects of chronic inflammation concerns C reactive protein as a risk factor for cardiovascular diseases. C reactive protein (CRP) has become the most commonly used marker for both acute and chronic inflammation in the study of early life epidemiology and early life effects on adult health. In recent years C reactive protein (CRP) has been included as a component in risk factor assessment of cardiovascular diseases (CVD). The American College of Cardiology/ American Heart Association and its expert panel suggest that a serum-CRP above or equal to 2 mg/L should be regarded as support for revising overall cardiovascular risk assessment upwards (Goff et al., 2014). This recommendation has so far been implemented in clinical practise in the USA but not in Sweden. The only laboratory cut-off in clinical practise used in Sweden is a serum-CRP above or equal to 9 mg/L, but this cut-off relates to viral (or at higher levels bacterial) infection and not to low grade inflammatory processes which mark a long-term risk for CVD. The difference between the two laboratory value cut-offs illustrates that even very low long-term levels of chronic inflammatory processes induce an increased risk of later life clinical expressions/symptoms, incidence and mortality of CVD. The fact that CRP has been included as an established risk factor in the clinical assessment of CVD also further stresses the multi-causal nature of chronic diseases such as CVDs, because risk factors for e.g. coronary heart disease not only include chronic infection/inflammation but also high blood cholesterol levels, tobacco smoking, hypertension, overweight/obesity, type 2 diabetes mellitus, oral contraceptive use among women, mental illness and psychosocial stress, high levels of coagulation factors and air pollution (Marmot & Elliott, 2005).

CRP is produced in the liver. The "C" in CRP derives from the fact that CRP reacts with the C-poly-saccharide in the capsule of the pneumococci bacteria, the most common cause of pneumonia. CRP is considered an acute phase protein in the so called acute phase reaction caused by tissue damage, because considerable amounts can be produced rapidly in the liver with a corresponding acute and rapid increase of its concentration in the blood in connection with increased cell destruction and cell death during for example an infection. It should be noted that CRP peaks at much higher serum concentration levels in most bacterial infections than in infections caused by virus, in some virus infections even very small or almost no increases in CRP

are observed. If and when the cell destruction and cell death decreases again in the aftermath of for example an infection, CRP decreases again within the time scope of a maximum of four days. However, in case of a chronically increased degree of cell destruction such as during a chronically ongoing inflammatory process, CRP will remain high (Nilsson-Ehle, 2003).

Within the topic of life course epidemiology, CRP has been most intensively investigated with reference to atheroschlerosis, i.e. the development of atheroschlerotic plaques in arteries. CRP seems to be involved in this first subclinical and, much later, clinical disease progression through at least three causal mechanisms. First, increased plasma levels of the pro-inflammatory cytokine IL-6 (indirectly detectable by increased CRP levels) during long time periods increases the progressive development of atheroschlerotic plaques by the activitation of endothelial cells, macrophages, T-lymfocytes and smooth muscle tissue. Second, increased CRP levels have been found in atheroschlerotic plaques were it seems to have a pathophysiologic role in the phagocytosis by the macrophages of both native and oxidated LDL-cholesterol. Third, CRP stimulates the endothelial cells to produce adhesion molecules which will bind monocytes to the endothelial cells (Nilsson-Ehle, 2003).

Two final comments concerning CRP in early life epidemiology and clinical epidemiology are warranted. First, it should be clear from the presentation above that the exact nature of the causal mechanism linking CRP to CVD is not known. It thus still seems reasonable to regard CRP as a risk marker of the inflammatory component cause of CVD pathogenesis, not necessarily as a cause or an intermediate factor in the causal pathway or web of causes in itself. Second, it should be noted that considerably lower CRP levels with a current recommended cut-off at 2 mg/L are relevant for the pathogenesis of atheroschlerosis and the prevention of cardiovascular diseases, compared to the clinical cut-off at 9 mg/L which relates to viral and bacterial infections. It is thus apparent from the American College of Cardiology/ American Heart Association recommendations that low-grade chronic inflammation is causally connected with chronic disease life course pathogenesis resulting in later life disease.

At the molecular level the causal link between infectious disease in early life and long term health consequences may be through dysregulation of DNA methylation at specific methylated regions of the DNA sequence that regulate imprinted genes, but so far this notion is still based on speculation with scarce

empirical support (see e.g. Liu et al., 2013). This research area will probably grow considerably in the years to come.

The "inflammation hypothesis" in this thesis proposes, partly supported by the literature above, that being exposed to a high disease load of infectious diseases in infancy (0-1 year), increases age-specific morbidity and mortality in later life.

1.5 The historical and geographical settings of the four empirical studies

1.5.1 The four parishes in western Scania 1760-1894 and the mortality decline

The foetal origins and inflammation hypotheses will first be tested in the two empirical historical studies, papers II and III, in this thesis. The four parishes Halmstad (in Skåne, not to be confused with the town of Halmstad in the county of Halland), Hög, Kävlinge, and Sireköpinge in western Scania will be investigated regarding the time periods 1760-1894 and 1766-1894, respectively. The demographic, economic and social development in these four parishes and the wider Scanian and Swedish contexts during this time period that coincided with the early phase of the general mortality decline have been described and discussed more extensively by other authors (see e.g. Bengtsson & Dribe, 1997; Quaranta, 2013). The four parishes were geographically situated approximately 10 kilometres from the west coast of Scania which is the southernmost part of Sweden. The two adjacent parishes Halmstad and Sireköpinge were located 20 kilometres south east of Helsingborg, while the two adjacent parishes Hög and Kävlinge were situated 15-20 kilometres south of Halmstad and Sireköpinge, just 15 kilometres north west of the town of Lund. The four parishes are compact in their geographical location. They also showed a variation in size, topography and socioeconomic circumstances that were commonly found in peasant societies (Bengtsson & Dribe; 1997). The life courses of the inhabitants may consequently to some extent be regarded as representative of historical rural settings (Bengtsson, 2004; Quaranta, 2013).

In the late 18th and early 19th centuries several reforms regarding the division of farmland were enacted in Sweden in order to increase agricultural

productivity. The initial amalgamation of small parcels of land into larger production units (*storskiftet*), encouraged by the government in the late 18th century, aimed to increase agricultural productivity by joining land lots in order to give each farmer just a few connected fields. A more radical reform, *enskiftet*, was decreed in 1807 with the same aim. A third reform, the parliamentary enclosure (*laga skiftet*), decreed in 1827, had even more profound effects and included arable land as well as pasture land and other land. The effect of these enforced reforms, Scania and the other more arable parts of Sweden were particularly affected, was also increased responsibility for the individual farmer (see Svensson, 2001; Olsson, 2002). A profound economic and social transformation ensued in Scania and Sweden with increases in exports, reform of the banking system, liberalisation of the market, rapid economic growth and eventually industrialisation starting at a grander scale in Sweden around 1870. In the mid-19th century Gross Domestic Product per capita (GDP per capita) started to rise, and this increase has continued into the 21th century with the exception of some short breaks connected with for example the First World War, the early 1930s depression, the Second World War, the oil crisis recession in the 1970s and the early 1990s recession (Figure 3). Due to increased travelling possibilities and the internationalisation of the labour market, large scale emigration started in the 1860s, peaked in the 1880s and the first decade of the 20th century, and Sweden remained a country of net emigration until approximately 1930. The public sector was also decentralised and expanded. The Compulsory Education Act (Folkskolestadgan) (1842) made it compulsory for every parish to provide basic education, and in 1882 schooling became compulsory. A Poor Relief Act was enacted in 1847 and the county councils (landsting) were founded in 1862 with public responsibility for the health care system and the hospitals (Schön, 2010). The modern municipalities were founded in 1863, only one year after the county councils (Andersson, 1993).

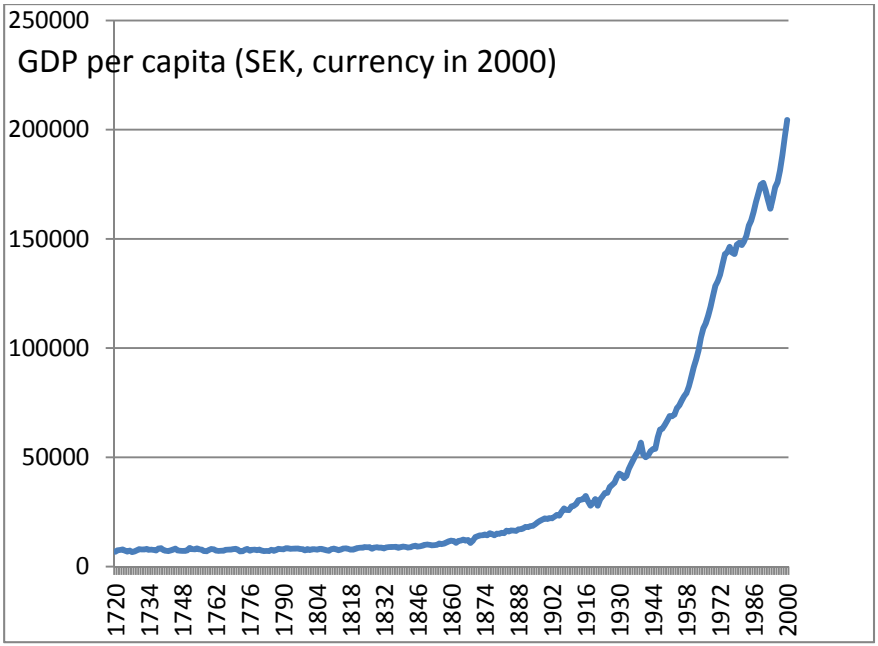

Figure 3. Gross Domestic Product per capita (GDP per capita) in Sweden 1720-2000, estimation with prices in 2000 as reference. (Historia.se, www.historia.se)

The four parishes consisted mainly of open farmland, only the northern part of the Halmstad parish was more wooded. The farming in the four parishes was dominated by the cultivation of grain, while animal production was much less prominent. The building of the railway through Kävlinge in 1886 resulted in the diversified industrialisation and consequent population growth of the Kävlinge community. The other parishes also experienced population growth but at a considerably lower growth rate (Bengtsson & Dribe, 2011). As a result of this development, the proportion of people with higher occupational status and skilled workers rose, while the proportion of farmers decreased. The proportion of farmers (measured as household heads) in the parishes decreased steadily from more than 40% in 1813-1839 to approximately 27% in 1870-1899 and less than 13% in 1930-1968 (Quaranta, 2013).

The mortality decline in Scania was similar to the mortality decline in the whole of Sweden (see above), but the mortality decline was more pronounced in Scania than in the rest of Sweden in the late 18th century (Bengtsson & Dribe, 1997). The decline of infant (0-1 year) mortality started in the late

18th century and continued throughout the 19th century. Childhood mortality in ages 1-10 started somewhat later at the end of the 18th century, with a temporarily increasing pattern in the middle of the 19th century. Adult mortality started to decline in approximately 1840, and old age mortality around 1850 (Fridlizius, 1984). The total fertility rate in Scania was above 5 and the age-specific fertility above the national average. Fertility also started to decline somewhat later in Scania, in the 1890s instead of the 1880s (Bengtsson & Dribe, 2009, 2010), so even in this regard the demographic patterns were similar to the national Swedish patterns though not identical. The distribution of land and income was not equal. Real estate records and personal income tax records show that the economically most privileged 5% of the population owned 36% of the land in 1800. In contrast, the landless constituted 50% of the households (Quaranta, 2013). Previous studies have shown that the landless and semi-landless experienced a more pronounced mortality response to short-term economic stress in Scania during the 19th century (Bengtsson, 2000; Bengtsson, 2004). Still, the overall socioeconomic differences according to occupation in mortality were in essence non-existent in the four parishes during the 19th century (Bengtsson & Dribe, 2011).

The development of mortality including IMR as well as rye prices in the four parishes have previously been described and judged to have acceptable external validity (see e.g. Quaranta, 2013). Figures depicting the development year-by-year are also presented in papers II and III of this thesis. The IMR in the year of birth is shared by all individuals born in a particular year to indicate disease load on infants, and in the four parishes it followed the same patterns as in the general population of Sweden with wide year-by-year fluctuations and trend values of IMR around 200-300/1000 a year during the studied 1760-1839 period (compare figure 1 above in the introduction of this thesis with figure 2 in paper III of this thesis by Bengtsson and Lindström (2003)). Crude death rates at ages 55-80 in the four parishes, cycles and extreme values in infant mortality rate in the four parishes, crude death rates in ages 20-60 in the four Scanian parishes 1686-1839 and cycles in the logarithm of local rye prices have also been presented (see figures 1,3,4 and 5, respectively, in Bengtsson and Lindström, 2003). Total death intensity (all causes of death) at ages 55-80, death intensity for airborne infectious diseases at ages 55-80, death intensity for "weakness due to old age" at 55-80 and death intensity for "other specified non-infectious diseases" at ages 55-80 are also presented in figures 1, 2, 3 and 4, respectively, in paper II (Bengtsson and Lindström, 2000). Figure 1 in paper II shows that the overall mortality for ages 55-80 was

generally higher for the late 18th century than for the later part of the 19th century. However, there was also a mortality "hump" in the 55-80 age group in the four parishes in the 1830s and 1840s, which seems to be consistent with Fridlizius' findings concerning the mortality of this age group in the same time period for the general population of Sweden (Fridlizius, 1984). Figures 2-4 in paper II demonstrate a decline in mortality at ages 55-80 by airborne infectious diseases until the 1820s, followed by an increase in the 1830s and 1840s, which partly explains the crude "humps" in mortality at ages 55-80 in these two decades. Still, an even more pronounced "hump" in mortality at ages 55-80 in the 1830s and 1840s is seen in the descriptive diagnostic group "weakness due to old age", then followed by a decline to even lower levels than before the mortality "hump" of the 1830s and 1840s in the later part of the 19th century.

Figure 5 in paper II shows the ratio of rye prices to population which is used as an approximation of real wages. It can be divided into three sub-periods which include the period 1760-1820 with an increase in rye prices, the period 1820-1865 with rye prices and wages becoming more stationary, and finally the 1865-1895 period with increasing real wages (Bengtsson and Lindström, 2000). The rye prices in papers II and III are local (county of Malmöhus), and their development over time accord well with the national development in Sweden (Jörberg, 1972).

1.5.2 Country of birth and adult mortality in modern Sweden 1980-2001

In modern populations both chronic inflammation originating in infancy and economic stress (not only specifically nutrition but psychosocial stress) in early life may also cause disease in adult life. This thesis will test these notions in paper IV, which will analyse the effects of early life IMR and GDP per capita in the country of birth and year of birth across eleven countries of birth including Chile, Czechoslovakia, Denmark, Finland, Germany, Greece, Italy, Norway, the USA, Yugoslavia and Sweden in a sample population of inhabitants born in their respective country of birth in 1921-1939 who lived in Sweden in 1980-2001. Current (1980-2001) individual level socioeconomic conditions in Sweden will also be included in the analyses.

Sweden has since the Second World War been a country of net immigration. In 1980 Sweden had a population of 8.3 million including 625,450 persons born in other countries than Sweden, and both the population born in other

countries than Sweden and the total population in Sweden have increased considerably since then. Studies of health differences between immigrants and natives in Sweden and other countries do not overwhelmingly point in one direction or the other. Some studies find that immigrants are healthier (Anson, 2004), while other studies draw the opposite conclusion (Lindström, Sundquist & Östergren, 2001). The causes behind such patterns are complex and often multi-causal. Health behaviours such as following a Mediterranean diet may for instance protect against especially coronary heart disease (Walker & Reamy, 2009). Health behaviours behind ethnic differences in health also include tobacco smoking (Lindström & Sundquist, 2002) and leisure-time physical activity (Lindström & Sundquist, 2001). Other plausible explanations include ethnic differences in access to health care and amenities such as access to a regular physician (Axén & Lindström, 2002). Findings may also be biased by the fact that there may be under-registration of return-migration to the country of birth, which would lead to under-registration of morbidity and mortality in the country of immigration (Persson, 2005).

Still, several principally different overall hypotheses concerning such health differences may be discerned. The first attributes current health differences between immigrants and natives to both current socioeconomic conditions in the current country of residence and economic and health conditions in the past in the country of birth (Davey Smith et al., 2003; Helgertz, 2010; Helgertz & Persson, 2014). The second more exclusively attributes current health conditions to current socioeconomic conditions in the country of immigration. Such socioeconomic conditions include for instance civil status, income, degree of labour market attachment, occupation and education, and in countries where immigrants are poorly integrated into their new country of residence they will be exposed to the risk of more health problems than natives (Davey Smith et al., 2003; Klinthäll, 2007, 2008). There is a want of studies which concern how early life experiences in the country of birth may affect adult and later life health conditions in the country of immigration. Accordingly, there is also a lack of studies combining the study of early life factors in the country of birth and current adult individual socioeconomic status in the country of immigration. Infant mortality rate (IMR) and Gross Domestic Product per capita (GDP per capita) will be used as early life indicators of increased economic stress (lower GDP per capita) and disease load (higher IMR) even for the survivors in the infant (0-1 year) group, and thus increased risk of morbidity and mortality in later life (Bengtsson & Lindström, 2000, 2003). GDP per capita is an indicator of absolute level of

economic development in a country (Lindström & Lindström 2006). Both the GDP per capita (van den Berg, Doblhammer & Christensen, 2009) and IMR (Bengtsson & Broström, 2009; Bruckner & Catalano, 2009; Gagnon & Mazan, 2009) are often used as indicators of early life disease load and economic indicators for particular birth cohorts in specific countries. Early life studies on immigrants and their health in adult life/later life including individual level measures of early life disease load and economic stress in the country of birth are very scarce for reasons of lack of data, a fact which often makes aggregate IMR and GDP per capita in the year of birth in the country of birth the only possible exposure variables. Data on IMRs stem from several sources including UN Demographic Yearbooks, national statistics and specific IMR research sources (Abouharb & Kimball, 2007). Data on annual GDP per capita stem from Maddison's work on historical statistics (Maddison, 2007).

1.5.3 The association between infant mortality rate (IMR) in the year of birth and self-rated health in Scania in 2008

Scania, situated in the southernmost part of Sweden, had 1,243,329 inhabitants in 2010, and in 2012 the population had increased to 1,263,088. In 2008, 80.5% of the population aged 18-80 years in Scania was born in Sweden, 3.4% in the other Nordic countries, 9.4% in the rest of Europe, and 6.7% in the rest of the world. The proportion of foreign born has increased continuously. Scania has in recent decades experienced an economic transformation from an industrial to a post-industrial society with an increasing proportion of non-manual employees and an increase in the workforce with high education, but also an increase in the proportion of unemployed (Grahn et al., 2009). In recent decades Scania has had a life expectancy similar to the Swedish average (Persson, 2005). In Scania the infant mortality rate (IMR) declined from 63.03/1000 in 1927 to 18.99/1000 in 1960 ("Befolkningsrörelsen", Statistics Sweden 1927-1960). The decline in IMR in recent decades has been similar to the Swedish national average (see section 1.2).

Associations between aggregate level IMR and individual level later life health outcomes have not been investigated in modern populations in developed countries to our knowledge, and the reason may be the lack of the earlier historical patterns of epidemic mortality crises caused by infectious disease epidemics in certain years which were preceded and followed by substantially

lower mortality levels in the temporally surrounding years, although even the basal mortality level in these non-epidemic years were considerably higher than the current IMR level. IMR has been declining continuously throughout the 20th century. The optimal study design for research questions regarding early life and life course epidemiology would be to follow individual study subjects and their individual data collected throughout the life course with three or more observation points over time (Hallqvist et al., 2004), including aggregate exposure data according to the "inflammation hypothesis". IMR may be seen as a communal "epidemic" risk factor, a marker for the test of the "inflammation hypothesis" in infancy. The fifth paper in this thesis, and the 2008 public health survey in Scania on which it is based, includes individual level self-reported data on father's socioeconomic status (occupation), economic stress in childhood and participants' own education. The two first items may be seen as proxies for provisions, including nutrition (although not possible to separate from other provisions), in childhood which may affect health in adulthood. Participants' own education may plausibly be expected to be associated with SES (e.g. father's occupation) in the family in which the participant grew up. The item used to assess the health outcome in adulthood is self-rated health (SRH), "How do you rate your general health status", with five optional answers including "very good", "good", "neither good nor poor", "poor" and "very poor", which is dichotomized with the two first alternatives as "good" SRH and the three latter as "poor" SRH. This SRH item has been frequently used internationally, and is considered to be a valid measure of health status due to the fact that it is a comparatively strong prospective predictor of for instance CVD and total mortality (see e.g. Idler & Kasl, 1991; DeSalvo et al., 2005; Cesari et al., 2008; Mohseni, 2008).

In this fifth paper early life health determinants such as communal IMR and the self-report of the individual respondent of father's socioeconomic status (occupation), economic stress in childhood and education are included, and their associations with self-rated health in 2008 are studied. The rationale is to keep the model simple and also to only assess early life variables in relation to current self-rated health. Current (2008) health determinants such as respondent's own current socioeconomic status and health related behaviours are regarded as intermediate in the chain of causality between potential early life determinants and self-rated health, and are thus excluded.

In conclusion, this thesis consists of four separately published parts, and a fifth part which is still a manuscript. The first part is a book chapter which further discusses the life course perspective to the modern secular mortality decline

with particular reference to socioeconomic differences in morbidity and mortality in Sweden. The second and third parts are historical empirical studies based on the Scanian Economic Demographic Database (SEDD) which at the point in time when these two studies were conducted consisted of records of births, marriages, deaths, and migration for four rural parishes based on church parish registers completed in 1760-1894. The second paper investigates the importance of early life conditions (disease load on infants and their mothers during preceding pregnancy) and economic conditions (rye prices) for mortality in later life, taking the causes of death in later life mortality into account. The third paper investigates the importance of early life (cohort effects) and current (period effects) conditions for mortality in later life (55-80 years), taking the causes of death during the infancy period (0-1 year) of a particular cohort as well as the causes of death of their mothers into account. The fourth and fifth papers are based on modern data. The fourth paper is based on data from the Swedish Longitudinal Immigrant Database (SLI) which in this study covers the years 1980-2001, and the fifth is based on the public health survey in Scania 2008. Both databases include items regarding individual age, sex, country of birth, and socioeconomic status defined as occupation and education. The SLI also contains information concerning individual income, while the public health survey in Scania 2008 also contains information regarding self-rated health (SRH), education, father's socioeconomic status (SES) defined as occupation and self-reported economic stress in childhood. In addition, the fourth paper includes the communal variables IMR and GDP per capita in the country of birth and the year of birth (1921-1939), and the fifth paper the communal variable IMR in Scania in the year of birth (1927-1960). The fourth paper investigates the early life conditions in terms of the IMR and the GDP per capita in the year and country of birth and current socioeconomic conditions in adult life in Sweden on cardiovascular, cancer, all other causes and total mortality among natives and immigrants born in eleven different countries using survival analysis with proportional hazards regression models. The fifth paper investigates associations between communal IMR in Scania in the year of birth, individual economic stress in childhood, father's socioeconomic status (occupation) in childhood, education and self-rated health.

Aims

General aim:

The overall aim of this thesis is to investigate hypotheses concerning plausible cohort mechanisms and associations, i.e. indications of long term early life effects, by which conditions in early life may have affected mortality and self-rated health in later adult life in Sweden during the past 250 years. It should be noted that the aim is to investigate whether such specific cohort mechanisms (studies II and III) and associations (studies IV and V) may have existed. The aim is not to investigate the relative impact of such early life or cohort mechanisms on the total secular mortality decline that started in the late 18th century in Sweden. The impact of early life cohort mechanisms have already been demonstrated on aggregated data by Kermack, McKendrick and McKinley (1934).

Specific aims:

To discuss period and cohort disease mechanisms in the secular mortality decline in historical and modern settings in Sweden and other countries. This aim also includes to discuss historical trends in socioeconomic mortality differences in a life course and cohort perspective, and to shortly discuss cohort effects on mortality and mortality predictions in terms of indicators and models.

To investigate the importance of early life conditions (disease load on infants and their mothers during the preceding pregnancy, nutrition during the foetal stage and first year of life and disease load during the first year of life) and current conditions for mortality in later life (55-80 years) in four parishes in Scania 1760-1894, also taking the causes of death mortality in later life into account.

To investigate the importance of early life (cohort effects) and current (period effects) conditions for mortality in later life (55-80 years) in four parishes in

Scania 1766-1894, taking the causes of death during the infancy period (0-1 year) of a particular cohort as well as the causes of death of their mothers into consideration. Early life factors include disease load during the birth year, food prices during pregnancy, birth season, and disease load on mothers during pregnancy.

To investigate associations between early life conditions, measured as infant mortality rate (IMR) and Gross Domestic Product per capita (GDP per capita) in the year of birth in the country of birth as well as current socioeconomic conditions in adult life such as income, education and being a welfare recipient, and the outcomes mortality in cardiovascular diseases, all cancers, all other causes of death and total mortality for men and women born in eleven different countries in 1921-1939 but living in Sweden in 1980-2001.

To investigate associations between infant mortality rate (IMR) in the year of birth as well as individual socioeconomic stress in childhood (father's socioeconomic status, economic stress in childhood and education), and, on the other hand, self-rated health in adulthood in a sample of adult men and women living in Scania in 2008, born in Sweden in 1927-1960.

2. Methods and material

2.1 Methods

Papers II-III

The analysis of the effects of early life exposures on mortality in later life is restricted by requirements on the data as well as methodological considerations. The time span of the data needs to be long enough in order to entail a life span from early life to adulthood. The indicators of early life exposures also need to be exogenous in relation to mortality later in life. This requirement formally excludes the possibility to for example analyse earnings of parents during the childhood of the participants in a study, because such factors are to some extent affected by unobserved factors which also directly affect participants' mortality in adulthood. Childhood conditions and later life health and mortality may also both be affected by unobserved heterogeneity, i.e. simultaneity bias. One way to avoid such problems is to utilize natural experiments including e.g. exogenous epidemics, wars and famines as indicators of extreme conditions in early life (van den Berg, Doblhammer & Christensen, 2009). Some examples of such natural experiments have already been cited in the text of the introduction (see section 1.4.1 under the heading "The foetal origins hypothesis" above). Papers II and III in this thesis present an alternative way which analyses the transitory component (deviation) in rye price at the time of birth as an indicator of food accessibility in early life, and the transitory component (deviation) in local infant mortality rate at the time of birth as an indicator to early life diseases, particularly early life infectious disease epidemics, an approach which has later been described as pioneering (van den Berg, Doblhammer & Christensen, 2009).

The analyses of aggregate level data have previously demonstrated the plausible size of the influence of cohort mechanisms on the early parts of the modern mortality decline (see e.g. Kermack, McKendrick & McKinley, 1934;

Fridlizius, 1989). In our first two historical aggregate and individual level data studies we do not analyse the impact of cohort effects on the early period of mortality decline. Instead we analyse plausible causal mechanisms between on the one hand social and economic exposure variables and, on the other hand, different groups of diseases using a Cox regression approach including communal (second level) social and economic variables. In estimating the parameters of the models, we use event-history analysis with time-varying external covariates, which enables us to conduct regression analyses on the change of life status, i.e. dying or giving birth to a child, measuring the effects of different explanatory variables (or covariates) on the hazard of the event. More specifically, we use the Cox proportional hazards model, which does not require any specification of the underlying hazard function.

The main interest in the two first historical empirical studies is to estimate the impact of different covariates on the hazard of death. Aggregate economic information is used as a time-varying covariate common to all individuals in the risk set at each point in calendar time (Kalbfleisch & Prentice, 1980; Bengtsson, 1993). Aggregated indicators such as the infant mortality rate, the crude death rate at ages 20-50 years and food (rye) prices are also used as fixed community covariates. The value of the community covariate is then shared by all individuals with the same birth year or with the same year of conception, depending on which indicator it is. The infant mortality rate during the year at birth is shared by all individuals with the same birth year to indicate the disease load on infants. The crude death rate at ages 20-50 during the year of conception in the second empirical study is shared by all individuals with the same year of conception to indicate the disease load on the mothers during the pregnancy. Food prices are similarly fixed to reflect the access to food during both the foetal stage and the birth year. We use the logarithm of local rye prices as an indication of the availability of food because grain dominated the diet and rye was the major crop. This indicator has been used in many studies and has been shown to have high validity (Bengtsson, 1993). The software program used is called MLIFE and was developed by Professor Göran Broström of Umeå University and Lund University. It is a GNI licence program and has specific features to facilitate the use of time-varying and fixed community covariates (Broström, 2000). (This description of methods is more developed in Bengtsson and Lindström, 2003.)

Paper IV

Until 1930 Sweden was a country of net emigration, and before 1945 immigration to Sweden was very small. For this reason very few individuals born outside Sweden grew up in Sweden among immigrants born in 1921-1939. In the total Swedish Longitudinal Immigrant database (SLI) 97.5% migrated to Sweden after age 18 and only 0.4% before age six. As a result, the vast majority of individuals in the SLI sample were exposed to the socio-economic conditions of their country of birth during their first years of life. There is a problem of potential under-representation of return migration, and, due to this fact, individuals who had no registered income or who had not received welfare transfer in a year were considered to have left the country and were, hence, excluded from the study.

The outcome is death or survival in a given year between 1980 and 2001. Thus we apply survival analysis using Cox proportional hazards regression. The STATA software statistical program was used in paper IV.

The dependent variable in this study is death by cause of death or just death (total mortality). Death was categorized into three broad diagnostic groups: cardiovascular diseases, all cancers and all other causes of death. Total mortality (all diagnoses) was also analysed. Information concerning deaths and their causes stem from the Causes of Death Register (dödsorsaksregistret), administered by the Swedish National Board of Health and Welfare. It covers all deaths of residents in Sweden, irrespective of citizenship. Causes of death in this register are determined from death certification and recorded according to the International Classification of Diseases (ICD) classification.

Paper V

The 2008 public health survey in Scania is a cross-sectional study. It is a survey in a series of surveys conducted every fourth year in order to monitor public health conditions in the adult population regarding self-rated general health, self-rated psychological health, health related behaviours, psychosocial conditions at work and outside work, and their socio-economic determinants. A total of 28,198 persons from a stratified random sample from the official population registers of people living in Scania born between 1927 and 1990 answered a postal questionnaire in the period August to September 2008. Two reminder letters were sent. The response rate was approximately 55% (approximately 53,000 in the original stratified sample). Paper V includes a

total of 13,491 respondents born in Sweden born in 1927-1960. In the group born in 1927-1960, another 1,900 respondents were born abroad, and 358 respondents had internally missing values regarding country of birth. The participation rate in the age interval born 1927-1960 was approximately 63%, i.e. somewhat higher than in the entire population born 1927-1990. Only respondents born in Sweden were included in the present study due to the fact that the number of other countries of origin is very high (approximately 180) and because most of these countries do not have data concerning IMR reaching back in time to the year 1927. The birth years 1927-1960 were chosen for reasons of statistical availability of regional birth (in Scania) and age specific mortality population data in official publications from Statistics Sweden (Befolkningsrörelsen 1927-1960). The research on the 2008 public health survey was approved by the Ethical Committee at Lund University (No. 2010/343), southern Sweden.

The statistical analyses in study V started with calculating prevalences (%) of poor self-rated health, birth year, father's socioeconomic status (occupation), economic stress in childhood and respondent's own education, stratified by sex. Infant Mortality Rate (IMR) is given according to age (born in 1927-1960 and thus aged 47-81 in August-September 2008) in Scania of birth cohorts included in this study. In the next step, logistic regression analyses were performed. In the first logistic regression model, crude IMR values were analyzed adjusting only for age and sex (model 1). In the second model, IMR trend and de-trended deviance in IMR were introduced instead of crude IMR (model 2). In the third model, only values of IMR deviation were introduced, adjusted for age and sex (model 3). In the fourth model, father's socioeconomic status (occupation) was entered together with the other variables in the previous model 3 (model 4). In the fifth model, the respondent's economic stress in childhood and the respondent's own education were entered into the previous model 4 (model 5). Finally, the interaction terms for IMR (relative/deviance)*socioeconomic status (father), IMR (relative/deviance)*economic stress in childhood and IMR (relative/deviance)*education were entered in addition to the other variables in model 5 (model 6). All analyses were performed using logistic regression models. Models 1-6 were also calculated with a one-year lag for IMR (born in 1928 with IMR for 1929 etc.) in logistic regression models instead of the not time lagged IMR, and the results are presented in a separate table in the end of paper V (table 4). The statistical analyses were performed using the PASW software package version 20.0 (Norusis, 2012).

It should be noted that the apparent longitudinal study design in papers II and III opens the possibility for interpretations concerning causality, while the limited longitudinal study design in paper IV and cross-sectional study design in paper V makes these studies primarily interpretable in terms of associations.

2.2 Data

Papers II and III

The analyses of how conditions during infancy and childhood at individual, family/household, and community levels influence mortality in later life require detailed data on economic conditions, household characteristics, and individual demographic behaviour as well as on date and preferably also cause of death. Such complex data are rare even for modern societies. The data must by necessity be longitudinal in order to permit the measurement of the influence of current economic fluctuations on future demographic behaviour. Longitudinal data must track members of the population through time and record changes in their characteristics when they take place. The time when demographic events occur must also be available. The data should ideally be updated on a continual basis. The longitudinal data must also be at the level of the individual, because this allows the differentiation of demographic responses to economic stress. Details on the households in which the individuals live are also necessary, since the standard of living of the individual depended on aggregate characteristics of the household such as size, income, wealth, and sex composition. In order to measure stress, time series concerning economic conditions in the community covered by social and demographic data must also be available. Such time series should consist of prices or wages or, preferably, both. Prices and wages should also be of local importance for the area studied. Wages should ideally be deflated by a price series to produce an estimate of real incomes. Additional community-level measures of stress, such as for instance disease load, can be constructed from individual level information, in this case the annual mortality rates of various age groups. The data must also be geographically specific. Coverage of the population must be complete in three respects. First, the data must cover the entire community, not just members of a particular socioeconomic group, because the demographic responses may vary between population strata.

Second, for any given time, the population that is actually present in the area and at risk of experiencing a demographic event must be possible to determine. The population should thus either be closed or entries and exits recorded. Third, the timing of demographic events must be complete. Incomplete recording of demographic events leads to inaccurate estimates of rates (Campbell, 2004).

The data from the Scanian Economic Demographic Database (SEDD), a joint project between the Centre for Economic Demography, Lund University and the Regional Archives in Lund, meet the requirements for the type of analyses described above. The database now includes nine rural parishes and one town. The data in this study is a subset of the SEDD since only the four parishes included in the analyses of this thesis were complete for analyses at the time of publication of papers II and III (Bengtsson & Lindström, 2000, 2003). The SEDD is based on data concerning for example causes of death and occupation which have been obtained from church books, poll-tax registers (mantalslängder), and income registers (inkomstlängder). Occupations were registered at birth and marriages in the church books and annually in the other registers. Poll-tax registers were the basis for tax collection and include information concerning family residence, the family's access to land, size of the landholding, mantal (which contains information for taxation concerning how many barrels of grain that the land could produce), and consequently the potential productivity of the farm (Dribe, 2000, see also Quaranta, 2013). It includes all married and previously married people aged 55-80 living in Hög, Kävlinge, Halmstad or Sireköpinge during any period of time between 1766 and 1894. It thus includes all persons aged 55-80 in 1766, immigrants aged 55-80 and those who became 55 years old during the period. These persons are considered exposed until they reach age 80, emigrate, are alive in 1894, or die. The parish register material is of high quality and shows few gaps in births, deaths, and marriages. Information concerning farm size, property rights, and various other items from the poll tax records and land registers are linked to the family reconstitutions based on the parish records of marriages, births, and deaths. The study period 1766-1894 was chosen because there is a gap in the information concerning landholdings prior to 1766. Data on individuals after 1894 were not available at the time when studies/ papers II and III were conducted and published. Causes of death were registered by the clergymen for the whole 1760-1894 period.

The four parishes consisted of open farm land, with the exception of northern Halmstad, which contained some forests. Halmstad and Sireköpinge were "noble" parishes where the peasants rented the land from the estate owners. Freehold and crown land dominated in Hög and Kävlinge. The parishes had 200-500 inhabitants each in late 18th century, but Kävlinge rapidly expanded during the last decades of the 19th century due to the building of the railway and the establishment of several factories. In total, n= 1,400 deaths in paper II and n= 1,398 in paper III. Demographic data from Sweden from 1749 and onwards are generally highly valid and reliable. The Swedish data are of higher quality than for instance data from England (Wrigley et al., 1997) which cover approximately the same historical period. First, Sweden had a state church 1527-2000, i.e. the church books cover the entire population. Second, the data contain both census type information and records about migration. We thus know the population at risk. Third, occupational information concerning farm types and sizes are available. Fourth, there are cause-of-death records. The quality of these records is high, indicated by the ratio of male to female births, the proportion of stillbirths, and the proportion of deaths during the first month (Bengtsson & Dribe, 2006). Changes in the nomenclature of medical diagnoses (in 1774, 1802, 1811, 1821, 1831, 1873, and 1891) and the succession of individual clergymen in the parishes seem to have had no effect on the validity and reliability of the medical diagnoses decided by the clergymen (Bengtsson, 1988). Infectious diseases were identified and diagnosed as grossly the same entities as today. The aetiology of infectious diseases, the most common cause of death during the period 1760-1894, was not known during most of the period (Ackerknecht, 1982).

The social structure of the agricultural sector is difficult to analyse because differences in wealth between different categories of farmers and other occupations tended to vary over time. Data from land registers on types of tenure must therefore be combined with poll tax records on farm size to improve the understanding of the social structure. The nobility was a small social group. Farmers included freeholders, tenants on crown land, tenants on church land, and tenants on nobility land. The size of the farm was measured as mantal. A mantal was not a measure of the actual size of the farm. Instead it was a tax-assessment unit for the estimation of potential production. The group semi-landless includes farmers with a mantal of less than 1/16. The landless workers constituted an additional social group.

Paper IV

The dependent variable in paper IV was cardiovascular, all cancer, all other causes and total mortality. Causes of deaths data come from The Causes of Death Register (Dödsorsaksregistret), administered by the National Board of Health and Welfare. The register covers all deaths of Swedish residents, regardless of whether they were Swedish citizens or citizens of other countries. The information concerning causes of death in the register were determined from death certification by a medical doctor (physician) and recorded according to the International Classification of Diseases (ICD) classification. The total number of deaths in the data set was 4031 for men and 2020 for women. Cardiovascular mortality accounts for 43% of male total mortality and all cancers 31%. Among women cardiovascular mortality accounts for 30% of the total mortality and all cancers 42%. Accordingly, the all other causes category accounts for 26% of male and 28% of female mortality.

Infant mortality rates (IMRs) for the different countries in paper IV were collected from several sources including the UN Demographic Yearbooks, national statistics and specific IMR research sources (Abouharb & Kimball, 2007). IMR at birth was defined as the infant mortality rate per 1000 live births in the year and country of birth of the specific individual. Annual Gross Domestic Product per capita (GDP per capita) for the countries of birth comes from Angus Maddison's compilation of historical statistics (Maddison, 2007), which can be downloaded on www.ggdc.net/maddison. GDP at birth measures the de-trended variation in the level of per capita production in the country and year of birth of the specific individual, measured in 1990 International Geary-Khamis dollars, i.e, fixed prices adjusted for national differences in purchasing power. The GDP time-series was de-trended with the Hodrick-Prescott filter with a lambda value of 100, which is often recommended for annual data (see e.g. Backus & Kehoe, 1992).

Socioeconomic information is annual and originates from official registers such as education and taxation registers administered by Statistics Sweden. Age was categorized into 5-year categories. Civil status indicates whether an individual is single (reference category), married, divorced or widow/widower. Country of birth was divided into eleven categories. Income level measures the disposable income after taxes, including income from employment, self-employment, capital and social transfers such as pensions, sickness benefits, housing subsidies and income support. The income level variables were categorized into six categories according to income level. Education was

dichotomized into completed secondary education or higher versus lower than completed secondary education. Welfare recipient was dichotomized according to whether the individual had received income support from the social services in the year of observation or not.

Paper V

Self-rated health was obtained in the 2008 public health survey questionnaire by the question "How do you rate your general health status?", with the five possible answers "very good", "good", "neither good nor poor", "poor" and "very poor". The five optional answers were dichotomised into good (the first two alternatives) and poor (the three latter alternatives) self-rated health.

Independent individual level variables were also obtained in the 2008 public health survey questionnaire. Birth cohorts according to birth year of participants born 1927-1960 were included in the study. Birth cohorts born in 1961-1990 were excluded from this study. In tables 3-4 in paper V, age was included as a continuous variable. Sex was stratified in tables 1-2, but both sexes were included and adjusted for in the same models in the multiple analyses in tables 3-4, due to the fact that the distributions by sex of both the outcome and exposure variables were very similar. Socioeconomic status (SES) of the father by occupational status was aggregated into the categories higher non-manual employees, medium-level non-manual employees, lower non-manual employees, skilled manual workers, unskilled manual worker, self-employed and farmers according to the official coding system of socioeconomic status (SES) by occupation by Statistics Sweden (Statistics Sweden, 1985). Economic stress in childhood was assessed with the item "Did your family experience economic hardship when you grew up?", with the three possible answers "No, no significant problems", "Yes, less severe problems and/or problems during short time periods" and "Yes, severe problems and/or problems during long time periods". Education was divided by length of education into the categories 13 years of education or more, 10-12 years of education and 9 years of education or less. The "other" group included participants who answered the "other" alternative on the education item. The latter education group is numerically small (see table 1 in paper V). The infant mortality rate (IMR) for Scania stems from Statistics Sweden's regional data for the years 1927-1960 concerning Scania in the southernmost part of Sweden. The IMR for the aggregate of Scania had to be recalculated from data given for the urban and rural parts of the Kristianstad and

Malmöhus counties given separately in the official statistics for the years 1927-1960 (Befolkningsrörelsen, 1927-1960). Three measures of IMR were included in the multiple analyses; crude IMR, relative IMR measured as yearly deviance from the time trend in IMR over the 1927-1960 period, and the IMR trend. The IMR (deviance/relative) and IMR (trend) measures were calculated from the IMR (crude) measure with the STATA insert program hprescott with Hodrick Prescott filtering factor 6.25 used for annual data (see reference in paper V). The IMR (deviance/relative) was calculated to remove the trend component in IMR.

3. Results

3.1 A life course perspective to the modern secular mortality decline and socio-economic differences in morbidity and mortality in Sweden

This review book chapter provides an overview of the recent research in the early life/life course epidemiology area, with special emphasis on Sweden. The review is partly a summary of historical and contemporary empirical findings, but partly also a summary of the various suggested causal mechanisms that may link health in early life to health later in life. The mortality decline in three specific diseases, respiratory tuberculosis, haemorraghic stroke, and bronchitis, which may have accounted for two-thirds of the total decline in mortality in ages 15-64 years from the mid-19th century to the first decade of 20th century Britain, all have clearly demonstrable influences from infancy and childhood. For this early period of the secular mortality decline the timing of improvements of conditions during infancy and childhood, and health improvements later in life is exactly as expected. However, this high degree of specificity and timing is often missing when contemporary data are investigated. The importance of cohort factors for the mortality decline needs to be clarified in contemporary data (Lindström & Davey Smith, 2007; see also preface by Bengtsson & Palmer, 2007, in this book).

3.2 Childhood misery and disease in later life: The effects on mortality in old age of hazards experienced in early life, southern Sweden, 1760-1894

This paper assesses the importance of early-life conditions relative to the prevailing conditions for mortality by cause of death in later life using historical data for four rural parishes in western Scania in southern Sweden (Hög, Kävlinge, southern Halmstad and Sireköpinge) for which both demographic and economic data are highly valid. Longitudinal demographic data for individuals are combined with household socioeconomic data and community data on food costs and the disease load using a Cox regression framework. The results support the hypothesis that the disease load experienced during the first year of life had a strong impact on mortality in later life (55-80 years), in particular on the outcome of airborne infectious diseases. Hypotheses concerning the effects of disease load on mothers during pregnancy and access to nutrition during the first years of life were not supported. Contemporary short-term economic stress on the elderly was generally of limited importance. Mortality in old age varied only to a limited extent by individual socio-economic group belonging. Cottagers had a significantly lower relative total mortality risk, RR=0.86 (p=0.05), in the final aggregate model than the reference farmer group when occupation was considered. Tenants had a significantly lower relative total mortality risk, RR=0.60 (p=0.00) in the final aggregate model than the reference self-owning farmer group when owner conditions were considered. The third socioeconomic variable farm size was not significantly associated with mortality (Bengtsson & Lindström, 2000).

3.3 Airborne infectious diseases during infancy and mortality in later life in southern Sweden, 1766-1894

In the third paper the importance of early life conditions and current conditions for mortality in later life was asssessed using historical data from four rural parishes in southern Sweden. Longitudinal demographic and socioeconomic data for individuals and household socioeconomic data from parish registers were combined with local area data on food costs and disease

load using a Cox regression framework to analyse the 55-80 year age group mortality (number of deaths= 1398). In this paper the impact of the infant mortality on old age mortality, particularly old age mortality from infectious diseases, persisted after controlling for variations in food prices during pregnancy and the birth year, and the disease load on mothers during pregnancy. The impact on mortality in later life stems both from the short-term cycles and the long-term decline in infant mortality. An asymmetrical effect and strong threshold effects were found for the cycles. Years with very high infant mortality, dominated by smallpox and whooping cough, had a strong impact, while modest changes had almost no impact at all. The effects of the disease load during the year of birth were particularly strong for children born during the winter and summer. Children severely exposed to airborne infectious diseases during their birth year had a much higher risk of dying of airborne infectious diseases in their old age. This study suggests that exposure to airborne infectious diseases during the first year of life increases mortality at ages 55-80 years. In contrast, socioeconomic status, measured by stratification into the groups freeholder/crown tenants, tenants on nobility-owned land, semi-landless/crofters and landless, was not associated with later life mortality (Bengtsson & Lindström, 2003).

3.4 Migration and health: a study of early life experiences and current socioeconomic situation on mortality of immigrants in Sweden

Previous research has shown differences in mortality in modern Sweden between immigrants and Swedish born living in Sweden. This study investigated the effects of early life conditions in the country of birth and current socioeconomic conditions in adult life in Sweden on cardiovascular, cancer, all other causes and total mortality among immigrants and natives born in Sweden. The Swedish Longitudinal Immigrant Database (SLI), which is a register-based representative cohort database, consists of individuals born between 1921 and 1939 in eleven different countries who were residents in Sweden between 1980 and 2001. Associations between socioeconomic conditions in adulthood as well as infant mortality rates (IMR) and Gross Domestic Product (GDP) per capita in the year and country of birth, and cardiovascular, cancer, all other causes of death and total mortality in 1980-

2001 were investigated by survival analysis with Cox proportional hazards regression. Current individual level socioeconomic conditions in adulthood in Sweden such as income, education and being a welfare recipient were significantly and strongly associated with mortality in all groups of diagnoses as well as total mortality, i.e. indicators of lower socioeconomic status (lower education, lower income) were significantly and strongly (high effect measures) associated with higher mortality. In contrast, indicators of early life conditions such as IMR and GDP per capita in the year of birth and in the country of birth were generally not associated with adult mortality, with the exception of IMR in the year and country of birth which was positively and significantly associated with cancer mortality among men, and almost among women (Klinthäll & Lindström, 2011).

3.5 Epidemic stress and socioeconomic stress in early life, and self-rated health in adulthood: A population-based study

Several previous studies have shown that between-year variation in infant mortality rate (IMR) in historical data in Scania was caused by epidemic airborne infectious diseases such as for instance measles, scarlet fever and whooping cough, and that such epidemic outbreak was also associated with long-term effects on different aspects of health in later life. This study investigated associations between the regional aggregate IMR in the year of birth in Scania, individual level father's socioeconomic status, economic stress in childhood and education, and self-rated stress in adulthood among a stratified random sample of Swedish-born adults in Scania born in 1927-1960 who answered a public health questionnaire in the autumn of 2008. The number of participants in this age interval was 13,491 and the participation rate approximately 63%. The associations were investigated in logistic regression models. Among men 33.0% reported poor current health and among women 35.0% reported poor current self-rated health. The de-trended between-year deviation in IMR in the year of birth was not significantly (5% significance level) associated with poor self-rated health in the models. In the final model, only the individual variables father's socioeconomic status (according to occupation), self-reported childhood economic stress and respondent's own education were significantly associated with poor self-rated

health, although the association between low socioeconomic status of the father and poor self-rated health was attenuated after the introduction of economic stress in childhood and education in model 5. Higher levels of economic stress in childhood and low education were positively and significantly associated with self-rated health. Interaction terms between IMR and each of the three individual level socioeconomic variables father's SES, economic stress in childhood and education were not significantly associated with self-rated health. Only individual variables depicting socioeconomic conditions in childhood such as father's socioeconomic status (occupation), economic stress in childhood and education, but not the aggregate regional IMR in the year of birth, were significantly associated with self-rated health in adulthood. In the models with one year lagged IMT (t+1), the relative IMR (deviance from trend) remained not statistically significant throughout the corresponding regression models. All patterns remained similar as in the not lagged IMR models, including the three interactions between IMR (t+1) and each of the three individual level socioeconomic variables which were statistically not significant (Lindström, 2015).

4. Discussion

4.1 General discussion and interpretation of results

The aim of this thesis is to investigate whether specific cohort mechanisms may have existed during different parts of the secular mortality decline. The aim is not to investigate the relative impact of such early life or cohort mechanisms on the total secular mortality decline that started in the late 18th century in Sweden and is still ongoing. The book chapter that constitutes paper I has discussed specific early life cohort effects. Studies II and III have investigated specific early life cohort effects in the forms of epidemic outbreaks and fluctuations of infectious diseases and yearly rye price fluctuations (nutrition) on later life mortality in the secular mortality decline, while the total downward mortality trend in non-epidemic years were not analysed. Studies IV and V should also be seen in the light of this discussion in the book chapter (paper I).

Timing and specificity are key factors in the study of life course epidemiology and the influence of early life factors on later life morbidity and mortality. Davey Smith and Lynch (2004) have stressed that the mortality decrease in the three specific diseases respiratory tuberculosis, haemorrhagic stroke, and bronchitis may have accounted for approximately two-thirds of the total decline in mortality for both men and women aged 15-64 from the middle of the 19th century to the first decade of the 20th century in Britain. Some other specific diseases including stomach cancer and rheumatic heart disease may account for some of the residual decline. These diseases show clear influence from infancy and childhood on later life morbidity and mortality. The timing for this time period is also very good. A wide variety of social, economic, nutritional and biologic factors such as decrease in child labour, increase in real wages, improved nutrition and increased height, a decrease in the proportion of working mothers, a decrease in family size, and improved housing conditions are relevant during this time period (Davey Smith & Lynch, 2004; Lindström & Davey Smith, 2007). The most important

diseases in relation to the first phases of the modern secular mortality decline discussed in paper I (the book chapter) are not possible to discern in the historical data from the Scanian Economic Demographic Database (SEDD) for the period 1760-1894, the time period during which the decrease in these diagnoses are most relevant, because non-infectious diseases within the areas of internal medicine and surgery are virtually impossible to separate and because the clergymen in the parishes were not required to record specific causes of death from these diseases after 1831 (Bengtsson, 1988).

The two historical empirical studies of this thesis, papers II and III, add empirical evidence concerning the influence of early life factors on later life morbidity and mortality in the early period of the modern secular mortality decline. The yearly variations in infectious diseases, measured as IMR in the year of birth and in it peaks in historical data caused by epidemic outbreaks, also seem to have been an important explanation of both the early life, particularly peaks of epidemics, origins of later life diseases (Bengtsson & Lindström, 2000), and these early life effects on the risk of infectious diseases in later life (Bengtsson & Lindström, 2003). Since IMR in infancy (0-1 year) was significantly associated with old age (55-80 years) mortality, we conclude that the inflammatory hypothesis was confirmed. Children exposed to airborne infectious diseases during the birth year had a considerably increased risk of death caused by airborne infectious diseases in their old age (55-80 years). The pathways linking exposure to infectious diseases in early life to infectious diseases in later life which have been previously discussed in the literature mainly concern the respiratory tract. Respiratory infections, atopy, reversible airway obstruction, chronic mucus hyper-secretion and irreversible airflow obstruction are interconnected through a complex web of causality (Kuh & Ben-Schlomo, 1997, 2004; see also Bengtsson & Lindström, 2003). Respiratory infectious diseases in infancy (0-1 year) have been proposed to be one cause or, alternatively, a component cause of chronic wheezing tendency (Samet & Tager, 1983; McKonnochie & Roghmann, 1984), chronic cough and phlegm (Samet & Tager., 1983; Colley, Douglas & Reid, 1973), irreversible impaired ventilator function (Samet & Tager, 1983; Britten, Davies & Colley, 1987), and their related mortality (Barker & Osmond, 1986a). These empirical findings may be explained by the notion that adaptations in the immune system in early life to disease load such as, in this case, infectious diseases may be harmful in later life, a notion discussed in connection with the inflammation hypothesis in section 1.4.2 (Stearns, 1989). It seems that the first year of life (birth year) may be a critical period

for the relationship between exposure to fluctuations and particularly outbreaks of epidemic diseases in the birth year and later life mortality, especially mortality from airborne infectious diseases.

In contrast, hypotheses concerning the effects of the disease load on mothers during pregnancy and a modified variant of the foetal origins hypothesis measured as rye prices and their variations prior to birth were not confirmed. Studies on modern data have suggested associations between early life exposures and adult CVD, most plausibly through the pathway of accumulation (Lawlor, Ben-Schlomo, & Leon, 2004).

Also in contrast to the empirical confirmation of the inflammatory hypothesis, individual later life socioeconomic characteristics such as occupation, ownership conditions and farm size had limited effect on later life (55-80) morality in paper II. The findings that cottagers had lower relative risk of later life mortality compared to the reference group farmers when occupation was considered and that tenants had lower risk of later life mortality compared to the reference group self-owners when owner conditions were considered, also go in the opposite direction to what might have been expected because lower socioeconomic status is significantly and positively associated with lower later life mortality. In paper III no significant associations between later life socioeconomic status (stratified into the groups freeholder/tenant, tenants on nobility-owned land, semi-landless/crofters and landless) and later life mortality were observed. These findings accord well with previous findings based on historical data which show no or weak associations between socioeconomic status and mortality (Bengtsson & van Poppel, 2011; Bengtsson & Dribe, 2011; Haines & Ferrie, 2011), which was also suggested by Livi-Bacci (1991).

Finally, the effects on an exposure to increased disease load measured as IMR during the year of birth were particularly strong for children born during the winter and summer. This finding is in accordance with previous findings from empirical studies on historical data in Sweden (Brändström, 1988; see also Doblhammer, 2003). Respiratory diseases were the most common cause of death in the winter, and water- and airborne infections during the summer (Preston & Haines, 1991; see also Doblhammer, 2003).

It should also be noted, once again, that papers II and III have investigated whether specific cohort mechanisms may have existed. They did not investigate the relative impact of such early life or cohort mechanisms on the total secular mortality decline that started in the late 18th century in Sweden.

It is highly plausible that the mortality decline in the population in southern Sweden was also caused to an important extent by a decline in tuberculosis, haemorrhagic stroke and bronchitis as described and hypothesized in parts of the literature referred to in paper I.

The two empirical studies based on modern data, papers IV and V, show weaker or no statistically significant associations between the aggregate early life exposure variables GDP per capita and IMR, and later life adult mortality and self-rated health, respectively. The exception from this pattern is the significant association between IMR and cancer mortality in paper IV. Established causal links between early life and long term effects of life course exposures to infectious diseases and some cancers exist, and such examples include the causal connection between helicobacter pylori infection and stomach cancer, the causal connection between hepatitis B virus and liver cancer as well was the causal connection between human papilloma virus (HPV) and cancer of the cervix (dos Santos Silva, 2004). In contrast, individual level indicators of current (adult) socioeconomic status (education, income, welfare recipient) are significantly and strongly associated with mortality in general (total, cancer and other mortality) and cardiovascular mortality in particular in paper IV. In paper V, the individual level indicators of socioeconomic status in early life father's occupation in childhood, economic stress in childhood and education are also significantly and strongly (high effect measures) associated with self-rated health which is a strong predictor of total mortality and cardiovascular mortality. The directions of the associations are also as expected in both paper IV and paper V, i.e. lower socioeconomic status is positively associated with higher mortality and poorer self-rated health, respectively (Marmot et al., 1978; Marmot & Wilkinson, 2006). In paper IV, current socioeconomic conditions in Sweden are more strongly associated with mortality than the early life indicators GDP per capita and IMR in the year of birth in the country of birth (Klinthäll & Lindström, 2011). Current socioeconomic conditions in Sweden in the 1980s and 1990s thus seem to be of greater importance than IMR differences in 1921-1939 in eleven countries in different stages of the mortality decline in the 20th century. Father's occupation in early life, economic stress in childhood and education are significantly associated with adult current self-rated health, although the results for father's SES are grossly attenuated after the introduction of economic stress in childhood and education. No such associations are found between IMR in the year of birth 1927-1960 and current self-rated health.

The sex difference in mortality in paper IV, i.e. 4031 male deaths of a total 18,673 men but 2020 female deaths of a total 16,022 women during the 1980-2001 period, reflect the patterns of development of sex differences in mortality and life expectancy in Sweden during the 20th century. The sex differences continuously increased to more than six years longer life expectancy for women in the early 1980s, and has since then continuously decreased again to less than four years in 2011 (see Human Mortality Database, www.mortality.org, but also Figure 1 concerning life expectancy in the introduction section).

The results of the four empirical studies are in good accordance with Omran's notion concerning the epidemiological transition presented in the introduction. Before the general secular mortality decline mortality was high and fluctuating, which precluded sustained population growth. Life expectancy at birth was low and varying, vacillating under the level of 40 years, according to Omran. This pre-modern "Age of pestilence and famine" was succeeded by an age when mortality progressively declined and peaks of epidemics eventually disappeared. Life expectancy at birth started to increase and then increased continually, i.e. this was the first phase of the modern secular mortality decline corresponding roughly to the major part of the 1760-1894 period analysed in papers II and III in this thesis. This "Age of receding epidemics" was in a later phase of the secular mortality decline succeeded by the "Age of degenerative and man-made diseases". This third period saw a continued mortality decline and a corresponding further increase in life expectancy. It also corresponds to the 20th and 21st centuries data analysed in papers IV and V in this thesis, although too far-reaching conclusions should not be drawn based on papers IV and V due to the risk of correlation in trends between dependent and independent variables.

During the 1760(1766)- 1894 period, higher IMR was significantly associated with higher mortality in general and mortality caused by airborne infectious diseases in particular in later life, which means that the inflammation hypothesis (see introduction) was confirmed. In contrast, the foetal origins hypothesis was not confirmed. Also, adult/later life socioeconomic status (measured as occupation, ownership and farm size) was not significantly associated with adult/later life mortality. The exceptions were that cottagers had significantly lower mortality than farmers (occupation) and that tenants had lower mortality than self-owned farmers (ownership) in paper II, and these exceptions were unexpected given the directions of the associations. No significant adult/ later life socioeconomic differences in

mortality were observed in paper III. The importance of IMR for cohort effects on mortality in later life may be seen in the light of Omran's second "Age of receding epidemics". The peaks and fluctuations in IMR caused by epidemics of airborne infectious diseases are the causes of the cohort effects on later life mortality we can discern in papers II and III, while socioeconomic status in later life has almost no association with later life mortality. Exposures to epidemics as well as fluctuations in infectious diseases follow no social stratification, and the health effects on the individual of many airborne and other infectious diseases are independent of nutritional status (Rotberg & Rabb, 1985).

In contrast, the results of the late 20th and early 21st centuries papers IV and V are in accordance with Omran's "Age of man-made and degenerative diseases", although one should be careful with too far-reaching conclusions from these two studies which are more associational in nature. The lesser importance of IMR and the much higher importance of different aspects of current socioeconomic status as potential determinants of mortality and self-rated health (that predicts total and cardiovascular mortality) during this period are characteristics of a still ongoing era dominated by chronic diseases in the developed world with cardiovascular diseases and cancers as the most prominent examples. The determinants of these diseases and their mortality are mostly economically and socially stratified, which is true for health determining risk factors such as smoking, poor dietary habits, low physical activity, psychosocial stress at work as well as outside work, obesity and overweight. These patterns were observed for current (adult) socioeconomic status in paper IV and early life (childhood) socioeconomic status in paper V. The "Age of man-made and degenerative diseases" thus seems to be characterised by not only current (period) socio-economically stratified effects on mortality of the predominating chronic diseases, but it may also be characterised by socio-economically stratified early life and life course effects on later life mortality in later middle-age and old-age. A challenge for future studies will thus be to further specify specific "critical" or "sensitive" periods and time windows during the life course which may be particularly critical or sensitive for socio-economically stratified early life disease or risk factor load in relation to later life disease. A competing hypothesis will be to investigate whether an accumulation of risk pattern persists rather than specific "critical" or "sensitive" periods (see introduction, section 1.4).

The policy implications of studies on effects of early life exposures on health and mortality in later life may be to target birth cohorts (all born in a

particular birth year) born in years with more exposures such as higher IMR:s or increased economic stress. While yearly variations to such exposures may be less pronounced in developed countries at the moment, such policy recommendations may apply to poorer and economically less developed countries at the current point in time (see van den Berg, Doblhammer & Christensen, 2009).

4.2 Strengths and limitations of the empirical studies

Papers II and III

The time span analysed in papers II and III is sufficiently long. The approach to deal with the problem of defining exogenous early life exposures to mortality in late adulthood has in papers II and III been to analyse the transitory component (deviation) in rye price at the time of birth as an indicator of food accessibility in early life, and the transitory component (deviation) in local infant mortality rate at the time of birth as an indicator of early life diseases, particularly early life infectious disease epidemics, an approach which has later been described as pioneering (van den Berg, Doblhammer & Christensen, 2009).

Still, the results in papers II and III should be interpreted with care, although the validity of the data is internationally high for the historical time period studied. A single theoretical basis did not exist in medical science in the middle of the 18th century (Bengtsson 1988). The aetiology of infectious as well as many other diseases was not known (Ackerknecht, 1982). A nosological system prevailed, i.e. causes of death were classified according to symptoms instead of primarily according to specific biological causes. Although medical science progressed into its modern form during the latter part of the 1760-1894 period studied, so that pathological-anatomical diagnosis by autopsy became generally accepted as the foundation for the determination of cause of death, in its practical applications the system remained nosological (Bengtsson, 1988). The classification system for causes of death also changed in 1774, 1802, 1811, 1821, 1831, 1873 and 1891, although the first four changes were small and had no effect on what the clergymen recorded in the parish registers. The nomenclature change in 1831 was the result of complaints from the clergymen. Their argument was that their 2-3 months medical training did not make them competent enough to

record causes of death. Starting in 1831, they were only required to register deaths from smallpox and other epidemic diseases, deaths in childbirth, accidents, homicide and suicide (Bengtsson, 1988). The classification of infectious diseases and accidents is thus prone to much less misclassification than other diagnoses and diseases in this data material, in addition also because symptoms are specific for several airborne infectious diseases. It is very difficult to interpret and correctly classify non-infectious internal medicine and surgical diagnoses in the data material gathered from 18th and 19th century church registers in Sweden registered by priests with 2-3 months of medical training. The consequently higher sensitivity and specificity of the data concerning infectious diseases may thus partly influence the findings of the two empirical studies, because other diseases or groups of diseases which might have had significant early life effects on mortality may be non-significant in the two studies due to misclassification. Table 2 in paper II (Bengtsson & Lindström, 2000) shows that 23.3% of all causes of death in the four parishes in 1760-1894 were not specified at all. Preston has suggested that deaths from unknown causes are most likely deaths from cardiovascular diseases (Preston, 1976, see also Crimmins & Finch, 2006), but it remains unclear whether this judgement can be generalized to the cause of death recordings of different historical periods.

Variation by individual clergymen in the validity of the recordings of causes of death has also been discussed (Puranen, 1984). However, there is no conclusive evidence of major variation in validity (Bengtsson, 1988).

The fact that the longitudinal study design and the use of time-varying external factors in papers II and III opens the possibility for interpretations concerning causality is a strength.

It should also be noted that the population followed by survival analysis in papers II and III is the part of the population born in the parishes that stayed in the parish. There is thus an element of potential selection since approximately 50% of the population migrated during their life time during the time period in this geographic area, although mostly to neighbouring or other geographically close parishes (Dribe, 2000, 2003, Quaranta, 2014). The fact that all persons included in papers II and III were individuals who remained in the parishes throughout their entire life from birth until the age of 55 or above probably represents a form of positive social selection of individuals who were likely to be less vulnerable to the exogenous exposures in the form deviation in rye price and deviation in IMR in early life. This

observation leads to the conclusion that the effects (associations) calculated are probably under-estimated (for discussion on selection, see van den Berg, Doblhammer & Christensen, 2009). Selection may also occur due to negative foetal events and foetal mortality caused by the exogenous exposures, but such selection would probably also result in under-estimation (Almond & Currie, 2011.).

Decomposition technique with a Hodrick-Prescott filter was used in papers II and III, and previous studies have suggested robust results independent of filter factors and techniques (van den Berg, Doblhammer & Christensen, 2009).

Paper IV

Selection bias is less likely in a study based on a random sample of register data. The problem of under-registration in migrant studies was also reduced by the elimination of study participants who had no registered income and thus could be assumed to have left Sweden.

Early life indicators are aggregate national level measures of IMR and GDP per capita, which is a weakness. IMR and GDP per capita may thus not reflect variations in these parameters within countries. It may be that they do not reflect damaging effects of early 20th century disease load and household nutrition, respectively. It should also be noted that cyclical variations are exogenous measures, while trends are not (van den Berg, Doblhammer & Christensen, 2009). Post-early neonatal mortality rates (PENMR) are most probably also more valid as indicators of early life disease exposure than IMR (Quaranta, 2014). However, for most countries and most time periods they are the only measures/ estimates available. Even studies which entail these aggregate measures are scarce. The statements concerning IMR in this paragraph also apply to strengths and limitations of paper V.

Misclassification by country of birth is not likely. Misclassification by diagnosis is less likely due to the combination of comparatively high autopsy rate, especially during the first part of the period 1980-2001, which yields high validity (Garne, Aspegren & Balldin, 1996), and the aggregation of diagnoses into broad groups of causes of death in paper IV. The variation in validity of diagnoses due to variation in autopsy rate in modern causes of death data clearly demonstrates the huge validity variation even in modern causes of death data.

Many potential confounders and mediating factors were taken into account in the statistical analyses in study IV, but some mediating factors such as for instance tobacco smoking, exercise, alcohol consumption and diet are missing because health related behaviours are not included in registers.

The limited longitudinal study design in paper IV makes this study primarily interpretable in terms of associations.

Paper V

The participation rate in the 2008 public health questionnaire study is approximately 55% (63% in the age range studied in paper V) which is normal in modern western studies based on postal questionnaires. The demographic composition regarding age, sex and education of those in the stratified random sample who chose to participate in the study is similar to that of register data covering the entire population in Scania. The exception is a substantial under-representation of persons born abroad among those in the sample who participated compared to the total population (Lindström, Fridh & Rosvall, 2014), but this is no problem in paper V because only participants born in Sweden were included. The risk of selection bias is thus limited. The study was restricted to only participants born in Sweden because many countries only have aggregate IMR data from 1952 and onwards. Some participants may have been born in other parts of Sweden than Scania, but we do not know the exact proportion.

The confounders age and sex were included. Father's socioeconomic status (SES) (occupation), economic stress in childhood and education were included as individual level determinant variables, while IMR is a contextual determinant variable. No other variables were included in the multiple logistic regression models in order to exclude potential intermediate variables in the hypothesized chain of causality between potential early life determinants and current (2008) self-rated health.

Self-rated health is internationally regarded as a valid indicator of health because it is a strong predictor of for example cardiovascular disease mortality and total mortality (Heistaro et al., 2001). The dichotomization of self-rated health into a binary variable follows the international definition and how it predicts CVD incidence and mortality as well as total mortality. This binary outcome has also been validated regarding the public health questionnaire in Scania (Mohseni, 2008), which is the rationale why ordered probit analysis

was not conducted. The validity of Swedish aggregate statistics on IMR is very high.

It is a methodological strength that the study to some extent avoids endogeneity by combining questionnaire data in Scania 2008 with aggregate IMR for the birth years 1927-1960.

Due to the cross-sectional nature of paper V causal inference is formally restricted. However, the aggregate IMR measure is truly retrospective and the three early life determinant individual variables from the questionnaire are also retrospective, although self-reported.

4.3 Conclusions

This thesis has investigated whether specific cohort mechanisms may have existed during different parts of the secular mortality decline. Significant associations between peaks and fluctuations in IMR in infancy (0-1 year) caused by airborne infectious diseases and mortality in later life, particularly adult mortality from infectious diseases, were observed in the two historical empirical studies covering the late 18th century and almost entire 19th century in the four originally rural parishes in western Scania. The inflammation hypothesis was thus confirmed. On the other hand, the foetal origins hypothesis was not confirmed because no significant association between yearly variation in rye prices during life in utero and mortality in later life was observed.

The support in the results from the two historical empirical studies for the inflammation hypothesis has implications for present-day prevention and public health policy in economically less developed countries. The results imply that actions to lower IMR in present-day economically less developed countries with comparatively high IMR:s and year-by-year variations in IMR due to infectious diseases will not only reduce the number of deaths in infancy but possibly also increase life expectancy in adulthood among those who would have survived in infancy even without actions to lower IMR.

In the two historical empirical studies of the period from the late 18th century and the almost entire 19th century socioeconomic differences in mortality were absent or weak, the exceptional patterns for cottagers and tenants even

showing reverse socioeconomic gradients with lower mortality in lower than in higher socioeconomic groups.

In contrast, the two studies on modern data show minor or no effects of IMR in the year of birth (1921-1939) in the country of birth (eleven countries) and mortality in 1980-2001 in Sweden, and between IMR in Scania in the year of birth (1927-1960) and self-rated health (a predictor of total mortality and cardiovascular mortality) in Scania in 2008. GDP per capita in the year of birth in the country of birth was also not associated with mortality in 1980-2001 in Sweden.

In the two modern time empirical studies, in contrast, individual level socioeconomic status in adulthood (study IV) and in childhood (study V) were significantly and strongly (strong effect measures) associated with adult mortality (study IV) and self-rated health (study V). In the postmodern later phase of the secular mortality decline socioeconomic differences in current (study IV) and early life (study V) associations with mortality and self-rated health, respectively, prevail. Still, too far-reaching conclusions should not be drawn from these predominantly associational studies, although this pattern is in accordance with Omran's "age of degenerative and man-made diseases" predominated by chronic diseases partly determined by socially stratified risk factors such as tobacco smoking, lack of exercise, poor dietary habits, obesity, overweight and psychosocial stress.

New empirical results may add to Omran's notion of the epidemiological transition, for instance increasing socioeconomic stratification of health and mortality in the modern and postmodern later phases of the secular mortality decline caused by the emerging predominance of chronic diseases such as cardiovascular diseases and cancers. Further studies of cohort effects on mortality may add to our understanding of this phase of the modern secular mortality decline.

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Paper I

A Life Course Perspective to the Modern Secular Mortality Decline and Socio-economic Differences in Morbidity and Mortality in Sweden

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During the past 200 years, most countries in the world have experienced a great increase in life expectancy. The timing of the onset of this decrease in mortality and corresponding increase in life expectance has vastly differed between different countries, and this is true for the pace of the development as well. Some countries have still not achieved the life expectancy experienced by the most developed countries already one hundred years ago or even earlier. Some countries have even experienced a backlash in the form of declining life expectancy in the 1990s due to, for instance, unemployment and alcohol consumption in some eastern European countries, and the HIV/AIDS epidemic in some African countries. Nevertheless, the general picture of improvement remains massively impressive, and in Sweden life expectancy has increased continuously for more than 200 years.

The secular mortality decline may be explained by a multitude of causes rather than one single cause. These causes may be categorised in different ways and from varying perspectives. Some causal effects (exposure leading to disease) are direct or short-term effects, others are long-term effects. The causes do not only include direct, *period effects* on mortality and survival such as the immediate effects of outbreaks of infectious diseases, the presence of endemic infections, as well as current hygiene, income, nutrition, housing and health care conditions. The causes also include long-term, sometimes very long-term, effects. The latter group of long-term causal mechanisms by which risk factors and protective factors affect health and disease many years later are often referred to as *cohort effects*, because different birth cohorts are exposed to different sets of risk factors as well as protective

factors during their childhood and adolescense that affect their health in later life.

This contribution will deal with long-term cohort or early life effects on disease in later life, their biological mechanisms in general (not only in Sweden) and their implications for socioeconomic differences in mortality, with particular reference to Sweden. It will also shortly deal with the possibility of making predictions concerning future mortality based on cohort mortality and its indicators in Sweden and in other countries. In the following sections, we will discuss the early life effects and then their biological mechanisms without particular reference to Sweden.

The Secular Mortality Decline: Early Life and Cohort Explanations and Their Indicators

By the term *period effect,* we mean effects on health and survival caused by health determinants (see above) with a short time period between exposure and health/disease outcome (exposure factors which affect the risk of disease may promote either salutogenesis or pathogenesis). For instance, most infectious diseases give rise to symptoms in the very short term (hours-days-weeks) after the initial exposure to infection. However, for some infectious diseases such as tuberculosis (caused by mycobacterium tuberculosis) and leprosy (caused by mycobacterium leprae), the time interval from exposure to disease/symptoms may be much longer (months-years) due to the slow pace of multiplication of the pathogen in the infected human host. Other diseases, especially non-infectious chronic diseases such as many cancers and forms of cardiovascular disease, may have much longer latent periods, i.e. time intervals from exposure of determinants to disease amounting to several decades.

For some diseases, the time lag between exposure and disease may even range from early life (intra-uterine or first year(s) of life) exposure resulting in old-age morbidity and mortality. This set of factors is causally related to the mortality decline and concerns the effects of cohort or early life events on mortality in later life. The general idea behind the notion of *cohort effects* is that varying forms of stress or heavy disease load on the different organs or organ systems in the human body experienced in early life, most importantly during pregnancy and the first year(s) of life after birth, may "program" the organs to increased susceptibility to various diseases much later in life. However, the notion of cohort or early life causes of disease in later life is not restricted to purely biological mechanisms. Early life events of psychological significance experienced in early life may also give rise to psychological problems or certain persistent personality traits in adulthood (Suomi 1997).

The cohort or early life explanation was proposed by Kermack et al. in 1934 (see also Davey Smith and Kuh 2001). They studied age-specific mortality in England, Wales, Scotland and Sweden. Their conclusion was that reductions attained at any particular time in the death rates of the various age groups depended primarily on the date of birth of the individuals, and only secondarily on the actual year of death. The essential beneficial effects on health and survival among adults and older persons were mainly caused by a decrease in disease load achieved in these birth cohorts during early childhood several decades earlier, according to Kermack et al. (1934).

The past decades have witnessed a renewed interest in the cohort or early life approach to disease in Sweden (Bengtsson and Lindström 2000, 2003) as well as in other countries (Preston et al. 1998), particularly in chronic disease epidemiology (Kuh and Ben-Shlomo 1997, 2004; Galobardes et al. 2004). This approach has been heavily supported particularly by the work of Barker and colleagues. They have both hypothesised and investigated the early life preconditions for later life development of cardiovascular diseases and the metabolic syndrome, i.e. coronary/ischaemic heart disease, hypertension, adverse levels of blood cholesterol and lipids, stroke, type II diabetes mellitus, and overweight/obesity (i.e. the components of what some call the "metabolic syndrome"). The causal mechanism behind these diseases induced in early life is suggested to be inadequate cellular development in utero due to lack of sufficient nutrition (Barker 1994, 1995, 1997, 1998, 2001). The concept of down-regulation of fetal growth has been developed further into the nutritional programming (or fetal origins) hypothesis. According to this hypothesis the development of cardiovascular and other diseases in later life depends on whether fetal growth retardation due to insufficient nutrition is "proportionate" or "disproportionate". The "disproportionate" growth retardation induced by insufficient nutrition during the mid and late trimesters of pregnancy seems to be responsible for cardiovascular diseases later in life, while the "proportionate" growth retardation of the first trimester is not (Barker 1995), although this distinction has later been tuned down by Barker (1998).

Not all evidence suggests an exclusive or even important role of malnutrition in the fetal origins hypothesis. For instance, maternal tuberculosis also impairs fetal growth (Riley 2001). The famine in rural Finland from 1866 to 1868 tripled death rates but did not alter the survivors' lifespans (Kannisto et al. 1997).

The original disease load mechanism proposed by Kermack et al. has been developed and further investigated. Later Fridlizius (1989) suggested that the development of diseases in later life might be due to exposure to certain

infectious diseases. For example exposure to smallpox in the late eighteenth century and exposure to scarlet fever in the mid nineteenth century, in the first five years after birth, resulted in reduced immunity against other diseases throughout life and thus a higher susceptibility to getting other infectious diseases in later life. In neither case did susceptibility to disease in adulthood seem to have been connected with nutrition in early life, because the risks of being infected with for instance smallpox and scarlet fever are to a high extent independent of nutrition (Rotberg and Rabb 1985). However, some findings of recent empirical investigations have suggested an association between nutrition and morbidity and mortality of scarlet fever epidemics in the Sundsvall region in northern Sweden (Curtis 2004). In contrast to nutrition, Fridlizius suggested deranged immunological balance between some specific infectious agents and the human host, which has implications for later life experiences of disease (Fridlizius 1989).

In recent years, the rather unspecified mechanisms suggested by Fridlizius have received some support from the bio-medical literature. Chronic inflammatory mechanisms may drive much of the influence of early life infections on later morbidity and mortality. Populations living in high mortality contexts are highly exposed to a wide variety of infectious diseases. Such populations also have high risks of acquiring chronic infectious diseases such as tuberculosis (Lawn et al. 2000) and infections caused by escherichia coli and helicobacter pylori (Cadwgan et al. 2000). These diseases lead to chronically elevated levels of inflammatory markers such as C-reactive protein, interleukin-6, tumour necrosis factor-α and fibrinogen that may mediate between early life infection and later life chronic disease morbidity and mortality (Finch and Crimmins 2004). Thus, reduced morbidity and mortality from infectious diseases in populations experiencing the great mortality decline could produce decreases in exposure to these markers of inflammation. Whether these inflammatory mediators actually have causal influence on chronic disease risk is not established (Timpson et al. 2005).

Helicobacter pylori is an established cause of peptic ulcers, and is associated (although maybe not causally) with coronary heart disease (Harvey et al. 2002). Infections caused by helicobacter pylori are most commonly contracted in infancy and childhood and they persist throughout life. Helicobacter pylori infections are now declining in most low-mortality countries due to improvements in public health and hygiene (Li et al. 2000).

Exposure to infections during the fetal, perinatal and postnatal stages may affect both anatomical/organ development and development of the immune system. The effects of infections during the fetal stage depend on a number of fetal and maternal factors such as nutrition, genetic factors, fetal development

stage and anatomical factors. Other examples of such infections are influenza and rubella. One example of a causal association between postnatal infection and adult disease is the association between Hepatitis B and primary liver cancer (Hall and Peckham 1997). A contemporary study from the USA on Americans aged 55–65 years shows that infectious disease during childhood multipled the incidence of lung conditions, such as emphysema and bronchitis, by four in the 55–65-year age group. Non-infectious diseases showed much weaker associations with adult disease (Blackwell et al. 2001). It thus seems plausible that the prenatal and postnatal development of the lungs and the immune system are sensitive to critical events which may influence susceptibility to infections, allergic reactions or toxic exposures, but the exact and specific timing and critical periods for such early life influence on health later in life remain to be disentangled (Strachan 1997). A study of children born in 1921–1935 in Scotland also shows reduced lung capacity (in 1986) for those who experienced pneumonia before the age of 2 years (Shaheen 1997). Factors in utero and during the first years of life may affect the development of asthma later in childhood and adulthood (von Mutius 2001). A review of the effects on human lifespans of the inflammation/infection exposure in early life has proposed a "cohort morbidity phenotype" which represents inflammatory processes that persist from early age into adult life (Finch and Crimmins 2004). Early life experience of diarrhoea with subsequent dehydration may plausibly lead to higher blood pressure, a risk factor for cardiovascular diseases in general and haemorrhagic stroke in particular in later childhood and adulthood, a hypothesis which has been found to be supported by some empirical findings (Davey Smith et al. 2006; Lawlor et al. 2006).

There is also some support in the literature of an effect of both nutrition and disease load (particularly infectious diseases) in early life. Unfavourable early life conditions generally seem to cause permanent biological damage, resulting in higher mortality in later life (Doblhammer and Vaupel 2001). The results of a large sample study of 15 million US deaths between 1989 and 1997 has also suggested effects of season of birth on mortality risk in later life. Being born during a season of hardships is associated with higher mortality in later life (Doblhammer 1999; Doblhammer 2008). Seasonal differences in exposure to infectious disease in early life are associated with mortality in adult life. Seasonal differences in the nutrition of the mother during pregnancy also seem to affect mortality in later life (Doblhammer 2002). A study from contemporary rural Gambia has shown that higher mortality levels are explained by permanently damaging effects during early life of disease exposure as well as malnutrition during the yearly dry-season. Both the damaging effects of disease load and malnutrition during the fetal stage of development are by some authors (Moore et al. 1997) attributed to effects on the immune system, a conclusion that may be supported by histori-

cal data (Bengtsson and Lindström 2000, 2003). Several recent studies, however, have cast doubt on this conclusion (Simondon et al. 2004; Moore et al. 2004).

Finch and Crimmins (2004) have recently argued that the inflammatory-infection and nutrition hypotheses are not competing or contradictory but complementary in linking two mechanisms of morbidity in early and later life. For example, childhood diarrheas impair cardiac muscle synthesis (Hunter et al. 2001), which could explain associations of infant diarrhea with later cardiovacular disease (Blackwell et al. 2001). Slowed infant growth in the Barker hypothesis might consequently hypothetically be explained by inflammatory reactions in combination with impaired nutrient absorption. There is growing evidence from historical data (1766–1894) in Sweden in support of the disease load (particularly infectious diseases) mechanism suggested in two articles by Bengtsson and Lindström (2000, 2003).

There is also a rapidly accumulating amount of evidence in support of the early life conditions or life course approach in general from modern data (Kuh and Ben-Shlomo 2004; Kuh and Hardy 2002; Davey Smith 2003). The relative abundance (compared to historical data) and diversity of variables in modern data make it possible to attempt to understand the interactions between different determinants and successive exposures during the life course. It should thus be noted that modern data support not only the critical period model, which may be exemplified by the already referred to fetal-origins hypothesis. Modern data also support models following Omran's assumptions concerning multicausality and interaction of different causal factors in demography and epidemiology (Omran 1971). In contrast to the simpler mono-causal critical period model and fetal-origins hypothesis, the accumulation of risk model assumes that effects accumulate over the life course, although some particular developmental periods may entail greater susceptibility (Ben-Shlomo and Kuh 2002). Harmful effects on health may increase with the duration and/or number of harmful exposures. Exposure to poor socioeconomic conditions may for instance lead to additive effects of experiencing low socioeconomic position during different parts of the life course, which may influence the risk of several diseases (Heslop et al. 2001). The accumulation of risk may also be due to the clustering of exposures (Ben-Shlomo and Kuh 2002).

In modern times, chronic diseases dominate the disease patterns both when it comes to morbidity and mortality. Such diseases include for instance cardiovascular diseases, cancers, rheumatoid arthritis, thyroiditis, and musculoskeletal disorders. Coronary heart disease is a good example (Davey Smith and Lynch 2005). It manifests itself during adulthood and old age, but the disease

process starts many years earlier with the gradual development of atherosclerosis. This development begins with fatty streaks in the artery walls of children (Berenson et al. 1987). Arterial lesions are also evident in young men suffering from violent death (Strong et al. 1999). Risk factors for coronary heart disease include blood cholesterol levels, smoking, obesity, diabetes mellitus, hypertension, oral contraceptive use among women, psychosocial factors, mental illness, chronic infection/inflammation, coagulation factors, and air pollution (Marmot and Elliot 2005). Several studies have demonstrated that unfavourable pre-adult measures of cholesterol, blood pressure and adiposity are associated with increased intimal-medial thickness, which is a presymptomatic measure of coronary heart disease (Li et al. 2003; Raitakari et al. 2003; Davey Smith and Lynch 2005). These risk factors do not only affect coronary heart diseases in a mono-causal way, but they may also affect coronary heart disease by interacting with each other in order to increase or attenuate each other's effects on the disease aetiology leading to coronary heart disease.

Historical Trends and Socioeconomic Mortality Differences in a Life Course and Cohort Perspective

The research area that concerns the mortality decline entails a number of important issues that can each contribute to the understanding of the modern mortality decline and its complexity. The eradication of smallpox mortality (Sköld 1996a, 1996b) and the variations in sex differences in mortality (Willner 1999) have been thoroughly investigated and discussed. Another issue concerns socioeconomic mortality differences and socioeconomic differences in the short term as well as secular mortality decline. This socioeconomic gradient to this day remains apparent, despite the development of the modern welfare state and active policies to redistribute income in many countries, e.g. Sweden. In fact, during the past two decades, Sweden has witnessed a continuous decline in age specific mortality rates in most age intervals and a corresponding increase in life expectancy. This mortality decrease is observed in all socioeconomic groups in Swedish society. However, the decrease has been more pronounced in higher socioeconomic strata (high education, high income, non-manual employees in higher positions according to occupational status) than in lower socioeconomic strata, which has resulted in increasing socioeconomic differences in life expectancy in Sweden during the late 1980s, 1990s and early 2000s (National Public Health Report 2001, 2005).

It is often stated that socioeconomic mortality gradients, with the poor having worse health and increased risk of death compared to the rich, are ubiquitous

phenomena, having always existed everywhere. This is an erroneous assumption, however (Davey Smith 2003). Reviewers (e.g., Macintyre 1998) often start with well-known historical examples, such as when Chadwick assembled data from different areas of Great Britain, and generalise to all situations. Chadwick's data, however, did suggest large socioeconomic differences in mortality in the first decades of the 19th century in Britain. The socioeconomic differences existed within many UK locales, although the high socioeconomic position gentry and professional population only lived on average 35 years in Liverpool compared to 55 years in Bath. The corresponding average for the labourer and artisan class was 15 and 25 years, respectively (Chadwick 1842; Wohl 1983). Although data from Geneva indicate presence of socioeconomic mortality differences in pre-modern society (16th century) (Perrenoud 1975) and data from an English township 1650–1830 also suggest permanent presence of socioeconomic mortality differences (King 1997), the generalisation by MacIntyre concerning the presence throughout history of socioeconomic differentials in mortality contrasts to important extent with the observation by Livi-Bacci (1991). According to Livi-Bacci, rudimentary older data from England suggest the absence of socioeconomic differentials in mortality in England from approximately 1550 to ca. 1750 (Livi-Bacci 1991). The data that Livi-Bacci refers to are calculations of life expectancy from demographic data on English peers (Hollingsworth 1977) compared with life expectancy of the total English population calculated from the Wrigley and Schofield reconstitution data (Wrigley and Schofield 1981). In fact, the ducal families in England seem to have had a somewhat lower life expectancy than peers in general as well as the general population during the period prior to 1750. This pattern remains even after the increased risk of violent causes of death (including the "Agincourt" factor, i.e. the death-in-combat factor) are taken into account (Hollingsworth 1957). Furthermore, the reigning families of Europe seem to have had a life expectancy of 34 years in the 16th century, 30.9 years in the 17th and 37.1 years in the 18th century, i.e. life expectancies which fairly well correspond with the life expectancies of the general population in the corresponding countries during the same period. In the city of Rouen, fluctuations in grain prices during the ancien régime had a similar effect in various social classes (Galloway 1987).

A similar pattern has been observed in the parishes in the Scanian Demographic Database in southern Sweden, where fluctuations in grain prices also had strong and similar effects in all social classes before the agrarian revolution in the early 19th century. In contrast, the onset and progress of the agrarian revolution resulted in both weaker associations between short-term fluctuations in grain prices and mortality. It also resulted in increasing socioeconomic differentials in the mortality response to fluctuations in grain

prices, as the more prosperous segment of the population seems to have become much less exposed to the effects of the fluctuations (Bengtsson 2000, 2004). These observations seem to constitute further proof in support of the notion that social differences in mortality were small or absent. Furthermore, the observations support the notion that socioeconomic differences in mortality increased during the 18th century because of the agrarian revolution.

Sweden started to gather and record demographic and socioeconomic data (including mortality), different measures of socioeconomic position and, in many parishes, causes of death for the whole country already in 1749. Hence, it is possible to go further back in time in Sweden than in probably any other country in the investigation of reliable demographic and socioeconomic data in order to better understand the dynamics of socioeconomic differences in longevity.

One explanation for the lack of socioeconomic differences in mortality in the rudimentary data presented by, for example, Livi-Bacci for England, may be that epidemic and endemic infectious diseases dominated the disease and mortality panorama in the general population, which is certainly not the case today. In many pre-modern societies, population density seems to have been positively associated with mortality due to increased risk of disease (i.e. infectious disease) exposure in densely populated areas. For instance, the remarkable healthiness of many frontier settlements in colonial North America in spite of their comparatively primitive material living conditions must have been partly due to the infrequent contact with others (Wrigley et al. 1997). The virulence of many such epidemic and endemic infectious diseases, e.g. smallpox, malaria, plague, typhoid, tetanus, yellow fever, encephalitis and poliomyelitis, are not at all influenced (or only minimally affected) by nutritional factors such as total energy intake, nutritional contents of the food and physical habitus. Other infectious diseases such as typhus, diphteria, staphylococcus infections, streptococcus infections, influenza, syphilis and systemic worm infections are only affected by such nutritional factors to a limited or variable extent (Rotberg and Rabb 1985). This means that the upper socioeconomic strata (i.e. the nobility) must have been exposed to risks of disease and death from common infections prevailing at that time to the same extent as members of the lower social strata. In fact, as social contacts and networks of the upper strata most likely were more extensive than among the lower classes, the exposure in those groups may even have been higher than in the lower strata. As many of the infectious diseases mentioned above decreased in importance during the time period studied, all age-specific mortality rates declined and life expectancy increased. Consequently, other diseases and diagnoses more related to nutritional status and the protecting effects of higher socioeconomic position increased in relative importance as

causes of morbidity and mortality, which would have served to increase socioeconomic differences in morbidity and mortality during the period under study. The result would be an increase in socioeconomic mortality differences and thus increased socioeconomic differentials in life expectancy.

In modern times, chronic diseases with long latent, asymptomatic phases between the induction/onset of the disease and the first symptoms dominate the patterns of morbidity and mortality in developed countries. Socioeconomic differences according to social characteristics such as occupational status, education and income are well-known and have been described extensively both in Sweden (National Public Health Report 2005) and other countries (Marmot 2004; Davey Smith et al. 1990; Kaplan and Keil 1993) regarding morbidity and mortality in a wide variety of diseases. A recent review of the literature on the association between socioeconomic circumstances during childhood and cause-specific mortality during adulthood shows similar results. Adverse socioeconomic conditions during childhood were positively associated with increased all-cause mortality (in 18 of 22 studies), overall cardiovascular mortality (in 5 of 9), coronary heart disease mortality (in 7 of 10), stroke (in 4 of 6), and accidents and violence (in 3 of 5 studies). No such associations were found for rheumatic heart disease mortality (only 1 study) and overall cancer mortality. For lung- and smoking-related cancer mortality, respiratory disease mortality, suicides, alcohol- and illegal drug-related mortality only few studies showing no associations or studies showing diverse results concerning the association between childhood socioeconomic circumstances and cause-specific mortality were demonstrated (Galobardes et al. 2004). It thus seems that the association between childhood socioeconomic circumstances and risk of cardiovascular diseases in adulthood is particularly important in explaining life course effects on adult mortality (Galobardes et al. 2006a; Galobardes et al. 2006b).

In Sweden only a few studies concerning socioeconomic conditions in childhood and health in adulthood have been conducted, but new data sets have been developed (Stenberg et al. 2007). Birth order position within the same family had statistically significant consequences for the health and survival (overall mortality) over the life course (Modin 2002). Socioeconomic inequities in overweight seem to reflect the cumulative influence of multiple adverse circumstances experienced from adolescence to young adulthood (Novak et al. 2006). Several Swedish studies demonstrate statistically significant associations between disadvantaged socioeconomic conditions during childhood as well as adverse socioeconomic mobility, and aspects of cardiovascular diseases such as all-cause and overall cardiovascular mortality (Rosvall et al. 2006), coronary heart disease (Wamala et al. 2001), myocardial infarction (Hallqvist et al. 2004), and carotid atheroschlerosis (Rosvall et

al. 2002). In one Swedish study, IQ in early childhood was found to be unrelated to adult cancer mortality (Batty et al. 2007). Childhood conditions such as family disruption and child abuse were found to be unrelated to adult sense of coherence (Krantz and Östergren 2004). The markedly few results from Sweden thus still seem to be consistent with other findings from the international literature.

Cohort Effects on Mortality and Mortality Predictions: Indicators and Models

A number of models exist to forecast future mortality in populations (Bengtsson and Keilman 2003). There are several reasons why these models should include a historical and long-term perspective on mortality and the development of age-specific mortality. First, living conditions, i.e. living standards and diet, public health institutions and medicine and other areas relevant for the physical well-being of the population, improve from one period to the next. Such changes in living conditions are termed *period* effects. Second, the health and remaining lifespan of people living today are determined not only by contemporary period factors but also by living conditions earlier in life. Living conditions during childhood may affect health in later life through *cohort* effects on mortality. Third, the prediction of future mortality calls for a multivariate approach, including not one but a multitude of factors to predict mortality. These factors include long-term early life factors (Bengtsson 2003).

It thus seems obvious that early life and cohort factors should be included in the models when making predictions concerning future mortality. The crucial question is what indicators to use in order to assess how early life and cohort factors influence future mortality. The original work by Kermack and colleagues (1934) analysed the relationship between early life mortality, including infant (0–1 year) mortality, and its association with the age-specific mortality of different birth cohorts later during their life courses. Age-specific mortality is now commonly used as an indicator of mortality trends (United Nations 1999). Given the plausibility and scientific evidence for early life effects on cohort mortality presented earlier in this paper, age-specific mortality seems to be an obvious choice of indicator for making predictions concerning future mortality in a population when considering early life cohort effects. Infant mortality seems to be the most crucial measure of all age-specific mortality intervals in this respect (Bengtsson et al. 1998).

Fogel (1994) has used height as an indicator of early life effects on life expectancy and health in later life. In fact, recently both age-specific early life

mortality (including infant mortality) and height have been demonstrated to be associated with mortality in later life using historical data from birth cohorts born before the 20th century in four North European countries (Crimmins and Finch 2006).

Timing and specificity are key factors in life course epidemiology. Davey Smith and Lynch (2004) have pointed out that the mortality decrease in the three specific diseases respiratory tuberculosis, haemorrhagic stroke and bronchitis may have accounted for approximately two-thirds of the the total decline in mortality for men and women aged 15–64 from the middle of the 19th century to the first decade of the 20th century in Britain. Some other specific diseases including stomach cancer and rheumatic heart disease may account for some of the residual decline. These diseases have demonstrable influences from infancy and childhood, which have already been discussed. The timing for this time period when it comes to early life/cohort effects is also very good. Underlying factors such as decrease of child labour, increase in real wages, improved nutrition and increased height, a decrease in the proportion of working mothers, a decrease in family size, and improved housing conditions are also present for this period (Davey Smith and Lynch 2004). There is often a lack of such a high degree of specificity and timing in modern data. Specific exposures and outcomes should always be identified as well as the exact timing. The high availability of data in Sweden will plausibly make this task possible to accomplish in the years to come.

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Paper II

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Childhood misery and disease in later life: The effects on mortality in old age of hazards experienced in early life, southern Sweden, 1760–1894

TOMMY BENGTSSON AND MARTIN LINDSTRÖM

Abstract. This paper assesses the importance of early-life conditions relative to the prevailing conditions for mortality by cause of death in later life using historical data for four rural parishes in southern Sweden for which both demographic and economic data are very good. Longitudinal demographic data for individuals are combined with household socio-economic data and community data on food costs and the disease load using a Cox regression framework. We find strong support for the hypothesis that the disease load experienced during the first year of life has a strong impact on mortality in later life, in particular on the outcome of airborne infectious diseases. Hypotheses about the effects of the disease load on mothers during pregnancy and access to nutrition during first years of life are not supported. Contemporary short-term economic stress on the elderly was generally of limited importance although mortality varied by socio-economic group.

1. INTRODUCTION

The modern mortality decline began rather modestly in the mid-eighteenth century in several Western countries, including England, France and Sweden and accelerated at the beginning of the nineteenth century (Fridlizius 1984. p. 75; Perrenoud 1984, pp. 44–46). However, the decline did not begin simultaneously in all age groups. In Sweden, progress towards lower age-specific mortality rates began among infants and children aged 1–10 years. The most pronounced development from the end of the eighteenth century onwards was the continuous decline in infant mortality (Fridlizius 1984, p. 77). In the 1–10 year age group, mortality declined from the end of the eighteenth century until the middle of the nineteenth, when a new pronounced increase in the age-specific mortality rate for this age group occurred. In the age group 25–50 years the decline did not begin until 1840, around fifty years after it had started in the younger age groups mentioned. At ages above 50 years a third pattern is found in Swedish aggregate data. Among the elderly, mortality actually increased until the beginning of the nineteenth century, and did not decrease until the second half of that century (Fridlizius 1984, p. 76).

The rapid and continuous decline in infant mortality seems to be treated as a separate issue in the discussion of the mortality decline. Fridlizius suggests, after having excluded all other plausible explanations, that the early decline among infants was due to a secular decline of the virulence of some of the most common infectious agents. This would indicate the end of something old rather than the beginning of something new (Ibid., p. 109). Previous studies of mortality in Sweden have found no correlation between infant mortality rates and socio-economic conditions and no correlation between infant mortality rates and short-term real wage changes at the aggregate level, whereas such correlations have been found for older age groups, especially adults above age twenty (Bengtsson and Ohlsson 1985). This has also been found for children over one year of age from analyses at the individual level (Bengtsson, 1996. p. 31). Taken together, there exists ample evidence that the determinants of infant mortality are different from those of other age groups. Economic factors are of rather small importance.

The aim of the study reported in this paper was to investigate cause-specific mortality at ages 55–80 years in four parishes in Scania in the southernmost part of Sweden during the period 1760–1894. We test hypotheses about the long-term effects of conditions in early life and short-term effects of contemporary conditions. In other words, we compare the roles of period and cohort factors in determining mortality among the elderly.

Old-age mortality is determined by a number of different factors, some of which relate to current economic and social conditions and some to conditions during the working and reproductive period. Others relate to the long-term effects of conditions before birth or during early childhood. This cohort explanation was first put forward in 1934 by Kermack, McKendrick, and McKinley, who studied age-specific mortality in England,

Wales, Scotland, and Sweden. They concluded that reductions attained at any particular time in the death rates of the various age groups depended primarily on the date of birth of the individuals concerned, and only indirectly on the particular year under consideration. Improved conditions appear to have brought about their beneficial results primarily through their action on children (Kermack et al. 1934. p. 703). This early-life experience perspective has received increased attention in recent years (Kuh and Ben-Shlomo 1997). It remains possible, of course, that variations in old-age mortality are due to contemporary effects – socio-economic conditions or variations in economic insecurity.

The possibility of a causal relationship between early life experience and old-age mortality has been discussed, especially in relation to intrauterine cellular development and cellular development during early childhood. Robert Fogel has questioned the Malthusian standpoint that sees malnutrition as a threshold phenomenon with malnutrition occurring below, and adequate nutrition occurring above, a certain intake level. He suggests that, instead, the secular increase in mean height and life expectancy and decreasing proportions of stunted persons in all Western populations during the past 200 years seems to confirm a linear relationship between nutrition and morbidity early in life, and longevity. Fogel´s attention to early life experiences is primarily focused on *in utero* development and on the first year after birth with some extension up to age three. The reason for this is that most stunting occurs before age three. Afterwards, even severely stunted children move along a given height centile without incurring further height deficits (Fogel 1994, p. 244). Fogel proposes the following as mechanisms that connect malnutrition *in utero* and during early life to chronic diseases in later life: (1) malnutrition which results in permanent, promptly visible physiological damage; (2) degradation of organ functioning, which, while reversible in the sense that the immediate level of performance is regained, nevertheless subtly undermines the durability of tissue and speeds up the eventual degradation of organs; and (3) degradation of organ performance which, in principle, could be reversed, but which in fact persists because the insult persists (Fogel 1993. p. 15). The evidence for these propositions seems to be that variations in the chemical composition of the tissues that make up the organs of the body, in the quality of the electrical transmission across membranes, and in the functioning of the endocrine system and other vital systems appear to be associated with variations in body height and weight (Robbins, Cothran and Kumar 1984; MacMahon and Bistrian 1990; Fogel 1994).

These propositions are supported by the work of D. J. P. Barker and colleagues, who have hypothesised that the preconditions for coronary heart disease, hypertension, stroke, diabetes, and chronic thyroiditis are initiated *in utero* without becoming clinically manifest until much later in life. The mechanism underlying these diseases induced very early in life seems to be inadequate cellular development *in utero* (Barker et al. 1989; Barker and Osmond 1990; Barker 1991, 1992, 1994). The concept of down regulation of foetal growth has been developed further into the nutritional programming (or foetal origins) hypothesis. According to this hypothesis the development of cardiovascular and other diseases much later in life is dependent on whether foetal growth retardation due to insufficient nutrition is 'proportionate' or 'disproportionate'. The 'disproportionate' growth retardation induced by insufficient nutrition during the mid and late trimesters of pregnancy seems to be responsible for cardiovascular diseases of later life, while the 'proportionate' growth retardation of the first trimester is not (Barker 1995, pp. 171–174). However, yet other mechanisms – such as altered gene expression, imbalance between cell types, altered organ structure, altered pattern of hormonal release and altered setting of hormonal responses – seem to be involved in these early preconditions for disease in later life (Sultan 1994).

Fridlizius has suggested another pathway of causation for the early genesis of diseases that appear in later life after a long period free of symptoms. According to Fridlizius, the genesis of diseases in later life could be due to exposure to certain infectious diseases, such as smallpox, in the first five years after birth, resulting in reduced immunity to other diseases throughout life and, consequently, a higher general risk of contacting other infectious diseases in later life. The proposition is mainly based on the statistical finding that some birth cohorts have higher age-specific mortality rates throughout their lifetime from infancy to old age. Deaths from smallpox among young children decreased and subsequently disappeared in the late eighteenth century and early nineteenth, a phenomenon that does not seem to have had any strong connection with vaccinations, since vaccination programmes on a large scale were not initiated until several decades after the decline began. Furthermore, the rise in mortality among children aged one year and above in the 1850s can be ascribed to the pronounced increase of scarlet

fever, caused by the streptococcus bacteria. In both cases, age-specific mortality rates were affected throughout the lifetimes of these age cohorts, the result being a reduction of age-specific total mortality among those born around 1800 and an increase among those born around 1850. In neither case did susceptibility to disease in adulthood seem to have been directly connected to nutrition in early life, since the risks of being infected with either smallpox or scarlet fever are uncorrelated with nutrition. Instead, Fridlizius suggests a changed immunological balance between some infectious agents and the human host for both smallpox and scarlet fever (Fridlizius, 1989, pp. 3–17). However, this balance between infectious agents and human host may also include certain aspects of human nutrition. Since this hypothesised mechanism applies to the first five years after birth, it is possible to elaborate a statistical model to test its plausibility. Clearly, the biological mechanism suggested by Fridlizius partly differs from the one proposed by Fogel.

Period determinants of old-age mortality, whether of social or economic origin, differ completely from the cohort factors discussed above. Secularly rising standards of living, especially during the nineteenth century, and trends in the development of social differences constitute one plausible explanation. McKeown has proposed, after excluding other possible causes, that improved standards of living and consequent improvements in nutrition made the major contribution to the mortality decline from the end of the eighteenth century onwards. McKeown also proposed a change in the relationship between the infective organism and the human host for the later part of the eighteenth century and the first part of the nineteenth (McKeown 1976).

A second explanation of contemporaneous variations in age-specific old-age mortality could be the diminishing short-term insecurity during the period studied in this paper. Bengtsson and Ohlsson have used aggregate mortality and real-wage data for Sweden to show that the demographic response to real-wage changes altered from the eighteenth to the first half of the nineteenth century. They interpreted their finding as an expression of an improvement in living conditions, denoting diminishing short-term insecurity (Bengtsson and Ohlsson 1984, 1985).

2. LONG-TERM DEVELOPMENT OF MORTALITY AND CAUSES OF DEATH

In 1686 a special church act was imposed in Sweden which made compulsory the registration at the parish level of all christenings, marriages, and burials. In 1749 a continuous compilation of tables at the national level, the so-called *Tabellverket*, was instituted for the systematic production of population data. In 1755 a statistical committee, the *Tabellkommissionen*, was established. This committee was a forerunner of the National Central Bureau of Statistics. The information compiled by the parish clergymen and reported to Stockholm from the middle of the eighteenth century included not only numbers of births and deaths but also causes of death (Nyström 1988, pp. 109–115). From this time on, causes of death were also reported in a similar way all over the country. In the four parishes used for this study, specific causes of death were registered from the 1750s onwards. This is the main reason why we have chosen the year 1760 as the starting point for our analysis. The choice of year for the end of the study period is 1894, which is when the registration of causes of death in the death books administered by the church ended.

Several problems concerning validity and reliability are connected with these cause-of-death data. Bengtsson has posed some relevant questions (Bengtsson 1988). First, what were the effects of the development of medical science? Second, how did changes in nomenclature and instructions affect the registration of the cause of death? Finally, how much did the diagnoses depend upon who made them? In other words, what were the effects of the individual clergymen or medical practitioners?

The answer to the first question seems to be that a single theoretical basis in medical science did not exist in the middle of the eighteenth century. Different old and new 'schools' competed and modern medical science was just emerging (ibid., pp. 112–114). Furthermore, the etiology of infectious diseases, the most common causes of death during the whole period studied, was not known. Proper diagnosis was impossible, except for symptomatic diagnosis, until the end of the nineteenth century (Ackerknecht 1982, pp. 176–185). The classification was instead based on the nosological system: causes of death were classified by symptoms and not according to biological causes. Although medical science developed into its modern form during the period studied, so that modern pathological-anatomical diagnosis by autopsy was generally accepted as the foundation for determining cause of death, in practice the system remained basically nosological during the whole period (Bengtsson 1988, p. 464).

The second consideration concerns changes in the nomenclature. The nomenclature was changed

several times, in 1774, 1802, 1811, 1821, 1831, 1873 and 1891. However, the first four changes were small and do not seem to have had an effect on what the clergymen recorded in the parish registers. The change in the nomenclature of 1831 was the result of pressures from the clergymen who argued that they were not competent to make a diagnosis. From that year on, they only had to register deaths from smallpox and other epidemic diseases, deaths in childbirth, accidents, homicide, and suicide (Bengtsson 1988, pp. 467–468). Another problem with the nomenclature is that new diagnoses were introduced and old ones excluded. However, this is a problem of less importance for us since we will aggregate our diagnoses into larger groups in order to increase the number of events for statistical analysis. In the four parishes studied, the registration does not seem to have been altered to any significant extent after the change of nomenclature in 1831 or the smaller change in 1874, though the number of unspecified causes seems to have risen towards the end of the period of study.

The third question concerns the effects of the clergymen who had to register the death and show their diagnosis of cause in the death books. Puranen has suggested that individual clergymen had a significant effect on death registration in the nineteenth century (Puranen 1984, pp. 64–72). However, Puranen compares parishes from different parts of the country and the method she uses makes her conclusion unconvincing (Bengtsson 1988, p. 470). For Västanfors, Bengtsson found no apparent differences in the rates of diagnosing different causes of death when comparing the diagnostic work of a clergyman when he started registration in the parish with the diagnostic work of his predecessor at the end of the latter's working period (Bengtsson 1988, p. 470).

Since the numbers of deaths from most causes are rather small we have grouped the diagnoses into nine aggregate categories. We will now describe the steps in which this work was done. The first and main task was to reclassify the diagnoses in terms of etiology instead of nosology, although of course some diagnoses are of a nosological rather than etiological character even today. The second step involved the procedure by which the diagnoses were aggregated into larger groups.

The diagnoses were interpreted with the help of the manual, "Swedish names of diseases in past times" (1988, third edition). This was written by a Swedish pharmacist interested in family research, Gunnar Lagerkranz, and supervised by, among others, several physicians and medical doctors (Lagerkranz 1988).

Some names of diseases were the same as those used today and depicted the same etiologically distinct diseases, e.g. stillborn, congenital heart disease, smallpox, measles, scarlet fever, cholera, diphteria, tonsillitis, 'typhoid fever', varicellae, pneumonia, tuberculosis, and pulmonary tuberculosis. Some Latin names used at the end of the study period to specify the cause of death of single individuals were also possible to interpret immediately. Furthermore, it was easy to interpret diagnoses attributing death to excessive alcohol consumption, freezing, accidents, poisoning, drowning, burning, suicide, murder, and execution.

In other cases, the interpretation could be made without much difficulty, since the old name of the disease referred to the same etiologically distinct disease known by another name today.

We can also mention the nonspecific terms for malignant tumours. The same can be said about the psychiatric diagnoses 'melancholia' and 'mother passion', even if their diagnostic criteria certainly differ from those of our own time.

In some cases, e.g. whooping cough, the diagnostic statements could be interpreted in two different ways. According to the manual, whooping cough can refer either to the whooping cough of our days, caused by *Bordetella pertussis*, or other kinds of throat, airway, or lung disease.

In other cases it was only possible to interpret the diagnosis as belonging to a whole group of etiologically similar diagnoses. However, most of them were aggregated into just two diagnostic aggregate groups – diseases that are not infectious and those with an infectious agent causing the disease. Other diagnoses, e.g. 'kidney suffering', gout, ache, and bone decay, also could not be etiologically classified without aggregation.

An even more problematic group of diagnoses are those that could not possibly be interpreted with reference to any kind of etiology, even after categorization. 'Weakness in old age' and 'weakness' are examples of this kind of diagnosis. They could refer to cardiovascular disease, malignant tumours in late stages, deficiency syndrome, or just old age without any kind of clear disease.

Finally, there remained a group of unclassifiable diseases. They did not seem to make any sense from an etiological standpoint and were thus classified into a category of their own.

For data of this kind, it seems that categorization does not mean loss of information but is, rather, a means of enabling us to make more use of it.

We initially grouped the diagnoses into the 29 different categories shown in Table 1. The

Table 1. *Mortality by cause of death at ages 55–80 years. Totals and frequencies.*

	Total	Frequency
1. Congenital heart disease	4	0.3
2. Weakness, old age	339	24.2
3. Smallpox	1	0.1
4. Measles	4	0.3
5. Nervous fever, typhoid fever	31	2.2
6. Blood poisoning	1	0.1
7. Dysenteria, 'rödsot'	4	0.3
8. Whooping cough	5	0.4
9. Ague	5	0.4
10. Diptheria, tonsillitis, inflammation of the throat	3	0.2
11. Sexually transmitted diseases	3	0.2
12. Other infectious diseases	7	0.5
13. Tumour, degenerative disease, cancer	51	3.6
14. Psychiatric diagnoses	1	0.1
15. Convulsions, paralysed, 'heart beat'	22	1.6
16. Mors subita, coronary heart disease, stroke	8	0.6
17. Disease of the throat	1	0.1
18. Pneumonia	65	4.6
19. Stitch and sting, chest disease	249	17.8
20. Coughing	3	0.2
21. Diarrhoea	30	2.1
22. Other symptomatic diseases of stomach	59	4.2
23. Kidney suffering	14	1.0
24. Gout, bone degeneration, ache	19	1.4
25. Frozen to death, accident, poisoning, drowning, etc.	18	1.3
26. Suicide	11	0.8
27. Other unclassifiable diseases of the gastrointestinal tract	89	6.4
28. Other unclassifiable infectious diseases	27	1.9
29. Not specified	326	23.3
Total	1400	100

Sources: Scanian Demographic Database reconstitutions for Hög, Kävlinge, Halmstad and Sireköpinge.

categorization was based on the categorization of diseases used by the National Bureau of Statistics in 1875. The categorization thus includes diagnoses that are not even theoretically possible as causes of death in the age group 55–80 years. As shown in Table 1, the three most common causes of death in that age interval were 'weakness due to old age' (24.2 per cent of all causes of death), chest diseases due to airborne infections (17.8 per cent) and the group that comprised those who did not have any kind of registered cause of death (23.3 per cent).

In the next step we assigned the 29 diagnostic groups to the nine final diagnostic groups illustrated in Table 2. All infectious diseases were classified into three groups: airborne infectious diseases; food-borne and water-borne infectious diseases; and other infectious diseases that it was not possible to assign to either of the first two groups. All cardiovascular diseases and diabetes mellitus together formed the fourth group. All kinds

Table 2. *Mortality by nine categories of cause of death at ages 55–80 years. Totals and frequencies.*

	Total	Frequency
1. Airborne infection diseases (3, 4, 8, 9, 10, 12, 17, 18, 19, 20)	343	24.5
2. Food-borne and waterborne infectious diseases (5, 7)	35	2.5
3. Other infectious diseases (6, 11, 21, 28)	61	4.4
4. Cardiovascular diseases and diabetes (16)	8	0.6
5. Accidents, crimes, etc. (25, 26)	29	2.1
6. 'Weakness due to old age' (2)	339	24.2
7. Cancer (13)	51	3.6
8. Other specified non-infectious diseases (1, 14, 15, 22, 23, 24, 27)	208	14.9
9. Not specified (29)	326	23.3

Note: Figures within parentheses refer to the numbering in Table 1.
Sources: As Table 1.

of accidents, crimes, and executions formed the fifth group. 'Weakness in old age' and 'weakness' formed the sixth group. The seventh group encompassed all forms of cancer and the eighth all non-infectious diseases of the gastrointestinal tract including vomiting, psychiatric diagnoses, congenital heart disease, and kidney suffering. All other causes were assigned to the ninth group (for details see Table 2). Table 2 shows that the largest groups of causes of death in the age interval 55–80 years during the period 1760–1894 in the four parishes studied were airborne infectious diseases, 'weakness of old age' and 'weakness', mortality due to specified non-infectious diseases, and mortality from unspecified causes. Those four groups are large enough to be analysed separately. We present results only for the three groups with specified causes of death.

In Figures 1–4 the mortality rates for the age group 55–80 years are shown. Figure 1 shows the crude death rate for all diseases and the trends calculated by means of an Hodrick-Prescott filter with a smoothing factor of 100. Mortality was generally higher in the eighteenth century than in the second half of the nineteenth century. However, there seems to have been a decrease in the crude mortality rate in the 1810s and 1820s, followed by a marked mortality 'hump' in the 1830s and 1840s, a finding that is very consistent with Fridlizius' findings from aggregate data for this age group, already mentioned in the introduction.

Figures 2–4 show the mortality rates for aggregated diagnostic groups. There was a marked decline in mortality from airborne infectious diseases until the 1820s, and thereafter a new increase in the 1830s and 1840s, especially the late 1840s. This partly explains the crude mortality 'hump' of these two decades. However, an even

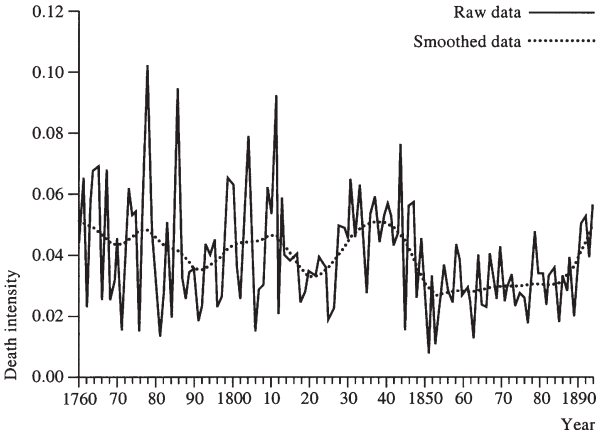

Figure 1. Death intensity at ages 55 to 80 years per person per year. Not age-standardised. All causes of death. Raw and smoothed data by use of a Hodrick–Prescott filter. *Sources*: Scanian Demographic Database reconstitutions for Hög, Kävlinge, Halmstad and Sireköpinge.

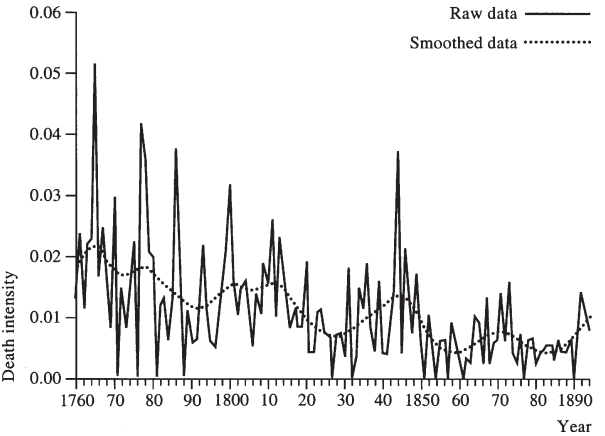

Figure 2. Death intensity for airborne infectious diseases at ages 55 to 80 years. Raw and smoothed data by use of a Hodrick–Prescott filter. *Sources*: As Figure 1.

larger 'hump' is seen for the 1830s and 1840s when the group 'weakness of old age' and 'weakness' are investigated. From the early 1840s on, the mortality from this cause of death rapidly declines and at the end of the study period this diagnosis does not seem to have been used very often. For the group of descriptive diagnoses of the gastrointestinal tract, mortality declines during the whole study period. This group does not seem to help explain the 'hump' of the 1830s and 1840s. Mortality from other specified causes rapidly increases from the 1840s onwards. Unclassifiable causes of death (not shown here) are evenly distributed throughout the whole study period.

The age interval 55–80 years was chosen for the study of old-age mortality for several reasons – sociological, medical, and pragmatic. First of all, the results of previous studies have indicated that 55 years of age was the most common age for retirement in agrarian Sweden during the 18th and 19th centuries. This was often the time in life when the oldest son had reached an age suitable for becoming the new head of the farm. Secondly, there are medical reasons for using 55 years as the lower

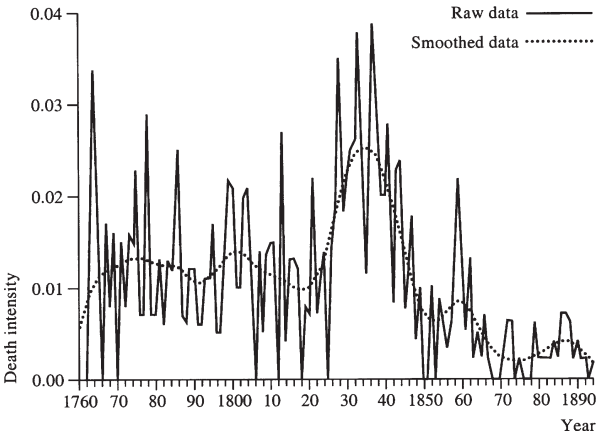

Figure 3. Death intensity for 'weakness due to old age' at ages 55 to 80 years. Raw and smoothed data by use of a Hodrick–Prescott filter. *Sources*: As Figure 1.

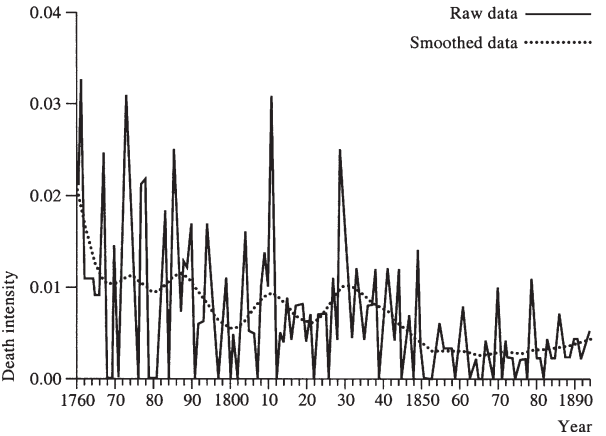

Figure 4. Death intensity for other specified non-infectious diseases at ages 55 to 80 years. Raw and smoothed data by use of a Hodrick–Prescott filter. *Sources*: As Figure 1.

limit. In our own modern age, this is the time in life when the most important groups of diseases – cardiovascular diseases and cancer – begin to have a significant impact on the mortality of a birth cohort. Accordingly it should be possible to test, for instance, Barker´s notion that cardiovascular morbidity and mortality in later life are especially dependent on intrauterine experience. However, as shown earlier, specific diagnoses related to cardiovascular diseases and diabetes were too few to make it possible to test this specific notion. A less specific variant of Barker´s hypothesis can be tested on overall mortality and on the specific diagnostic groups as finally aggregated in the manner described above. It must be remembered that the small number of specific diagnoses that relate to cardiovascular mortality with great certainty relate to only a small fraction of all deaths from cardiovascular diseases. The aggregated group of causes of death that we have named 'weakness' and 'weakness due to old age', a group that constitutes a quarter of all causes of death in the population studied, probably consists mostly of deaths related to cardiovascular causes. It is of course still interesting to note that such a large fraction of all causes of death during the 18th and 19th centuries

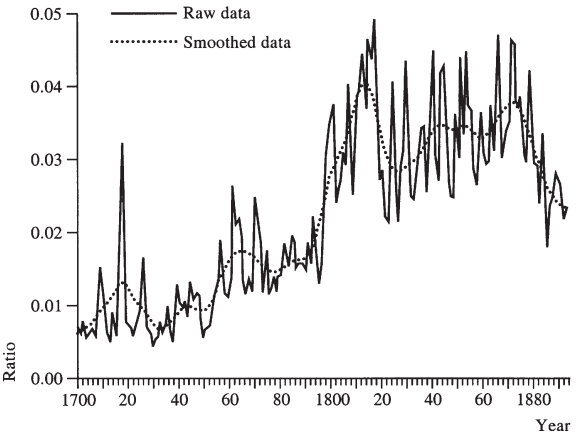

Figure 5. Ratio of rye prices to population, 25 Scanian parishes, 1700–1895. Raw and smoothed data by use of a Hodrick–Prescott filter. *Sources*: Bengtsson and Oeppen (1993); Bengtsson and Dribe (1997).

were related to airborne infectious diseases even in this old-age group. The upper limit of 80 years of age is chosen for the combined reasons of small numbers and uncertainty about the validity of the data in this numerically small group.

3. MODEL AND DATA

The data are from the Scanian Demographic Database, and consist of records of births, marriages, deaths, and migrations for nine rural parishes and one town. The material for two parishes goes back to 1646 and for the others to the 1680s. This parish register material is of high quality and shows few gaps for births, deaths, or marriages. Migration records are less plentiful, but continuous series do exist from the latter part of the 18th century. Information about farm size, property rights, and various other items from the poll tax records and land registers are linked to the family reconstitutions based on the parish records of marriages, births, and deaths. The migration records have so far been linked to the other sources only for the period 1865 to 1895. For the preceding period, a person is considered to be at risk as long as we have information about other members of the family or about the size of the farm belonging to the family. The period 1760–1894 was chosen as our period of study because causes of death began to be registered by the church in the four parishes in the years just before 1760, and because registration by the church ended in 1895.

The parishes are located about 10 km from the coast in the south-west of Scania, which is the southernmost county of Sweden. Nearby towns are Lund, Eslöv, Landskrona, and Helsingborg at a distance of between 10 and 30 km. The sampled parishes are compact in their geographical location, showing the variations that could occur in peasant society with regard to size, topography, and socio-economic conditions, and they offer good, early source material. The nearby towns are all very small. While the sample consists of nine rural parishes and one town we will here focus on four of the rural parishes: Kävlinge, Hög, Halmstad, and Sireköpinge. Kävlinge, Hög, Sireköpinge, and southern Halmstad can be characterized as open-country farmland, while northern Halmstad was more wooded. Halmstad and Sireköpinge are 'noble' parishes, while the elements of freehold and crown land predominated in Kävlinge and Hög. The parishes had between 200 and 500 inhabitants. Kävlinge grew rapidly in the last decades of the 19th century owing to the establishment of several factories after the railway was built.

The parishes in southern Sweden were rather small. The population aged 55–80 years increased from just under 100 individuals in 1760 to approximately 550 individuals in 1880 in the four parishes. After 1880, a fall began in the group of the population aged 55–80 years, mostly as a result of migration to cities and other urban areas.

The ratio of prices to population is shown in Figure 5. Based on the price and wage development, we divide the period into three sub-periods: 1760 to 1820, which is characterized by rapidly increasing grain prices; 1820 to 1865, when the increase in grain prices and wages were slowing down; and

1865–1895, when real wages were increasing rapidly. The price and wage development was due to a number of factors – local demand for grain, external demand for grain, supply and demand for labour inside and outside the agricultural sector, commercialization of agriculture, enclosure movements, and changes in agricultural technology. Thus our periodization is based upon fundamental changes in the rural economy of the parishes included in our sample, as they became more commercialized and industrialized.

Information on occupations comes from the sources discussed above. For married women with no registered occupation of their own, the husband's occupation is used. Based on this information, all married persons were divided into three groups: (1) farmers and nobility, (2) artisans, non-agricultural labourers, and public servants, and (3) cottagers, farm labourers, lodgers, poor, etc. The last group grew in both absolute and relative terms during the entire 19th century. Thus, a proleterianization of these rural parishes took place along with the structural changes and the commercialization of the rural sector. The first occupational group, however, grew even more, both totally and in relative terms, among persons aged 55 to 80 years – from 13 per cent during the first period to 22 per cent during the last period.

Looking at ownership, we find that the proportion of persons who owned their farm did not change relative to other groups in the second period while the proportion of tenants declined. This is partly a result of the division of farms belonging to free-holders, and partly a result of sales of land belonging to the nobility. Parts of estates were sometimes enclosed by their owners into small farms and sold thereafter. During the entire period, the proportion of landless persons aged 55 to 80 years increased from four per cent during the first sub-period to eleven per cent during the last.

The information about the size of the farm is given in *mantal*. This was not a measure of the actual size of the farm but rather its potential for production. This measure is difficult to use for comparisons over time since the production capacity changed with land reclamation, use of new crops, and other improvements. For example, a farm with a *mantal* of one quarter was considered to be the smallest taxable unit in the early 18th century and further subdivision was prohibited. This limit was lowered to one-eighth *mantal* by the end of the eighteenth century.

In the period 1760 to 1820, 15 per cent of all persons aged 55 to 80 years owned farms of one eighth of a *mantal* or higher, while in the period 1865 to 1895 the figure was 4 per cent. Meanwhile, the number of persons with smaller farms and, especially, the number without land increased rapidly. A vast majority of all persons, however, were landless throughout the entire period studied. A large proportion, 43 per cent, had no sons living in the parish while a third had two sons or more.

Thus the economic structure changed rapidly at the beginning of the 19th century when grain exports for international markets grew rapidly, when enclosures took place, and when new agricultural methods became widely used. The population increased and so did the proportion of landless. With the expansion of the industrial sector, job opportunities outside agriculture grew at the end of the century. At the same time imports of grain from overseas put a pressure on the rural sector. During this period, real wages grew at the same time as population increased. Scania experienced modern economic growth. Throughout the entire 19th century infant mortality declined. Mortality among the elderly, which is the subject of our analysis, started to decrease in the latter part of the century.

When analysing the effects of economic fluctuations on macro-demographic data, traditional econometric and time-series methods, such as distributed lag models, Box–Jenkins models, and spectral analysis, have been used. Since the focus has been on fluctuations rather than trends, the latter are removed from the series by a filtering process, often constructed by use of a simple moving average filter. This filter also removes the possible effects of changes in age-distribution. This is necessary since, for most countries but not for Sweden, crude death rates or number of total deaths have been analysed, not age-specific rates. Despite differences in filtering processes and in estimation techniques, the results are similar to those discussed above. The fact that the results are similar despite the use of various filtering and estimation techniques indicates that the underlying process is very strong. Still, from aggregate studies we only know about average responses for very large populations.

To learn more about the response for different social groups, we need information about occupation, age, family size, structure and other variables. These data may come either from family reconstitutions or from annual censuses, like the catechetical records or poll taxation records for Sweden. Often the populations that we study will be rather small owing to the laborious task of constructing appropriate datasets. Two problems then appear. First, we will get information that

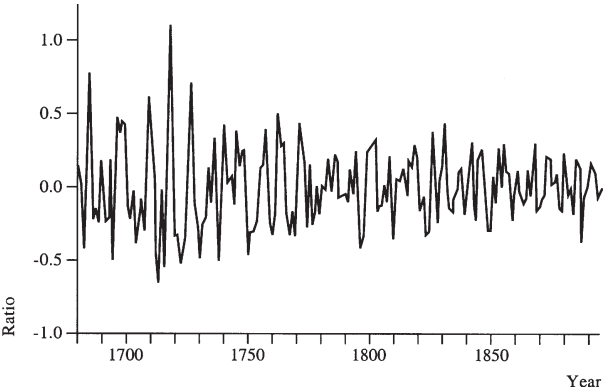

Figure 6. Rye prices, detrended by use of a Hodrick–Prescott filter, 1680–1895. *Sources*: As Figure 1.

refers only to certain rather small areas. Secondly, econometric and traditional time series methods cannot be used since random variations tend to dominate when the number of events per year is low. Thus, when it comes to socio-economic differences in the mortality response to economic fluctuation, no standard method exists. For this reason Bengtsson has been experimenting with another method – a combination of event history analysis and time series analysis within an event history analysis framework. In doing this, he has combined macro information about economic variations with micro demographic data. The macro-economic variables are treated as time-varying community covariates. This is done within a continuous time framework, using Cox regression techniques. This way of dealing with the problem is still in its early stage though it has expanded recently (Bengtsson 1989, 1993, 1996).

Cause-specific death rates are shown in Figures 1–4. Since the population size is rather small at the beginning of the period, the variance is rather large. Still, it is evident that both mean and variance diminishes over time. This pattern is the same as that for the entire country. In addition to the long-term trend, pronounced long swings appear with downswings in the 1750s and 1790s.

The transition we are modelling is from being alive at age 55 and living in a union, to 80 years of age or death. The explanatory variables include birth-year, sex, number of sons, occupation, land ownership and farm size. All of these variables, except sex and birth-year, are time varying at individual or family level. In addition, the price of rye is used as a community variable indicating periods of short-term economic stress. To make the price variable stationary, the difference between the log of the original observations and the trend calculated by a Hodrick-Prescott filter with a smoothing parameter of 100 (see Figure 6) has been estimated. The reason why we want it to be stationary is that we would like it to be an indicator of short-term economic stress. The price data, as well as the wage data, are local and refer to the price shortly after the harvest period in the Autumn (Jörberg 1972; Bengtsson and Dribe 1997). The data are collected for official purposes. In the models, we analyse the mortality effect within one year after the harvest since experiments with lags show that the effect of bad harvests dies out very quickly.

Not everyone was adversely affected if grain prices increased, whether due to bad harvests or to changes in demand. Farmers with a surplus for the market could actually benefit. This might also be the case for tenants with fixed long-term rents. Though wages followed prices in the long run they showed less variation than prices in the short run, at least until the middle of the nineteenth century. Thus, families dependent on wages might suffer from high prices. Changes in the level of real wages are modelled by use of dummies for different periods when analysing the entire period from 1760 to 1895, and by analysing each time period separately.

We will now turn to the indicators of the conditions in early life. Unlike the economic and socio-economic variables, which are time-varying, variables such as sex and year of birth are time invariant for individuals. Thus they follow the individual throughout his or her life. Furthermore they are collective, which means they are the same for all members of the same birth cohort. We have experimented with various variables, some referring

to conditions during the foetal stage, others to the first years of life, some to nutritional intake and others to the disease load. Thus we basically have four types of indicators of conditions early in life: access to nutrients for the mother during pregnancy; the disease load on the mother during pregnancy; access to nutrients for the child; and the disease load during the first year(s) of life.

Price of rye at nine months prior to birth is used as a proxy for exposure to malnutrition during the foetal stage, which we assume influences the diet of the mother. The mother's exposure to diseases during pregnancy is approximated with the death rate for adults in reproductive ages (20–50 years) for the 6 months prior to birth. These two variables are as close as we can come to estimate the Barker effects of conditions during the foetal stage on length of life.

Kermack et al. suggested that exposure to diseases during childhood is of importance for length of life, which is close to the hypotheses that Fridlizius tested for Sweden. This is estimated by mortality at ages 0 to 5 years as an early-life variable affecting individuals at age five and later; another early-life indicator at community level. In addition, infant mortality is added as another disease load variable that affects individuals at age one and later in life. Finally, the price of rye at time of birth is used as an indicator of access to food in early life. We have conducted several experiments with this variable. It turns out to be of negligible importance and the results are not reported in the tables owing to limits of space. Notice that we are using the price of rye both as a variable indicating current short-term economic stress and as an early-life indicator. The difference is that the latter is fixed for the individual by his date of birth, while the former changes over time.

Interactions were also included to test for variations in response to short-term economic stress (current rye prices) by sex and socio-economic conditions (occupation and farm size).

Our statistical method belongs to the category of Cox regressions. We have accordingly calculated semi-parametric models. The program we used, called LIFE, was developed by Professor Göran Broström, Department of Statistics, University of Umeå, partly within the framework of a methodological project being conducted by the Research group in Population Economics in Lund. The time-varying covariates are treated by right censoring and left truncating spells every time a covariate changes. The effects of time-varying community variables like price of rye on the variables and time periods are treated similarly.

Before model estimations, we must examine whether the assumption of proportional hazards required by Cox regression is fulfilled or not. We have made Nelson–Aalen plots, using the logarithm of the cumulative hazard function, for the period 1760 to 1895, by sex, number of sons, occupation, ownership, farm size, and parish. Corresponding diagrams have been plotted for each different sub-period. Generally, the assumption of proportional hazards is fulfilled, but when it comes to the cumulative hazards for each parish the curves cross each other not only for the entire period but also for the sub-periods. For this reason, we have stratified the sample by parish. Another reason for this procedure is that we do not have any *a priori* reasons to expect similarity between the parishes. Some of the other curves, such as the curves for occupations, cross slightly and in some cases the curves run very close together. It would have been possible to change the categories and to change the age interval to improve the estimations, but keeping the definitions as they are is of value for comparative reasons. Also, the crossings are not that systematic. Some crossing, due to similarities and randomness, do not alter the estimations much.

4. RESULTS

Tables 4 and 5 show the relative risks and the Wald p-values for each covariate along with number of deaths, maximum log-likelihood, and chi square statistics. For all reported estimates, we can dismiss the H_0 hypotheses that the variables included in the models have no influence. The risk for each covariate category is shown relative to the reference category, given in Table 3, which also shows the averages of the individual and household covariates. Some examples will explain how the relative risk should be interpreted. In model 1 of Table 4, the coefficient for females is 0.96 and the reference category consists of males. This means that females have a 4 per cent lower risk of dying. In the same model, the relative risk for a one-unit change in birth-year is 0.99, which means that the risk of dying was falling by 1 per cent per year. A one-unit increase in logged current rye prices (covariate 10), which is a 272 per cent increase in raw prices, gives a 63 per cent increase in mortality. A birth cohort experiencing a one-unit higher infant mortality rate during the first year of life had an 80 per cent increase in risk of dying at ages 55 to 80 years (model 3). To put it another way, a 100 per 1000 higher infant mortality rate, by no means extraordinary during this period, increases the risk

Table 3. Averages of individual and household covariates, 1760–1895, and by sub-periods

	1760-1895	1760-1820	1820-1865	1865-1895
1. Year of birth	1790.9	1736.7	1785.9	1818.7
2. Sex[0] male, *reference*	0.52	0.58	0.52	0.49
3. Sex[1] female	0.48	0.42	0.48	0.51
4. Occupation [1] farmer, *reference*	0.20	0.13	0.20	0.22
5. Occupation [2] artisans	0.41	0.50	0.41	0.37
6. Occupation [3] cottagers	0.39	0.37	0.39	0.41
7. Owner[0] freeholder, *reference*	0.08	0.04	0.09	0.11
8. Owner[1] tenant	0.25	0.30	0.27	0.21
9. Owner[2] other	0.67	0.66	0.64	0.68
10. Farm size[1] large, *reference*	0.09	0.15	0.08	0.04
11. Farm size[2] small	0.09	0.01	0.07	0.14
12. Farm size[3] none	0.83	0.84	0.85	0.82

Sources: As Table 1.

Table 4. *Mortality at ages 55–80, 1760–1895*

	Model 1		Model 2		Model 3		Model 4	
	Relative risk	*p*-value	Relative risk	*p*-value	Relative risk	*p*-value	Relative risk	*p*-value
1. Year of birth	0.99	0.00	0.99	0.00	0.99	0.00	0.99	0.00
2. Sex[1] female	0.96	0.47	0.96	0.46	0.95	0.39	0.96	0.44
3. Occupation[2] artisans	0.87	0.07	0.87	0.07	0.87	0.09	0.87	0.08
4. Occupation[3] cottagers	0.85	0.05	0.85	0.04	0.86	0.06	0.86	0.05
5. Owner[1] tenant	0.59	0.00	0.59	0.00	0.59	0.00	0.60	0.00
6. Owner[2] other	1.12	0.42	1.13	0.42	1.12	0.42	1.13	0.40
7. Farm size[2] small	0.80	0.24	0.81	0.24	0.82	0.27	0.81	0.25
8. Farm size[3] none	0.96	0.80	0.96	0.80	0.97	0.81	0.96	0.79
9. Early-life Indicator:								
Rye price	1.07	0.52						
CDR 20–50 years			1.13	0.79				
CDR 0–1 years					1.80	0.03		
CDR 0–5 years							2.46	0.22
10. Rye price	1.63	0.59	1.62	0.59	1.65	0.58	1.63	0.59
11. Period 1820–1865	1.07	0.71	1.07	0.72	1.09	0.63	1.11	0.59
12. Period 1865–1895	1.19	0.15	1.18	0.15	1.17	0.20	1.20	0.13
13. Sex[1] * Rye price	1.21	0.52	1.21	0.52	1.22	0.51	1.21	0.52
14. Occupation[2] * Rye price	1.15	0.75	1.15	0.75	1.14	0.76	1.14	0.76
15. Occupation[3] * Rye price	2.83	0.02	2.83	0.02	2.84	0.02	2.84	0.02
16. Owner[1] * Rye price	0.97	0.97	0.97	0.97	0.96	0.97	0.97	0.97
17. Owner[2] * Rye price	1.20	0.83	1.20	0.83	1.19	0.83	1.20	0.83
18. Farm size[2] * Rye price	2.19	0.46	2.19	0.46	2.15	0.47	2.17	0.47
19. Farm size[3] * Rye price	0.29	0.11	0.29	0.11	0.29	0.10	0.29	0.11
Max Log Likelihood	7608.7	–7608.9	–7606.4	–7698.1				
χ^2	156.1	155.8	160.7	157.2				
Degrees of freedom	19	19	19	19				
Number of deaths	1 400	1 400	1 400	1 400				

Note: See Table 3 for reference categories.
Sources: As Table 1.

of dying by 80 per 1000 at ages 55–80 years. The interactions show to what extent a certain category, for example cottagers (covariate 15), is more negatively influenced by increasing rye prices.

Table 4 illustrates four models, using the four early-life indicators of stress in early life, one at a time. Thus in model 1 we use rye prices 9 months prior to birth (covariate 9) as an indicator of access to food for the mother during the pregnancy. In model 2 we use the disease load on mothers instead, and in models 3 and 4 the disease load on the child. The effects of variables other than the early-life indicators are much the same in all models. The table shows that age-specific mortality within the age interval 55–80 years of age declines in the period 1760–1894, even after controlling for all

other variables included in the model. The result seems quite plausible since we have not made any other effort to model long-term developments in wages and welfare other than by using period dummies. Generally we find that current socio-economic conditions influence the risk of dying and that lower socio-economic strata are more vulnerable to short-term economic stress. The group of cottagers and farm labourers (covariate 4) has a lower risk of dying than peasants, but are much more vulnerable to short-term economic stress (covariate 15). The analysis also shows that the tenant farmers had a significantly lower age-specific mortality, only 59 per cent of that of freeholders. We are unable to find any significant effects of sex, farm size, and time period. Thus, it seems plausible that periods of economic stress affected the mortality of cottagers, farm labourers, widows, and the poor more than that of any other professional group.

When it comes to the effects of early-life variables, the most important finding is that the disease load during the first year of life (model 3) has a strong and significant impact on mortality later in life. All the other three early-life indicators of stress during early life are non-significant, though the estimated relative risk for the disease load during the first five years of life is very high (model 4). These interesting results support the hypotheses of Kermack, McKendrick, and McKinley and to some extent Fridlizius but not the hypotheses of Fogel and Barker. We also tested a model in which the price of rye at the time of birth is used as an indicator of access to nutrients during the first year of life, assuming that lower rye prices leave more food for breast-feeding mothers than when food prices are high, but found no support for this hypotheses (details not shown). Thus we have been able to show that the disease load during the first year of life, which varies greatly from year to year and generally declines rapidly from the beginning of the 19th century onwards, has a strong influence on mortality among the elderly. This indicator of early-life conditions is therefore used in the analysis of cause-specific mortality and the analysis by sub-period.

Table 5 illustrates the results of estimations of three cause-of-death specific models using the disease load during first year of life as an early-life indicator. A competing risk framework has been used. Model 3, all causes, is reproduced here to make comparisons easier. Model 5 shows the estimates for airborne infectious diseases while Models 6 and 7 show it for weakness in old age and from mortality in "other specified non-infectious diseases" (see Table 1 and 2 for the construction of the groups). After controlling for the others factors, we find that the disease load during the first year has a strong impact both on mortality from airborne infectious disease and on mortality from specified non-infectious diseases, but not on the deaths labelled 'weakness due to old age'. The effects are indeed very strong. A one-unit change in crude death rate at age 0–1 years increases mortality in air-borne infectious diseases by 465 per cent. This means that if a person is born in a year with an infant mortality rate of 200 per 1000, the risk of dying of airborne infectious diseases is 46.5 per cent higher than if he or she had been born in a year with an infant mortality rate of 100 per 1000. The effects on specified non-infectious diseases, as defined previously, are somewhat lower – 34.1 per cent – but still very high.

5. SUMMARY AND DISCUSSION

Old-age mortality can be interpreted in different ways. It can be interpreted as caused by events in early life which led to irreversible or partly irreversible tissue damage but with a long interregnum without symptoms. Alternatively, it can be interpreted as the result of stressful life events in later life that were the proximate causes of death. Several hypotheses about stressful life events causing death much later in life and even in old age have been presented. One such possible relationship is that proposed by Fogel: a relative lack of nutrition before birth causes irreversible tissue damage and might even, more specifically, disrupt hormonal and other physiological metabolic pathways causing, for instance, cardiovascular disease and diabetes mellitus type II much later in life (the Barker hypothesis). Another possibility, proposed by Fridlizius and others, is that stressful events, more specifically having had infectious diseases when aged 0–5 years, might lead to irreparable damage to the immune system, eventually causing death in old age. The contemporary and more direct effects on mortality in old age might be caused either by a secularly rising standard of living or the diminishing short-term insecurity caused by decreasing fluctuations in real wages. These hypotheses have been tested in this paper.

The causes of death registered by the church in the four parishes in our sample, from 1760 until the end of registration in 1894, were aggregated into diagnostic groups in two steps. Other individual-level variables, like age, sex, and socio-economic variables (different professional groups, different

Table 5. *Mortality at ages 5–-80 by cause of death, 1760–1895, with rude death rate 0–1 years as the early-life indicator*

	Model 3 All causes		Model 5 Airborne		Model 6 Old age		Model 7 Non-infectious	
	Relative risk	*p*-value	Relative risk	*p*-value	Relative risk	*p*-value	Relative risk	*p*-value
1. Birthyear	0.99	0.00	0.99	0.02	0.98	0.00	0.98	0.00
2. Sex[1] female	0.95	0.39	0.84	0.11	1.11	0.35	1.09	0.55
3. Occup[2] artisans	0.87	0.09	1.05	0.75	0.59	0.00	0.83	0.36
4. Occup[3] cottagers	0.86	0.06	0.84	0.33	0.63	0.01	0.76	0.20
5. Owner[1] tenant	0.59	0.00	0.62	0.09	0.62	0.28	0.75	0.51
6. Owner[2] other	1.12	0.42	1.13	0.66	1.52	0.31	1.50	0.34
7. Farmsize[2] small	0.82	0.27	0.74	0.36	2.36	0.15	0.47	0.20
8. Farmsize[3] none	0.97	0.81	0.83	0.43	1.65	0.31	0.95	0.88
9. Early-Life Indicator: CDR 0-1 years	1.80	0.03	4.65	0.00	1.46	0.45	3.41	0.05
10. Rye price	1.65	0.58	1.36	0.85	0.96	0.99	0.31	0.61
11. Period 1820–1865	1.09	0.63	0.81	0.54	0.56	0.13	1.22	0.66
12. Period 1865–1895	1.17	0.20	0.83	0.40	2.16	0.00	1.28	0.39
13. Sex[1] * Rye price	1.22	0.51	2.74	0.08	1.03	0.95	0.65	0.55
14. Occup[ation2] * Rye price	1.14	0.76	1.19	0.84	1.56	0.60	1.57	0.67
15. Occupation[3] * Rye price	2.84	0.02	3.97	0.14	3.39	0.15	2.06	0.52
16. Owner[1] * Rye price	0.96	0.97	1.02	0.99	0.73	0.89	18.04	0.20
17. Owner[2] * Rye price	1.19	0.83	1.71	0.72	0.29	0.59	7.32	0.38
18. Farm size[2] * Rye price	2.15	0.47	0.57	0.77	14.82	0.41	0.27	0.71
19. Farm size[3] * Rye price	0.29	0.10	0.12	0.08	2.53	0.71	0.17	0.29
Max Log Likelihood	–7606.4		–1901.4		–1579.2		–1125.3	
χ^2	160.7		119.11		242.12		93.98	
Degrees of freedom	19		19		19		19	
Deaths	1400		343		339		208	

Note: See Table 3 for reference categories and Table 1 or 2 for definitions of causes of death.
Sources: As Table 1.

landowner conditions, and different farm sizes) from the church registers were used in a multivariate analysis using the Cox proportional hazards regression model in the computations. The two different early-life-event hypotheses and the two period hypotheses were also operationalized in this model by using aggregate data on rye prices.

The results of the Cox regression analyses show consistently lower mortality rates for tenant farmers compared to freeholders and the landless throughout the study period 1760–1894. No particular aggregated group of causes of death specifically explains this highly significant difference in overall mortality. This finding supports Winberg (1975), who has argued that the tenant farmers experienced more economic and social security than freeholders because of the obligations that the estate owner had towards his tenants in pre-industrial society.

Another finding is that the professional group that includes cottagers, farm labourers, widows, and the poor seems to have had lower mortality than the other professional groups. This finding is not easy to interpret, and all these results are just on the verge of being significant. On the other hand, a more consistent and more significant finding is that this professional group has very high mortality rates in the age group 55–80 years when rye prices in the previous year are high. This finding seems to indicate that this professional group, not surprisingly, was the vulnerable one in periods of economic hardship.

Finally, our most interesting and important finding, the one that relates to the hypotheses about effects of early-life conditions on old age mortality, is that the disease load during the first year of life is the early-life indicator variable that significantly influences mortality rates later in life. No such significant influence on old-age mortality is found for the early-life variables that indicate stressful events during intra-uterine life (such as the relative lack of nutrition) or during the entire early-childhood period from 0 to 5 years. We find that the effects of the stress on a newborn child related to a high disease load during the first year of life is particularly strong on mortality among the elderly from airborne infectious disease but also from other specified non-infectious diseases. Not only is the

mortality among the elderly affected but also in ages 25–55 years (Bengtsson 1997, p. 16). Thus the adverse impact on the development of the child of a high-mortality environment during first year of life has an enduring impact on health and mortality in later life.

NOTES

Tommy Bengtsson is Visiting Professor of Historical Demography at Odense University, and Professor of Economic History and Demography at Lund University, Sweden, and Martin Lindström is at the Department of Economic History and Department of Community Medicine, Lund University, Sweden. This paper has been written within the research project 'From Hunger to Modern Economic Growth. Demography and Family Behaviour in Sweden, 1650–1900', with financial support from the Bank of Sweden Tercentenary Foundation and The Swedish Council for Social Research. The data used are part of the Scanian Demographic Database, which is a product of a collaborative project between the Research Group in Population Economics, Department of Economic History, Lund University, and the Provincial Archives, Lund. For more information about the database, see Reuterswärd, E and Olsson, F (1993). We are grateful for comments from many of our friends and in particular from George Alter, Göran Broström, Cameron Campbell and Roger Schofield.

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Paper III

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Airborne infectious diseases during infancy and mortality in later life in southern Sweden, 1766–1894

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Background The importance of early life conditions and current conditions for mortality in later life was assessed using historical data from four rural parishes in southern Sweden. Both demographic and economic data are valid.

Methods Longitudinal demographic and socioeconomic data for individuals and household socioeconomic data from parish registers were combined with local area data on food costs and disease load using a Cox regression framework to analyse the 55–80 year age group mortality (number of deaths = 1398).

Results In a previous paper, the disease load experienced during the birth year, measured as the infant mortality rate, was strongly associated with old-age mortality, particularly the outcome of airborne infectious diseases. In the present paper, this impact persisted after controlling for variations in food prices during pregnancy and the birth year, and the disease load on mothers during pregnancy. The impact on mortality in later life stems from both the short-term cycles and the long-term decline in infant mortality. An asymmetrical effect and strong threshold effects were found for the cycles. Years with very high infant mortality, dominated by smallpox and whooping cough, had a strong impact, while modest changes had almost no impact at all. The effects of the disease load during the year of birth were particularly strong for children born during the winter and summer. Children severely exposed to airborne infectious diseases during their birth year had a much higher risk of dying of airborne infectious diseases in their old age.

Conclusions This study suggests that exposure to airborne infectious diseases during the first year of life increases mortality at ages 55–80.

Keywords Early life, life course perspective, infant mortality, old-age mortality, airborne infectious disease

The decline in old-age mortality in Sweden and other Western countries started in the mid-19th century, several decades later than the decline in infant mortality.[1,2] Old-age mortality is determined by a number of factors, some of which relate to economic and social conditions during the old-age period of life (period determinants). Others are related to the long-term effects of conditions *in utero* or during early childhood (cohort determinants).

Period determinants of old-age mortality include long-term changes in hygiene and public health,[3] and nutrition and standards of living in general,[4] but also short-term insecurity in access to food, etc.[5,6]

Kermack, McKendrick, and McKinley proposed the cohort explanation in 1934. They studied age-specific mortality in England, Wales, Scotland, and Sweden. Their conclusion was that reductions attained at any particular time in the death rates of the various age groups depended primarily on the individuals' date of birth, and only secondarily on the current year. The essential effects on health and survival among adults and older people were mainly caused by beneficial effects and improvements achieved in these birth cohorts during childhood several decades earlier.[7] This life-course perspective has been given more attention in recent years.[8,9] The plausible causal relationship between early life experiences and old-age mortality has been discussed, particularly in relation to intrauterine

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cellular development and cellular development during early childhood. Robert Fogel has proposed several plausible causal mechanisms that connect malnutrition, whether due to a lack of nutrients or increased demands as a result of disease, *in utero* and during early life to chronic diseases in later life.[10] The propositions regarding the effects of conditions before birth are supported by the work of Barker, among others, who suggested that the preconditions for coronary heart disease, hypertension, stroke, diabetes, and chronic thyroiditis are initiated *in utero* without becoming clinically manifest until much later in life.[11,12] In contrast, Fridlizius suggested that the genesis of disease in later life could be due to exposure to certain infectious diseases, such as smallpox, in the first 5 years after birth, resulting in reduced immunity to other diseases throughout life and, consequently, a higher general risk of other infectious diseases in later life.[13] This notion is supported by some studies that have suggested that lower respiratory tract illness in the first year of life is associated with later cough, phlegm, and impaired ventilatory function, independently of smoking and social class. Illness after the first year of life was not associated with any risk, which supports the idea of a critical period of influence for infection.[14,15] The hypothesis implies that factors other than nutrition were important early life determinants of mortality in later life, because the outcome of smallpox infection as well as some other important infectious diseases is almost completely unrelated to the nutritional status of the infected individual.[16] It also implies that it is not the conditions *in utero* that are important but rather the situation during infancy and early childhood. Fridlizius does not, however, discuss the possible effect on later health of the nutritional loss due to having experienced a non-nutritional disease or any infectious disease. Thus the cohort hypothesis put forward so far involves whether low nutritional intake or increased nutritional demands due to disease affect mortality in later life and whether the conditions *in utero* or during the first years of life are of the most importance. The problem in historical analysis has been that these four hypotheses have never been confronted with each other.

In a previous paper, Bengtsson and Lindström investigated these cohort hypotheses for four parishes in southern Sweden, 1766–1894.[17] They used a multivariate Cox regression model on longitudinal demographic data for individuals combined with household socioeconomic data, local area data on food prices, and disease load. While the focus was on cohort hypotheses, the analyses included both variables measuring period short-term economic stress and trends and cohort variables measuring the disease load on mothers during pregnancy and children during the first years of life and access to nutrition in early life. The hypothesis that access to nutrition was of primary importance was not supported by the results. Furthermore, no effects of conditions *in utero* were found. In contrast, the disease load experienced during the year of birth showed a consistent impact on mortality in later life, particularly on the outcome of airborne infectious diseases during old age. However, the previous study has some important limitations that we deal with in this paper. Firstly, different early-life indicators of stress were analysed in separate multivariate models, one at a time, due to technical constraints. Secondly, effects of long-term trends and short-term fluctuations in disease load during early life, threshold effects, and the patterns of disease load during the first year of life were not specified. Thirdly, possible seasonal effects of the date at birth were not taken into account. This is of potential importance as both diets and the exposure to disease vary seasonally. Mortality peaked in the winter season during the January–April period and was at its lowest from July to October.[18,19] It has also been shown that the season of birth has a strong influence on life expectancy.[20] The purpose of this paper is to eliminate these limitations so as to allow us to better understand the causal mechanisms of the previously observed effects of conditions in early life on old-age mortality, in particular on mortality from airborne infectious diseases.

Computer software development now allows us to analyse four or more time-varying community covariates simultaneously, which means that we can estimate the net effects of the disease load during the first year of life (infant mortality rate) and the disease load on the mother during pregnancy (measured indirectly by the crude death rates among adults aged 20–50 years), and the food prices during pregnancy and the first year of life will also be analysed as plausible determinants of old-age mortality. We are particularly interested in whether the large annual variations of food prices influence mortality in later life as one would expect it to reflect changes in nutrition. Variation in food prices also has a strong influence on current mortality. The effects of trends in infant mortality as opposed to fluctuations (cycles) from year to year on old-age mortality will be investigated by decomposing the infant mortality rate into two components using a Hodrick Prescott filter with a filtering factor of 100 (for a discussion of and references to this method, see ref. 21). The same filter is used to divide the crude death rates among adults aged 20–50 years into trend and cycle components. Furthermore, the cycle component of the infant mortality rate is divided into five categories to enable us to estimate potential threshold effects, and thus some years with a very high disease load have a proportionately stronger effect on old age mortality than other years. Furthermore, causes of death are identified for such years. The problem of seasonality is dealt with by including a season dummy (winter, spring, summer, autumn) as a covariate in the multivariate model, and also by analysing the season effect separately in four independent multivariate models. In addition, effects of sex, birth year, birthplace, present place of residence, present socioeconomic status (SES) (freeholders/crown tenants, tenants on nobility-owned land, semi-landless/crofters, landless), and current access to food (rye prices) are included in the model, based on both the variables available in this data collection[17] and in previous literature.[19]

Material and Methods

The sample consists of all married or previously married people aged 55–80 and living in Hög, Kevlinge, Halmstad, or Sireköpinge during any period between 1766 and 1894. Thus, it includes all those aged 55–80 in 1766, immigrants aged 55–80 and those who turned 55 years of age during the period. These people are considered exposed until they reach age 80, emigrate, are alive in 1894, or die (Figure 1). The data are from the Scanian Demographic Database and consist of records of births, marriages, deaths, and migrations for nine rural parishes and one town, while only the four parishes used in this paper are complete for analyses. The material for two parishes dates back

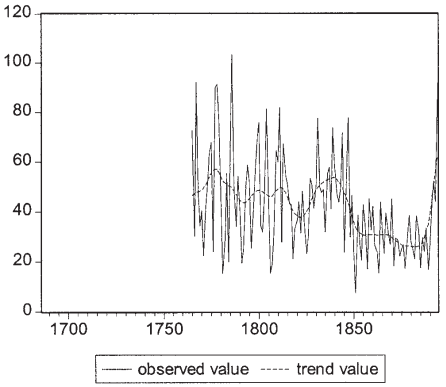

Figure 1 Crude death rate at ages 55–80 in four Scanian parishes, 1766–1894. Per thousand

to 1646 and for the others to the 1680s and continues until 1895. The parish register material is of high quality and shows few gaps in births, deaths, and marriages. Migration records are less plentiful, but continuous series exist from the latter part of the 18th century. Information concerning farm size, property rights, and various other items from the poll tax records and land registers are linked to the family reconstitutions based on the parish records of marriages, births, and deaths. The study period 1766–1894 was chosen because there is a gap in the information about landholdings prior to 1766 and the data on individuals are not available to us after 1895. We also have records throughout the study period on causes of death registered by the clergymen. For the period before the mid-18th century, we have, however, little information about causes of deaths, which we will come back to later.

The sampled parishes are compact in their geographical location, showing the variations that could occur in peasant society with regard to size, topography, and socioeconomic conditions, and they offer good early source material. The entire area was open farmland, except northern Halmstad, which was more wooded. Halmstad and Sireköpinge were 'noble' parishes, in which the farmers rented the land from the estate owners, while freehold and crown land dominated in Kävlinge and Hög. The parishes had 200–500 inhabitants each in the latter part of the 18th century. Kävlinge rapidly expanded during the last decades of the 19th century due to the establishment of several factories.

Demographic data from Sweden dating from 1749 and onwards are generally highly valid and reliable both at the aggregated and individual level. The data are of much higher quality than, for example, those for England[22] covering the same historical period. Firstly, Sweden had a state church from 1527 to 2000, which means that the church books cover the entire population. Secondly, we have both census type information and records about migration and thus know the population at risk. Thirdly, we have occupational information and data on farm types and sizes. Fourthly, we have cause-of-death records. The quality of the death records in the parishes of this study is high, as indicated by the ratio of male to female births, the proportion of stillbirths, and the proportion of deaths during the first month.[23] The validity and reliability of historical data on causes of death in Sweden have been thoroughly discussed elsewhere.[17] In summary, changes in the nomenclature of medical diagnoses (in 1774, 1802, 1811, 1821, 1831, 1873, and 1891) and the succession of individual clergymen in the parishes seem to have had no effect on the validity and reliability of the medical diagnoses made by the clergymen.[24] Furthermore, some diseases, especially infectious diseases such as smallpox, were identified as the same diagnostic entities (based on distinct symptoms) and denoted by the same names as today.[17] The aetiology of infectious diseases, the most common cause of death during the whole study period, was not known; proper diagnosis was impossible, except for symptomatic diagnoses, until the end of the 19th century.[25] The system remained basically nosological during the whole period.[24]

The social structure of the agricultural sector is often difficult to analyse as differences in wealth between the various categories of farmers and occupations are unclear and subject to change with the passage of time. Data from land registers on types of tenure must therefore be combined with information from poll tax records concerning farm size in order to arrive at a better understanding of the social structure. From these sources we can conclude that the nobility was a rather small group and it has therefore been excluded from our sample. The peasants were divided into two categories: freeholders, tenants on crown land, and tenants on church land constituting the first group, while tenants on nobility-owned land constitute the second one. We only include peasants with farms larger than 1/16 *mantal* in these two categories as it has been argued that peasants with smaller farms could not support themselves. A *mantal* was not a measure of the actual size of the farm but a tax-assessment unit based on potential production. A third group, which we label semi-landless, includes farmers with land smaller than 1/16 *mantal* and crofters. The fourth group is the landless workers.

In estimating the parameters of the models, we use event-history analysis with time-varying external covariates, which makes it possible to run regressions on the change of life status, i.e. dying or giving birth to a child, measuring the effects of different explanatory variables (or covariates) on the hazard of the event. More specifically, we use the Cox proportional hazards model, which does not require specification of the underlying hazard function. The main interest in this case is to estimate the impact of different covariates on the hazard of death. The aggregated indicator of the food prices is included in the regressions as a communal, or external, covariate.[26,27] This means that the aggregate economic information is used as a time-varying covariate common to all individuals in the risk set at each point in calendar time.[27] Aggregated indicators—the infant mortality rate (Figures 2 and 3), the crude death rate at ages 20–50 years (Figure 4), and the food prices (Figure 5)—are also used as fixed community covariates. The value of the community covariate is then shared by all individuals with the same birth year or with the same year of conception, depending on which indicator it is. The infant mortality rate during the

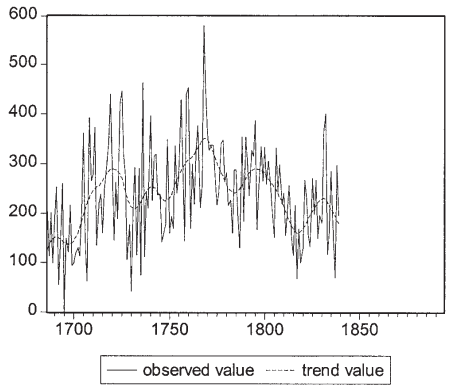

Figure 2 Infant mortality rate in four Scanian parishes, 1686–1839. Per thousand

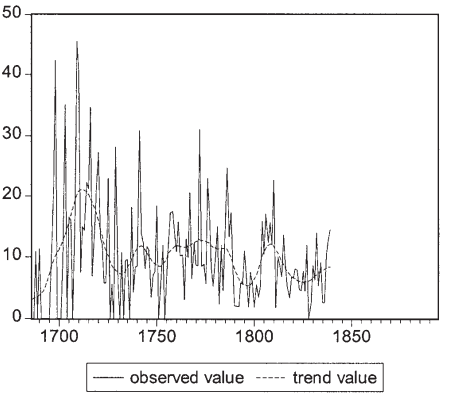

Figure 4 Crude death rate in ages 20–50 in four Scanian parishes, 1686–1839. Per thousand

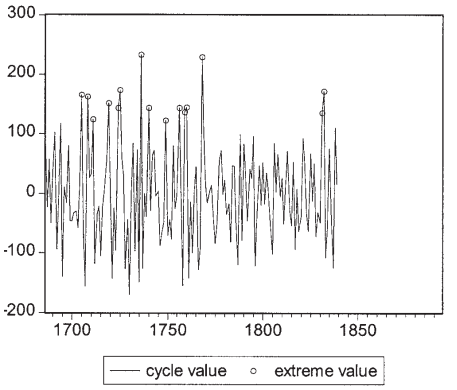

Figure 3 Cycles and extreme values in infant mortality rate in four Scanian parishes, 1686–1839. Per thousand

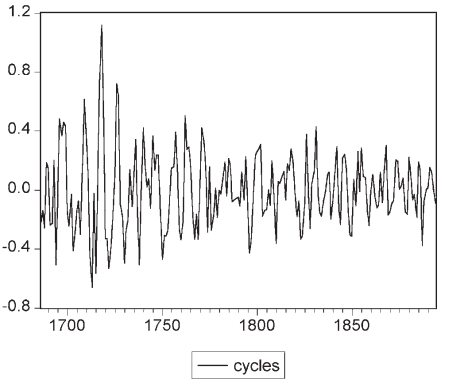

Figure 5 Cycles in the logarithm of local rye prices, 1686–1894

year at birth is shared by all individuals with the same birth year to indicate the disease load on infants. The crude death rate at ages 20–50 during the year of conception is shared by all individuals with the same year of conception to indicate the disease load on the mothers during the pregnancy. Food prices are likewise fixed to reflect the access to food during both the fetal stage and the birth year. We use the logarithm of local rye prices as an indication of the availability of food because grain dominated the diet and rye was the major crop. This indicator has been used in many previous studies and has been shown to have high validity.[27] The software program used is called MLIFE and was developed by Professor Göran Broström of Umeå University and Lund University. It is a GNI licence program and has specific features to facilitate the use of time-varying and fixed community covariates.[28]

Results

Table 1 shows the average of each covariate, or category, the likelihood ratio *P*-value test for the covariate, the relative risk, and the Wald *P*-value for each covariate or category. The 'average' depicts the mean value of the covariate or category. In the case of sex, it shows the proportion of men and women in percentage at risk (similarly to birth season, parish, socioeconomic group, and birthplace). The average birth year is 1775.2 and infant mortality is 20% on average, while crude death rate in

Table 1 Estimation of effects of sex, birth year, birth season, birthplace, parish of residence, socioeconomic status, infant mortality rate at birth, crude death rate at ages 20–50 years at conception, and cycles in the logarithm of rye prices at conception, at birth and currently in four Scanian parishes, 1766–1894. The number of deaths is 1398

Covariate	Average	LR[a] *P*-value	Relative risk	Wald *P*-value
Sex		0.857		
Male	54.1%		1	(ref.)
Female	45.9%		1.010	0.857
Birth season		0.119		
Winter	26.6%		1	(ref.)
Spring	21.5%		1.104	0.193
Summer	22.1%		1.091	0.259
Autumn	29.8%		0.942	0.413
Parish		0.448		
Hög	13.7%		1	(ref.)
Kävlinge	16.6%		0.927	0.391
Halmstad	46.8%		1.013	0.877
Sireköpinge	22.9%		1.056	0.504
Socioeconomic group		0.013		
Freeholders/crown tenants	7.8%		1	(ref.)
Tenants on nobility-owned land	9.9%		0.870	0.440
Semi-landess/crofters	15.1%		0.759	0.067
Landless	67.2%		0.994	0.965
Birthplace		0.363		
In parish	29.3%		1	(ref.)
Other parish	70.7%		1.056	0.365
Birth year	1775.2	0.000	0.997	0.000
Infant mortality rate, at birth	0.20	0.000	2.925	0.000
cdr, ages 20–50, at conception	0.01	0.911	0.669	0.911
Log of rye prices				
At conception	0.00	0.604	1.065	0.604
At birth	0.00	0.860	1.021	0.860
Current	0.00	0.420	1.128	0.420
Overall *P*-value: 0.0000				

[a] Likelihood ratio.

ages 20–50 years is about 1%. The likelihood ratio test compared the full model with one in which the covariate is excluded, whether it is a nominal covariate or categorized. It is known to be a very robust test. The relative risk gives the risk relative to a reference category, such as the risk for mortality among females relative to men. In the case of nominal covariates, it shows the change in risk associated with a one-unit change in the covariate. For example, the relative risk for birth year is the value associated with being born one year later. The final column shows the Wald test *P*-value for each category. This test is less robust than the likelihood ratio test, particularly for small samples.

Table 1 shows that the disease load in the year of birth, measured by the period infant mortality rate for that year, had a strong impact on mortality among the elderly when also considering other conditions close to birth simultaneously. The effects of the disease load on the mother during pregnancy, measured by the crude death rate among adults 20–50 years of age and food prices during the pregnancy as well as during the first year of life, are minor. This holds true also when trend and cycle effects are analysed separately (not shown here). The likelihood ratio tests in Table 1 show that each of these variables can be excluded and the same is true of the current time effect of food prices. A likelihood ratio test comparing the estimations of a reduced model, in which neither of these variables is included, with the full model shows that they can be excluded as a group. The χ^2 value only decreases from 58.69 to 57.48 when the degrees of freedom go down by 4.

The effect of the disease load during the year of birth is strong and highly significant. A one-unit change in the disease load increased the mortality risk by approximately 50%, from an average of 0.042 to about 0.06. The effects of birth year and SES are also significant. Being born one year later is associated with a 0.3% lower death risk. The finding regarding SES seems at first paradoxical as the semi-landless—crofters and people with very small farms—have lower death risks than the better-off freeholders and tenants. They have, on the other hand, lower mortality than the landless, which is what one would expect from an economic point of view. A possible explanation is that the size and composition of the semi-landless group changes over time, partly as a result of the agricultural reforms at the beginning of the 19th century. We have therefore estimated the model similarly to the one shown in Table 1 with controls for various time periods. While we are not reporting these details in this paper, we did find that the results are stable throughout the 19th century. Thus, the lower mortality for the semi-landless group relative to the better-off groups is not a result of its increase in size in a period with lower mortality but is genuine. A possible explanation of the lower mortality among the semi-landless is the fact that they often lived in cottages outside the villages and that they were therefore less exposed to infectious diseases. Furthermore, we did not find effects of gender, the time of the year when the birth occurred, which parish the elderly lived in, and whether people were living in their native parish or not.

In as much as the disease load during the birth year had such a strong effect on mortality at later ages, we have tried to specify it better. The infant mortality rate between 1686 and 1839, when the elderly people were born, fluctuated substantially. Figure 2 shows that the infant mortality rate changes annually, but also a secular trend. The estimated effect shown in Table 1 could either be a result of the short-term changes or the long-term ones. This infant mortality rate was therefore divided into two components using a Hodrick Prescott filter with 100 as the filter term, which resulted in the short-term component called cycle, shown in Figure 3, and the long-term component shown as the broken line in Figure 2. For a discussion of the method in this context see ref. 21. Table 2 shows that not only the long-term development of the infant mortality rate but also annual changes influenced mortality in later life.

In order to estimate potential non-linear effects in the short-term response, we categorized the cycles of the infant mortality rate into five spells, using the values –120, –60, +60, and +120 per thousand as limits. Fifteen years have an infant mortality rate above 120 after the trend removal. They are marked with rings in Figure 3. As shown in Table 3, these years have a very strong impact on mortality among the elderly. Thus the effect of the disease load during the birth year is neither symmetrical nor linear. Since they have such a strong influence, we have tried to find out what they are characterized by. Unfortunately, we have no record of causes of death for the four parishes before 1740,

Table 2 Estimation of effects cycles and trend in infant mortality rate at birth, sex, birth year, birth season, birthplace, parish of residence, and socioeconomic status in four Scanian parishes, 1766–1894. The number of deaths is 1398

Covariate	Average	LR[a] *P*-value	Relative risk	Wald *P*-value
Sex		0.849		
Male	54.1%		1	(ref.)
Female	45.9%		1.010	0.849
Birth season		0.118		
Winter	26.6%		1	(ref.)
Spring	21.5%		1.102	0.204
Summer	22.1%		1.087	0.277
Autumn	29.8%		0.938	0.385
Parish		0.415		
Hög	13.7%		1	(ref.)
Kävlinge	16.6%		0.925	0.380
Halmstad	46.8%		1.014	0.868
Sireköpinge	22.9%		1.059	0.481
Socioeconomic group		0.013		
Freeholders/crown tenants	7.8%		1	(ref.)
Tenants on nobility-owned land	9.9%		0.865	0.422
Semi-landess/crofters	15.1%		0.752	0.059
Landless	67.2%		0.983	0.899
Birthplace		0.294		
In parish	29.3%		1	(ref.)
Other parish	70.7%		1.066	0.296
Birth year	1775.2	0.001	0.997	0.001
Infant mortality rate, at birth				
Trend	0.20	0.006	4.849	0.006
Cycle	0.00	0.014	2.348	0.014
Overall *P*-value: 0.0000				

[a] Likelihood ratio.

Table 3 Estimation of non-linear effects of cycles in infant mortality rate at birth, sex, birth year, birth season, birthplace, parish of residence, and socioeconomic status in four Scanian parishes, 1766–1894. The number of deaths is 1398

Covariate	Average	LR[a] *P*-value	Relative risk	Wald *P*-value
Sex		0.801		
Male	54.1%		1	(ref.)
Female	45.9%		1.014	0.801
Birth season		0.204		
Winter	26.6%		1	(ref.)
Spring	21.5%		1.091	0.253
Summer	22.1%		1.102	0.205
Autumn	29.8%		0.961	0.585
Parish		0.515		
Hög	13.7%		1	(ref.)
Kävlinge	16.6%		0.929	0.408
Halmstad	46.8%		1.015	0.853
Sireköpinge	22.9%		1.048	0.563
Socioeconomic group		0.013		
Freeholders/crown tenants	7.8%		1	(ref.)
Tenants on nobility-owned land	9.9%		0.856	0.389
Semi-landess/crofters	15.1%		0.753	0.060
Landless	67.2%		0.985	0.906
Birthplace		0.406		
In parish	29.3%		1	(ref.)
Other parish	70.7%		1.051	0.407
Birth year	1775.2	0.000	0.997	0.000
Infant mortality rate, at birth				
Very low	6%	0.896	1.028	0.896
Low	11%	0.926	1.010	0.926
Normal	63%		1	(ref.)
High	13%	0.280	0.912	0.285
Very high	7%	0.019	1.508	0.013
Overall *P*-value: 0.0000				

[a] Likelihood ratio.

so we have to use information from neighbouring parishes for the first part of the period. Table 4 shows the results. For two years, 1708 and 1724, we have no information on neighbouring parishes either. The mortality peaks for all other years prior to 1740 are associated with smallpox in the neighbouring parishes. It is therefore likely that the peaks in the four parishes we use in this analysis, prior to 1740, are also due to smallpox since it was easily spread. Taken together with the information for the four parishes after 1740, we find that smallpox and/or whooping cough occurred in 13 out of the 15 years.

The interaction effects between the disease load in the first year of life and sex, birth season, parish, and socioeconomic group were estimated by adding the interaction to a model similar to the basic model shown in Table 1. The only difference was that the infant mortality rate was the only early-life indicator included, since the likelihood ratio test showed that the other ones could be excluded. The size of the data set does not allow us to estimate all interaction effects simultaneously. Separate models were therefore used. Using the likelihood ratio test to evaluate the results, we cannot show any interaction effects between infant mortality rates and sex, parish, socioeconomic group, and birthplace (not reported here). The coefficients for the interaction with birth season are quite strong, but still not significant (likelihood ratio *P*-value, 0.285). Children born during the winter and summer seem to be much more affected by diseases than those born during the spring and autumn. To release the models from the assumptions regarding proportionality between the other covariates and from sharing the same baseline hazard function, separate models for each birth season were estimated. Table 5 shows the results of the four estimations. It shows that the effect is particularly strong for children born during the first 3 months of the year, but it is also strong for those born during the summer. This indicates that our choice of measure of the disease load during the first period of life after birth (the infant mortality rate during the birth year) might possibly be improved. Such improvement would most likely lead to even stronger results. Thus we are on the safe side in terms of measurement using the infant mortality rate in the birth year as the indicator of health at the beginning of life.

Discussion

Old-age mortality during the study period was affected by both long-term changes in the disease load during the years of birth and variation in the disease load from one year to another, even after controlling for variations in food prices and the disease load at ages 20–50. The effects of the changes in the disease load from one year to another were mainly due to outbreaks of

Table 4 Prevalence of smallpox and whooping cough in years with extremely high mortality compared with years before and after in four Scanian parishes and their surroundings

1705	smallpox in Scania and in neighbouring parishes (Lackalänga, Stävie, V Karaby) in 1706
1708	no information available
1711	smallpox in Scania
1719	smallpox in a neighbouring parish (V Karaby) in 1718
1724	no information available
1725	smallpox in a neighbouring parish (Reslöv) in 1726
1736	smallpox in neighbouring parishes (Lackalänga, Stävie)
1740	smallpox
1749	whooping cough
1756	smallpox
1759	smallpox
1760	smallpox
1768	smallpox, whooping cough
1831	whooping cough
1832	whooping cough

Sources: 1740–1832 cause of death records from Hög, Kävlinge, Halmstad, and Sireköping (Scanian Demographic Database), 1706 and 1719–1736 church books for Lackalänga, Stävie, V Karaby, and Reslöv parishes, which are located very close to the parishes in our sample, 1705 and 1711 Persson (2001:135).

Table 5 Estimations of effects of infant mortality rate at birth for birth season cohorts after controlling for sex, parish, socioeconomic group, birthplace, and birth year in four Scanian parishes, 1766–1894

Covariate	No. of deaths	LR[a] *P*-value	Relative risk	Wald *P*-value
Infant mortality rate, at birth for				
Winter cohort	379	0.002	5.940	0.002
Spring cohort	320	0.504	1.527	0.504
Summer cohort	309	0.025	3.957	0.024
Autumn cohort	390	0.257	1.802	0.254

[a] Likelihood ratio.

infectious diseases such as smallpox, whooping cough, pneumonia, measles, etc. Moderate changes in the disease load during the birth year had no significant impact on old-age mortality. The other hypothesized causal cohort mechanisms, i.e. that the disease load on the mother during pregnancy (crude death rates among adults aged 20–50) and the food prices during both pregnancy and the first year of life would affect old-age mortality among those aged 55–80 years, could not be confirmed. Thus we find no effect of external conditions during the fetal stage, either of nutritional access or of the disease load on mothers, and no effect of nutritional access during the first year of life. But the disease load during the birth year mattered a lot regarding mortality among the elderly.

The results agree to some extent with those of Fridlizius,[13] who proposed that adult and old-age mortality was mainly affected by the disease load during the first 5 years of life. Fridlizius also suggested that exposure to especially infectious diseases, e.g. smallpox, but also, to some extent, other infectious diseases during the first years of life would affect survival during adulthood through an irreversible damaging effect on the immunological system. There is, however, no medical evidence to account for such a causal mechanism. Furthermore, our findings regarding the long-term component of the infant mortality influence on old-age mortality are in agreement with those of Fridlizius, since he filters out the short-term components by estimating the effects of the disease load during the first 5 years of life. The short-term fluctuations in infant mortality are also of great importance during the first year of life, as shown in this paper.

The influence of the short-term variations in infant mortality on old-age mortality was mostly due to peaks in infant mortality caused by different infectious diseases, particularly by smallpox and whooping cough. These infectious diseases are so virulent that they must have penetrated the entire area. Smallpox is one example. It was mainly a childhood disease during the 18th century.[29,30] Approximately 95% of all deaths due to smallpox in Sweden during the 18th century occurred under age 10.[29,31] The 18th century patterns of total childhood dominance in smallpox mortality indicate that most of the adult population during this period had already been exposed to smallpox as children but had survived. Those cohorts exposed to such infectious diseases during infancy may also be much more susceptible to high morbidity and mortality rates even in old age as an effect of this exposure than cohorts exposed to epidemics of smallpox and other infectious diseases later in childhood. The causal biological mechanisms in early life that might explain these significant associations are only partly understood, although long-term effects on morbidity and mortality seem to have some support in the literature.[32] The pathways that have been discussed mostly concern infectious diseases of the respiratory tract. Respiratory infections, atopy, reversible airway obstruction, chronic mucus hypersecretion, and irreversible airflow obstruction are interconnected by a complex web of associations and putative causal relationships.[8] Respiratory infectious diseases in infancy (ages 0–1 year) have been suggested to be one cause of a chronic wheezing tendency,[33,34] chronic cough and phlegm,[33,35] irreversible impaired ventilatory function,[33,36] and the related mortality.[37] Two historical cohort studies in England suggest that respiratory infectious diseases in the first year of life are associated with later cough, phlegm, and impaired ventilatory function, independently of smoking habits and social class. Infectious respiratory diseases after the first year of life did not seem to be a risk, which supports the idea of a critical period of influence for infection. Mortality from chronic respiratory diseases was also associated with early bronchitis and pneumonia.[14,15] These studies have been interpreted as evidence of persistent lung damage from respiratory infectious diseases during the first year of life.[8]

This study deals with exposure to smallpox and other airborne infectious diseases during the latter part of the 18th century and whether this exposure during infancy affected mortality later in life. The results and conclusions of this study could most probably be generalized to other geographical areas and countries than Sweden, and also to the 20th century. As smallpox was eradicated in human populations as late as in the late 1970s, long-term effects of smallpox on morbidity and mortality are still highly interesting and will remain so for many years to come.[33]

Several studies on more recent 20th century data series show that there is a strong association between low SES and both mortality and general practice consultations for adult respiratory

disease.[38] Although most of these socioeconomic differences are probably due to socioeconomic differences in smoking behaviour, independent associations between SES and symptoms of mucus hypersecretion[39,40] and ventilatory function[41] have been demonstrated. A significant socioeconomic gradient in bronchitis mortality was observed before the occurrence of socioeconomic differences in smoking behaviour.[42] However, the present study on an older historical data series does not demonstrate the same results. We find no effects of rye prices experienced in early life, an indicator of economic hardship, the consequences of which varied greatly in different socioeconomic strata, on old-age mortality. In contrast, highly contagious infectious diseases such as smallpox, which affected different socioeconomic strata similarly, had this effect on old-age mortality.

This study suggests that airborne infectious diseases are important for the causal mechanisms linking infant mortality to old-age (55–80 years) mortality. The variations in infant mortality that affected old-age mortality were mainly caused by both trends and short-term cycles in infant mortality from airborne infectious diseases. Furthermore, old-age mortality was mainly affected by these cohort mechanisms through an increase in old-age mortality from infectious diseases.[17] The combination of these two patterns may seem paradoxical, as exposure to airborne infectious diseases during the first year of life might be expected to result in lesser susceptibility to such diseases in later life because of stronger immunity. However, the results may instead indicate a more general vulnerability throughout life caused by weakening effects in other aspects of the airborne infectious diseases of infancy. In fact, Bengtsson has also shown that the negative impact is not found only at ages 55–80, but also at ages 20–55.[43]

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Commentary: Infectious diseases during infancy and mortality in later life

G Doblhammer

Do the very first years of life determine old-age mortality? This question has stimulated an extensive debate since 1973, when Forsdahl published his first paper[1] about the effect of very poor living conditions in childhood and adolescence on adult mortality. Further work by Barker and colleagues led to the formulation of the 'fetal-origins' hypothesis, which states that chronic disease later in life is caused by nutritional deficiencies *in utero*.[2] While these theories are developed on the basis of studies of mortality in the 20th century, Fridlizius[3] suggested that, in the 19th century, exposure to infectious disease in the first 5 years of life causes an increased risk of infectious disease later in life.

Bengtsson and Lindström set out to test whether the critical early-life period for old-age mortality is *in utero* or during the first year of life, and whether the underlying mechanism is related to nutrition or infectious disease. They use individual-level data based on church records from four parishes in southern Sweden for the time period 1766–1894.[4] The high quality of the Swedish demographic data both in historical and contemporary times is well known. The time period in their study coincides with a period of mortality decline on a cohort basis, which implies that, in terms of life expectancy, the year of birth had more predictive power than the year of death.[5]

The authors use infant mortality during the year of birth to measure the disease load in the first year of life and the crude death rate of women at ages 20–50 years 9 months prior to birth to measure the disease load *in utero*. Similarly, they use rye prices at the time of birth to account for differences in nutrition in the first year of life and rye prices 9 months prior to birth to account for fetal differences in nutrition. They find that both long-term trends and short-term fluctuations in infant mortality significantly influence late life mortality. The effect of

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the short-term fluctuations is mainly the result of years with particularly high infant mortality, primarily caused by smallpox or whooping cough. They did not find an effect of the crude death rate at ages 20–50 and of rye prices on late life mortality.

The study is convincing in demonstrating the effect of infant mortality, and thus the disease load in the first year of life, on old-age mortality. It is less convincing in the treatment of the measures that pertain to the environment *in utero*. Much depends on the time point that these measures are fixed to. For both measures Bengtsson and Lindström choose to fix them 9 months prior to birth. However, both rye prices and mortality are highly seasonal and this seasonality may have distorted their results.

In a footnote of their book about the population history of England, Wrigley and Schofield report seasonal mortality indices for Sweden (ref. 6, p. 296). Between 1749 and 1855 mortality in Sweden differed by 36%, reaching its peak in March and its minimum in July. On the basis of these indices one finds that the seasonal pattern of the mortality indices 9 months prior to birth is highly correlated with the seasonal pattern of the average mortality indices of the first trimester ($\rho = 0.83$, $P = 0.001$) and the third trimester ($\rho = -0.78$, $P = 0.002$) of pregnancy. There is little resemblance, however, with the seasonal pattern for the whole 9-month period ($\rho = -0.46$, $P = 0.131$). A better approach would have been to use the crude death rate for the whole 9-month period of pregnancy. This would also guarantee that the effect of extremely high mortality in only one of the 9 months of pregnancy is not missed. A similar argument pertains to rye prices.

Since the authors did not find any significant results for the crude death rate and the rye price in their first model they did not explore these variables in the same careful manner as they did with infant mortality. One would wish they had used the same threshold approach as they had used for infant mortality, i.e. exploring periods of extremely high rye prices or adult mortality.

The authors include the season of birth in their models and find an effect of borderline significance. Those born in spring and summer tend to have the highest mortality risk at ages 55–80, those born in autumn the lowest. This is consistent with the results for contemporary populations in Austria and Denmark,[7,8] although the excess mortality in the historical Swedish population is much larger (Denmark: 3%, Sweden: 14%).

In their final model they find that the effect of infant mortality on late-life mortality is particularly large for the winter- and the summer-born. Historically, in Sweden, as in many other countries, infant mortality was highly seasonal with peaks in the winter and the summer months.[9] Respiratory diseases were mainly responsible for the mortality during the winter months, while water- and airborne infections were virulent during the summer months.[10] Also smallpox is a highly seasonal disease with large outbreaks occurring during the winter months, rarely during the summer.[11] Thus, extremely high infant mortality mainly occurred during winter and summer. The particularly large effect of infant mortality on old-age mortality for the summer- and winter-born has an important implication: in terms of infectious disease the critical time-period early in life is the very first months of life because those born during seasons with high infant mortality also experience increased old-age mortality.

The overall month-of-birth pattern in this study, however, indicates that the spring- and summer-born suffer from the highest mortality risk later in life, which suggests also that other factors than infectious disease play an important role. In terms of pre-natal nutrition the spring-born were particularly disadvantaged, because the last trimester of the pregnancy, which is the time of peak-growth *in utero*, falls into a season when nutritional deficiencies were most likely. This lends further support to the view that Bengtsson and Lindström do not find an effect of nutrition or infectious disease *in utero* because of the specification of their variables rather than because it does not exist.

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Paper IV

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Migration and health: a study of effects of early life experiences and current socio-economic situation on mortality of immigrants in Sweden

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Objectives. Previous research has demonstrated mortality differences between immigrants and natives living in Sweden. The aim of this study is to investigate the effects of early life conditions in the country of birth and current socio-economic conditions in adult life in Sweden on cardiovascular, cancer, all other cause and total mortality among immigrants and natives in Sweden.
Design. The cohort data concerning individual demographic characteristics and socio-economic conditions stems from the Swedish Longitudinal Immigrant Database (SLI), a register-based representative database, and consists of individuals from 11 countries of birth, born between 1921 and 1939, who were residents in Sweden between 1980 and 2001. The associations between current socio-economic conditions as well as infant mortality rates (IMR) and Gross Domestic Product (GDP) per capita in the year and country of birth, and total, cardiovascular, cancer and 'all other' mortality in 1980–2001 were calculated by survival analysis using Cox proportional hazards regression to calculate hazard rate ratios.
Results. The effects of current adult life socio-economic conditions in Sweden on mortality are both stronger and more straightforward than the effects of early life conditions in the sense that higher socio-economic status is significantly associated with lower mortality in all groups of diagnoses; however, we find associations between infant mortality rates (IMR) in the year and country of birth, and cancer mortality among men and women in the final model.
Conclusions. Socioeconomic conditions in Sweden are more strongly associated with mortality than early life indicators IMR and GDP per capita in the year of birth in the country of origin. This finding has health policy and other policy implications.

Keywords: early life conditions; infant mortality rate; GDP per capita; immigrant mortality; socio-economic status; Sweden

Introduction

Empirical evidence suggests that migration and health are two population processes that are related to each other. International as well as Swedish studies concerning migration and health have mostly compared the health among foreign-born immigrants with the health of natives. Such studies sometimes find that immigrants are healthier than native-born people (Anson 2004), though sometimes they find that

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the health of immigrants is poorer compared to natives (Lindström *et al.* 2001). The causes behind these patterns are complex. A Mediterranean diet may, for instance, significantly decrease the risk of coronary heart disease (Walker and Reamy 2009). However, no studies have managed to demonstrate the association between early life experiences in the country of origin, migration, current socio-economic position and health. The demonstration of such effects would require taking all these factors into consideration.

A wide variety of factors may explain ethnic differences in health and immigrant health. Factors such as culture, beliefs, racism, biology/hereditary factors and access to health care and amenities may contribute to ethnic differences in health (Axén and Lindström 2002, Davey Smith *et al.* 2003, Lindström 2008). However, three principally different hypotheses concerning the importance of socio-economic factors for the association between migration and health may be discerned. A first hypothesis attributes health differences today to both socio-economic conditions and health conditions in the past. Socioeconomic circumstances in early life are important factors to take into account when explaining differences in health status later in life, e.g., migrants from less developed countries that have grown up in a risk environment regarding health also have a higher risk of health problems compared with the native population in developed immigration countries (Davey Smith *et al.* 2003). According to a second hypothesis, health is primarily affected by the existing socio-economic situation, including civil status, income, degree of labour market attachment, occupation, education, etc. Such factors have an important impact on the health situation of the individual. In cases where immigrants are poorly integrated into the host society they will also experience more health problems than natives (Davey Smith *et al.* 2003, Klinthäll 2007, 2008). A third plausible hypothesis states that there is a 'healthy migrant effect'; that is, migrants are healthier than natives because they are positively selected. Those who are healthy, young, ambitious, and so on are more likely to migrate than the rest of the population in the country of origin, and consequently immigrants will also have better health than the native population in the immigration country (Lu 2008).

In recent decades there has been an immense increase in interest in the life course approach to chronic disease epidemiology (Kuh and Ben-Schlomo 2004, Bengtsson and Mineau 2009). The life course approach is sometimes discussed in terms of *cohort* effects on health and survival as opposed to diseases caused by health determinants with a short time period between exposure and health/disease outcome. For example, many infectious diseases have period effects on health because they cause symptoms in the very short-term (hours-days-weeks). In contrast, cohort effects are the results of the varying forms of stress or heavy disease load on the human body in early life, most importantly during pregnancy and the first (infant) year of life, on the susceptibility to various diseases much later in life (Lindström and Davey Smith 2008). Results suggesting cohort explanations were first put forward in 1934 in a study of age-specific mortality rates in England, Scotland, Wales, and Sweden, which showed that mortality reductions attained at any particular point in time were primarily due to date of birth of the studied individuals and only indirectly depended on the year under consideration (Kermack *et al.* 1934). In recent decades the notion (or cohort hypothesis) that early life conditions may affect the risk of disease and death later in life was first confined to cardiovascular diseases and the metabolic syndrome (Barker 1995). One study demonstrated that Mexican Americans who migrated in

early life experienced higher death rates with cardiovascular disease than migrants who immigrated later (Colón-López *et al.* 2009). A Swedish–Iranian study showed a strong association between migration status and the prevalence of hypertension and smoking when elderly people of Iranian origin living in Sweden were compared with elderly people of Iranian origin living in Iran (Koochek *et al.* 2008). However, more recently the cohort hypothesis has been applied to other groups of diseases. Cancer tumours develop in stages, with great variation in growth velocity prior to clinical detection. Since the early 1990s a number of studies have evaluated factors in utero or very early in life after birth, with results suggesting a causal link between early life conditions and different forms of cancer in later life (Potischman *et al.* 2004).

Infant mortality rate (IMR) as well as economic stress are early life indicators even for the survivors in the infant age group for exposure to increased stress and disease load during the first year of life, and thus increased risk of morbidity and mortality in later life (Bengtsson and Lindström 2000, 2003). Gross Domestic Product per capita (GDP/capita) is used as a measure of the absolute level of material and economic development in a country (Lindström and Lindström 2006), and may be recorded for each birth year and country of birth of immigrants in modern Sweden. Both the GDP per capita (van den Berg *et al.* 2009) and the IMR (Bengtsson and Broström 2009, Bruckner and Catalano 2009, Gagnon and Mazan 2009) measures are commonly used as indicators of early life material and economic development and stress for a particular birth cohort in a particular country. Studies investigating later life effects on health caused by earlier life conditions in the country of origin, stress during the process of migration, or earlier life experiences in the new country are very scarce. One important reason is that indicators of early life conditions at the micro-/individual level data are mostly simply not available. The use of aggregate country level data such as IMR and GDP per capita at birth, as in this study, is mostly the only option available, and even studies using this kind of aggregate data are still scarce.

The effects of current socio-economic position, defined as occupational status, education and/or income, on ethnic differences in mortality have been analysed and discussed for many years (Davey Smith *et al.* 1998), and are still considered necessary to take into consideration in studies on the effect of early life factors on health in later life (Palloni *et al.* 2009). Prevalent diseases such as ischaemic heart disease and stroke are distributed with higher manual than non-manual employee incidence and mortality rates *within* different UK ethnic minority groups. These minority groups also have higher proportions of both manual employees and unemployed than the UK majority population (Harding and Maxwell 1997), a pattern also observed in Sweden (Persson 2005), which would be a compositional factor explaining the finding in some studies of poorer health and higher mortality in some immigrant groups in some countries. Still, this discussion concerning ethnic differences in health, disease and mortality remain largely unresolved. Other studies demonstrate that such ethnic differences remain even after adjustment for socio-economic position. One Swedish study has for instance demonstrated that male and female immigrants from Finland and southern Europe as well as refugees from non-Western countries had high odds ratios of long-term illness, which could not be explained by material deprivation and a sedentary lifestyle (Sundquist and Johansson 1997).

Several studies have demonstrated that immigrants have better health and lower death rates than natives (see above). This may be due to methodological problems

associated with the assessment of data such as under-registration of return migration; that is, many immigrants return to their country of birth while still registered in their country of immigration as they get ill or die in their country of birth (Persson 2005). However, such differences may also be due to 'healthy migrant' effects, which may be explained by the fact that migrants represent a comparatively healthy group not representative of the entire population in the country from which they migrated (Palloni and Morenoff 2001). The healthy migrant pattern may be particularly strong for immigrant populations that migrated in order to get jobs or even better paid jobs in the new country (Lu 2008). This may be the reason why the results of studies comparing immigrants' health with natives' health vary across countries. Patterns of immigrant health and mortality differ somewhat across immigration countries, across immigrant groups and across diagnoses, but there seems to be strong support for the healthy migrant effect. There are two exceptions that are particularly interesting: Irish immigrants in the UK and Finnish immigrants in Sweden, both being characterised by large-scale, unemployment-driven, short-distance labour immigration. This type of migration is less likely to be positively selected, and there are indications of this being one reason for the absence of a healthy migrant effect (Ringbäck-Weitoft *et al.* 1998). The healthy migrant effect will not be directly tested in the article for reasons of feasibility. Our focus is on the effect of conditions during early life in the country of origin, taking into account current socio-economic position in Sweden.

The population in this study consists of individuals from 11 countries of birth, born between 1921 and 1939, who were residents in Sweden between 1980 and 2001. In 1980 Sweden had 8,317,235 inhabitants, of which 625,450 were born in other countries than Sweden. People born in the Nordic countries constituted 55% of the foreign born (Finland 40%, Denmark 7%, Norway 7% and Iceland 1%). Another 14.5% of the foreign born had their origins in Western Europe (Germany 6%), 9% in south-eastern Europe (Yugoslavia 6%), and 4.4% in the Middle East (Turkey 2.3%) (Biterman 2010). The 2009 Public Health Report reveals that the prevalence of poor self-rated health increases with the distance of the country in which the immigrants were born: Sweden 4%, Sweden with both parents born abroad 6%, born in the 15 first EU membership countries 7% (adjusted for social conditions 6%), other parts of Europe 13% (adjusted for social conditions 9%) and countries other than Europe 17% (adjusted for social conditions 10%). In contrast, the death risk of immigrants born in the first 15 EU membership countries is significantly higher than among people born in Sweden while the death risk of immigrants born in countries outside Europe is significantly lower. The death risk of immigrants born in European countries other than the 15 first EU membership countries does not significantly differ from the death risk of people living in Sweden. The two dominant causes of death in Sweden have for decades been cardiovascular diseases and cancer. In the total population the mortality rate among men from cardiovascular diseases (CVD) was 420/100,000 per year and among women 250/100,000 per year in 2004–2006. The corresponding mortality rates for cancer in the same years were 300/100,000 per year among men and 210/100,000 per year among women. The total annual death rate among men in Sweden in 2006 was 1190/100,000 per year and among women 830/100,000 per year (Danielsson 2009).

The main hypothesis of this study is that a significant association exists between early life conditions in the country of birth, i.e., infant mortality rate as well as GDP

per capita at the year of birth in the country of birth, and later life mortality in cardiovascular diseases, cancer (all cancers), and all other causes. A complementary hypothesis is that this significant association is stronger for cardiovascular diseases and all cancers than for all other causes, both because of the support in the literature for associations between early life conditions and cardiovascular diseases and many forms of cancers is strong, and because the 'all other causes' group is a less clear-cut aggregate of many different diagnoses. A second main hypothesis is that current socio-economic conditions in Sweden are significantly associated with mortality in cardiovascular diseases, all cancers, and all other causes, i.e., that lower socio-economic status groups have higher mortality in these three aggregate groups of diagnoses than higher socio-economic status groups.

Objective

The aim of this study is to investigate the associations between, on the one hand, early life conditions, measured primarily as infant mortality rate (IMR) and GDP per capita in the year of birth in the country of birth as well as current socio-economic conditions in adult life, and, on the other hand, mortality in cardiovascular diseases, all cancers, and all other causes of death, for women and men born in different countries, but living in Sweden in the period 1980–2001. The study was ethically approved by the Ethical Committee at Lund University, Sweden.

Study design and setting

Study population and study design

The data-set used for this study is a sample from the Swedish Longitudinal Immigrant Database (SLI). The SLI is a register-based representative database with demographic and socio-economic information on a random sample of about 550,000 Swedish residents from 17 countries including a control group of native Swedes. The longitudinal structure of the data implies that each observation is sorted chronologically by individual, creating individual event histories ending with emigration, death or the end of the observation period in 2001. Detailed information on income from work, unemployment benefits, social welfare payments, housing subsidies, etc. is available from 1980 and, hence, we analyse mortality for the period 1980–2001. The sample used for this study is a panel of male and female individuals from 11 countries of birth, born between 1921 and 1939 and resident in Sweden between 1980 and 2001. The included countries of origin (Chile, Czechoslovakia, Denmark, Finland, Germany, Greece, Italy, Norway, United States, former Yugoslavia and Sweden) were selected due to the availability of information on infant mortality rates and GDP per capita for the period 1921–1939. Before 1921 and 1939–1945, this information is lacking for several countries. For the six remaining birth countries in the database (Ethiopia, Iran, Iraq, Poland, Turkey and Vietnam), information on GDP and/or infant mortality rates is lacking for the whole or part of the period 1921–1939. Before 1945 there was little immigration to Sweden. Due to this fact very few individuals included in the sample grew up in Sweden. For those for which we have information on year of immigration, 97.5% of the sample used for this study immigrated after age 18 and only 0.4% immigrated before age six. Hence, the

individuals included in this study were exposed to the socio-economic conditions of their country of birth during their first years of life. In order to minimise the problem of under-registration of return migration, individuals who have not received any form of income or welfare transfer whatsoever in a year are treated as having left the country and, hence, excluded from the sample.

Dependent variables

The dependent variable is death by cause of death, categorised into three broad groups; cardiovascular disease, all cancers, and all other death causes. Mortality information stems from The Causes of Death Register (*dödsorsaksregistret*), which is kept by the Swedish National Board of Health and Welfare, and covers all deaths of residents in Sweden, irrespective of citizenship. Causes of death in the register are determined from death certification and recorded according to ICD classification.

Independent variables

Infant mortality rates have been collected from a large-scale data-set on infant mortality rates, based on several sources, such as the UN Demographic Yearbooks, national statistics and specific IMR research sources; see Abouharb and Kimball (2007). Annual GDP per capita for the different origin countries stems from Angus Maddison's work on historical statistics (see Maddison 2007), and can be downloaded from www.ggdc.net/maddison. Socioeconomic information is measured annually and stems from official registers such as taxation and education registers kept by Statistics Sweden.

Appendix A and B show the number of individuals and number of deaths by birth country, for men and women respectively, as well as means and standard deviations of the independent variables included in the regressions. The total number of deaths in the data-set is 4031 for men and 2020 for women. Cardiovascular disease mortality accounts for 43% of the male deaths, whereas cancer accounts for 31%. Regarding women, 42% of the deaths were caused by cancers, whereas cardiovascular disease caused 30% of the female deaths. For both men and women, 'other causes' account for less than 30% of the deaths in our data. Independent variables are: *Age group*, in five-year categories; *Civil status* is included as a dummy variable indicating whether an individual is single (reference category), married, divorced or widowed. *Country of birth* is accounted for by dummy variables; *IMR at birth*, the infant mortality rate per 1000 live births in the year and country of birth of the individual; *GDP at birth* measures the de-trended variation in the level of production per capita in the country and year of birth of the individual, measured in 1990 International Geary-Khamis dollars (i.e., fixed prices adjusted for national differences in purchasing power). We de-trended the GDP time-series using the Hodrick-Prescott filter with a lambda value of 100, as frequently recommended for annual data (e.g., Backus and Kehoe 1992); *Income level* measures the total disposable income after taxes, including income from employment, self-employment and capital, as well as social transfers such as pensions, sickness benefits, housing subsidies and income support. Disposable income was categorised into six dummy variables according to income level. *Higher education* is a dichotomous variable indicating that the individual has completed secondary education or higher; and *Welfare recipient* is a

dichotomous variable indicating that the individual has received income support from the social services authorities in the year of observation.

Statistics

The outcome of interest is death or survival in a given year between 1980 and 2001 and, hence, we choose to apply survival analysis using Cox proportional hazards regression. The STATA software statistical program was used.

Results

Table 1 shows the estimation results of three simple models, where the effect of early life conditions and birth cohort on the risk of death from any cause is estimated. The point estimates in the three models show that the relative risk of death in the period 1980–2001 was 150–165% higher for the cohort born in the 1920s, compared to those born in the 1930s. In model 1, infant mortality in the year of birth in the country of birth is included as the only indicator of early life conditions, and Table 1 shows that higher infant mortality rates are associated with a higher risk of death for men, however, there is no significant effect of IMR at birth for women. In model 2, variation from the GDP trend is included as indicator of early life conditions, and being born in a year with unusually high rate of economic growth in the birth country is associated with around 50% lower risk of death, compared to those born in a 'normal' year, the effect being slightly stronger for women compared to men. In model 3, both IMR and GDP at birth are included as indicators of early life conditions, but the effects of birth cohort, IMR and GDP at birth do not change much compared to the results in models 1 and 2. A high economic growth rate in the

Table 1. Estimation of mortality risk, Sweden 1980–2001, for immigrants and native Swedes, born 1921–1939. All cause mortality, men and women analysed separately.

	Model 1[a]		Model 2[b]		Model 3[c]	
	Haz. R.	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Men $n = 18{,}673$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	2.50**	2.35–2.66	2.57**	2.41–2.73	2.56**	2.40–2.72
IMR at birth	1.08**	1.01–1.15			1.07*	1.00–1.14
GDP at birth			0.50**	0.43–0.59	0.51**	0.43–0.59
Women $n = 16{,}022$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	2.58**	2.36–2.83	2.64**	2.41–2.88	2.65**	2.42–2.90
IMR at birth	0.96	0.87–1.06			0.95	0.86–1.05
GDP at birth			0.47**	0.38–0.59	0.47**	0.37–0.59

Note: Cox proportional hazards regression, results displayed as hazard ratios.
**Indicates statistical significance at 5% level, *Indicates statistical significance at 10% level.
[a]Model 1 adjusted for IMR at birth and birth cohort.
[b]Model 2 adjusted for GDP at birth and birth cohort.
[c]Model 3 adjusted for IMR at birth, GDP at birth and birth cohort.
Source: Swedish Longitudinal Immigrant Database (SLI).

year of birth is associated with a lowered death risk for both men and women, and a high infant mortality rate at birth increases the risk of death for men but not for women.

Table 2 shows extended models. In model 4, demographic variables such as age category and civil status are included. The results show that age is positively associated with the risk of death; the higher the age, the higher the hazard ratio. Married individuals display a lower risk compared with singles (significant for men only) whereas divorced and widowed individuals display a higher risk. The effects of birth cohort and early life conditions become weaker when the demographic variables are introduced. The hazard ratio for birth cohort decreases from 2.56 to 1.23 for men and from 2.65 to 1.36 for women, compared to model 3, apparently because birth cohort captures the age effect in models 1–3. The effects of early life conditions become weaker and statistically insignificant, except regarding the effect of GDP at birth for women, which is significant at the 10% level.

In model 5, indicators of the current socio-economic situation in Sweden are included in the estimations. Income is categorised into six income levels and the results show that individuals with higher incomes display lower death risks than individuals with low incomes. The relationship is however not completely linear; the second lowest income category displays hazard ratios that are similar (for women) or higher (for men) compared to the lowest income category. The reason is partly that the poverty indicator 'Welfare recipient' captures some of the income effect for the lowest income category. There may also be a problem of unregistered emigration; some of the individuals in the lowest income category may have some registered income although they have left Sweden and are consequently not in the population at risk. As discussed above, individuals with zero disposable income are omitted from the sample in order to minimise the problem of unregistered emigration. There is a significant negative relationship between educational level and death risk; individuals who have completed secondary education or higher display about 25% lower death risks compared to those who have lower education, significant for both men and women. Regarding recipients of social welfare payments, there are significantly increased risks of death for both men and women. Compared to non-recipients, the point estimates show that the risk is 63% higher for male recipients and 75% higher for female welfare recipients. Hence, model 5 shows that there are clear effects of current socio-economic conditions in Sweden, both for men and women. On the other hand, the results regarding early life conditions are less clear. The effects of IMR at birth are negative in model 5, which is not in the expected direction. A high rate of economic growth in the year of birth is associated with lower risk of death, which is in the expected direction, but this result is significant for women only.

In model 6, birth country indicators are included in the estimations. The introduction of birth country indicators affects the hazard ratios for IMR at birth, which become positive for both men and women, however statistically insignificant. Male immigrants from Denmark, Finland and Norway display higher risks of death compared to native Swedes, controlling for early life conditions, demographic factors, and current socio-economic situation, and immigrants from Greece display lower risk of death. Regarding female immigrants, only those born in Denmark and Norway display higher death risks, whereas Chileans and Greeks display significantly lower risks of death. The results show that the effect of current

Table 2. Estimation of mortality risk, Sweden 1980–2001, for immigrants and native Swedes, born 1921–1939. All cause mortality, men and women analysed separately.

	Model 4[a]		Model 5[b]		Model 6[c]	
	Haz. R.	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Men $n = 18{,}673$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	1.23**	1.10–1.36	1.21**	1.09–1.34	1.21**	1.08–1.35
IMR at birth	1.04	0.97–1.12	0.90**	0.84–0.97	1.10	0.75–1.62
GDP at birth	0.92	0.77–1.10	0.92	0.77–1.11	0.89	0.74–1.07
Age 41–45	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Age 46–50	2.05**	1.38–3.05	2.14**	1.44–3.18	2.08**	1.39–3.09
Age 51–55	2.67**	1.81–3.94	2.83**	1.91–4.18	2.68**	1.81–3.96
Age 56–60	3.70**	2.50–5.49	3.87**	2.61–5.75	3.58**	2.41–5.33
Age 61–65	6.00**	4.01–8.98	6.06**	4.03–9.10	5.48**	3.63–8.26
Age 66–70	8.73**	5.74–13.3	8.13**	5.33–12.4	7.23**	4.71–11.1
Age 71–75	12.40**	7.97–19.3	11.20**	7.15–17.5	9.81**	6.23–15.4
Age 76–79	20.70**	12.9–33.1	18.20**	11.3–29.4	15.80**	9.74–25.8
Single	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Married	0.90**	0.82–0.97	0.94	0.86–1.02	0.89**	0.82–0.97
Divorced	1.45**	1.32–1.59	1.40**	1.27–1.53	1.32**	1.20–1.45
Widowed	1.25**	1.08–1.45	1.25**	1.08–1.44	1.18**	1.02–1.37
Income level 1			*1.00*	*reference*	*1.00*	*reference*
Income level 2			1.18**	1.07–1.30	1.18**	1.08–1.30
Income level 3			0.89**	0.80–0.98	0.90**	0.82–1.00
Income level 4			0.77**	0.68–0.87	0.79**	0.70–0.89
Income level 5			0.60**	0.51–0.70	0.62**	0.53–0.72
Income level 6			0.59**	0.51–0.67	0.61**	0.53–0.70
Higher education			0.74**	0.66–0.83	0.75**	0.66–0.84
Welfare recipient			1.62**	1.44–1.83	1.62**	1.44–1.83
Sweden					*1.00*	*reference*
Chile					0.61	0.29–1.31
Czechoslovakia					1.17	0.80–1.70
Denmark					1.23**	1.07–1.41
Finland					1.46**	1.26–1.69
Germany					0.95	0.76–1.19
Greece					0.60**	0.45–0.81
Italy					0.97	0.72–1.31
Norway					1.26**	1.11–1.43
USA					1.03	0.78–1.38
f. Yugoslavia					0.98	0.67–1.44
Women $n = 16{,}022$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	1.36**	1.17–1.59	1.35**	1.15–1.57	1.28**	1.09–1.50
IMR at birth	0.91	0.81–1.02	0.80**	0.72–0.89	1.42	0.85–2.37
GDP at birth	0.79*	0.61–1.01	0.79*	0.61–1.02	0.80*	0.61–1.04
Age 41–45	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Age 46–50	1.36	0.83–2.24	1.42	0.86–2.33	1.37	0.83–2.26
Age 51–55	1.72**	1.06–2.80	1.78**	1.09–2.90	1.68**	1.03–2.75
Age 56–60	2.18**	1.33–3.56	2.17**	1.32–3.57	2.03**	1.23–3.34
Age 61–65	3.27**	1.96–5.46	3.13**	1.87–5.25	2.87**	1.70–4.84

Table 2 (*Continued*)

	Model 4[a]		Model 5[b]		Model 6[c]	
	Haz. R.	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Age 66–70	4.78**	2.79–8.20	4.20**	2.43–7.25	3.79**	2.18–6.59
Age 71–75	6.51**	3.65–11.6	5.58**	3.11–10.0	5.02**	2.77–9.10
Age 76–79	9.68**	5.21–18.0	8.18**	4.36–15.3	7.26**	3.83–13.8
Single	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Married	0.96	0.85–1.09	0.98	0.86–1.11	0.93	0.81–1.06
Divorced	1.26**	1.10–1.44	1.28**	1.11–1.46	1.19**	1.04–1.37
Widowed	1.19**	1.04–1.38	1.25**	1.08–1.44	1.19**	1.03–1.39
Income level 1			*1.00*	*reference*	*1.00*	*reference*
Income level 2			1.05	0.95–1.17	1.06	0.95–1.18
Income level 3			0.81**	0.70–0.93	0.82**	0.71–0.94
Income level 4			0.70**	0.57–0.86	0.71**	0.58–0.88
Income level 5			0.63**	0.47–0.85	0.65**	0.48–0.87
Income level 6			0.61**	0.45–0.83	0.63**	0.46–0.85
Higher education			0.75**	0.63–0.90	0.75**	0.62–0.90
Welfare recipient			1.75**	1.46–2.10	1.82**	1.52–2.19
Sweden					*1.00*	*reference*
Chile					0.27**	0.10–0.75
Czechoslovakia					0.85	0.51–1.44
Denmark					1.19*	0.97–1.46
Finland					1.06	0.87–1.30
Germany					0.98	0.73–1.30
Greece					0.46**	0.31–0.70
Italy					0.95	0.61–1.49
Norway					1.19**	1.00–1.42
USA					0.83	0.52–1.31
f. Yugoslavia					0.69	0.42–1.14

Note: Cox proportional hazards regression, results displayed as hazard ratios.
**Indicates statistical significance at 5% level, *Indicates statistical significance at 10% level.
[a]Model 4 adjusted for IMR at birth, GDP at birth, birth cohort, age and civil status.
[b]Model 5 adjusted for IMR at birth, GDP at birth, birth cohort, age, civil status, income, education and welfare.
[c]Model 6 adjusted for IMR at birth, GDP at birth, birth cohort, age, civil status, income, education, welfare and birth country.
Source: Swedish Longitudinal Immigrant Database (SLI).

socio-economic conditions on all cause mortality is stronger and more straightforward compared to the effect of early life conditions.

Table 3 shows model 5 estimated by cause of death. Contrary to our expectations, cardiovascular mortality is negatively associated with infant mortality in the country of birth in the year of birth, both for men and women. The effect of GDP at birth is statistically insignificant. The effects of age, civil status and socio-economic status are stronger for men than for women.

Table 3 shows that cancer mortality is positively associated with age, whereas other associations are rather weak. Welfare recipients display a 40–50% higher risk compared to non-recipients, significant for men and women. For women, higher income is weakly associated with lower risk of death from cancer, whereas men display the highest risk in the second-lowest income category. Higher education is

Table 3. Estimation of mortality risk, Sweden 1980–2001, for immigrants and native Swedes, born 1921–1939. Mortality by cause of death, men and women analysed separately.

	Cardiovascular		Cancer		Other causes	
Model 5[a]	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Men $n = 18{,}673$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	1.30**	1.10–1.52	1.07	0.89–1.29	1.24**	1.00–1.54
IMR at birth	0.75**	0.66–0.85	0.97	0.85–1.10	1.08	0.94–1.23
GDP at birth	0.97	0.73–1.29	0.90	0.65–1.24	0.89	0.63–1.26
Age 41–45	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Age 46–50	2.90**	1.31–6.40	2.16*	0.97–4.85	1.69*	0.96–2.98
Age 51–55	5.48**	2.53–11.8	3.29**	1.50–7.24	1.37	0.77–2.44
Age 56–60	7.17**	3.29–15.6	5.73**	2.60–12.6	1.54	0.85–2.78
Age 61–65	12.00**	5.44–26.5	8.99**	4.01–20.1	2.16**	1.16–4.02
Age 66–70	16.70**	7.41–37.6	13.20**	5.73–30.3	2.47**	1.27–4.79
Age 71–75	22.70**	9.80–52.7	17.30**	7.24–41.5	3.71**	1.80–7.66
Age 76–79	43.70**	18.2–105.1	22.80**	8.99–58.0	5.70**	2.57–12.6
Single	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Married	0.94	0.83–1.07	1.06	0.92–1.23	0.79**	0.66–0.93
Divorced	1.41**	1.23–1.62	1.12	0.94–1.33	1.69**	1.42–2.00
Widowed	1.33**	1.07–1.65	1.25*	0.96–1.63	1.11	0.82–1.51
Income level 1	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Income level 2	1.29**	1.12–1.50	1.20*	1.00–1.43	1.03	0.87–1.22
Income level 3	1.01	0.87–1.18	1.01	0.84–1.22	0.63**	0.52–0.76
Income level 4	0.81**	0.68–0.98	1.01	0.82–1.25	0.52**	0.42–0.65
Income level 5	0.63**	0.50–0.80	0.92	0.71–1.19	0.31**	0.22–0.43
Income level 6	0.54**	0.43–0.68	0.93	0.73–1.17	0.36**	0.27–0.48
Higher education	0.72**	0.60–0.87	0.74**	0.61–0.90	0.76**	0.59–0.97
Welfare recipient	1.73**	1.44–2.08	1.41**	1.11–1.78	1.66**	1.33–2.07
Women $n = 16{,}022$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	1.76**	1.31–2.36	1.17	0.93–1.48	1.29*	0.96–1.75
IMR at birth	0.82**	0.68–0.98	0.85**	0.73–0.99	0.72**	0.59–0.88
GDP at birth	0.83	0.51–1.37	0.82	0.56–1.19	0.72	0.44–1.18
Age 41–45	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Age 46–50	0.99	0.31–3.15	1.37	0.68–2.78	1.79	0.73–4.39
Age 51–55	1.48	0.50–4.38	1.91*	0.96–3.81	1.84	0.75–4.50
Age 56–60	2.06	0.70–6.10	2.44**	1.21–4.94	1.94	0.78–4.86
Age 61–65	3.37**	1.10–10.3	3.35**	1.60–7.00	2.76**	1.06–7.18
Age 66–70	5.76**	1.80–18.4	3.58**	1.63–7.85	3.93**	1.43–10.8
Age 71–75	8.21**	2.42–27.9	4.38**	1.86–10.3	5.08**	1.70–15.2
Age 7679	12.40**	3.42–44.6	4.83**	1.87–12.5	9.39**	2.92–30.2
Single	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Married	0.95	0.75–1.19	0.95	0.79–1.14	1.05	0.81–1.35
Divorced	1.23*	0.96–1.58	1.03	0.84–1.27	1.80**	1.39–2.34
Widowed	1.23*	0.96–1.58	1.12	0.89–1.40	1.50**	1.13–2.00
Income level 1	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Income level 2	1.22**	1.01–1.48	0.98	0.83–1.16	0.98	0.80–1.21
Income level 3	0.83	0.63–1.08	0.84	0.69–1.04	0.73**	0.56–0.95

Table 3 (*Continued*)

	Cardiovascular		Cancer		Other causes	
Model 5[a]	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Income level 4	0.63**	0.41–0.97	0.78*	0.59–1.04	0.62**	0.42–0.91
Income level 5	0.66	0.36–1.20	0.69*	0.45–1.05	0.52**	0.29–0.93
Income level 6	0.48**	0.24–0.96	0.80	0.53–1.19	0.42**	0.22–0.81
Higher education	0.62**	0.42–0.90	0.82	0.64–1.06	0.76	0.54–1.08
Welfare recipient	1.45**	1.01–2.08	1.51**	1.14–2.02	2.49**	1.83–3.39

Note: Cox proportional hazards regression, results displayed as hazard ratios.
**Indicates statistical significance at 5% level, *Indicates statistical significance at 10% level.
[a]Model 5 adjusted for IMR at birth, GDP at birth, birth cohort, age, civil status, income, education and welfare.
Source: Swedish Longitudinal Immigrant Database (SLI).

associated with lower risk of death from cancer, but statistically significant for men only. The effects of early life conditions are insignificant, except for IMR at birth, which is negatively associated with cancer mortality for women.

The third column in Table 3 shows that death from causes other than cardiovascular disease and cancers are strongly associated with income level, for men as well as for women. Welfare recipients display significantly higher risks than non-recipients and higher education is associated with lower risk, significant for men only. Both men and women display a cohort effect, where hazard ratios are higher for those born in the 1920s compared to those born in the 1930s. The effects of early life conditions are insignificant, except for IMR at birth, which, for women only, shows a negative association with death from causes other than cardiovascular disease and cancers.

Table 4 shows model 6 estimated by cause of death. Comparing model 5 and model 6, we can see that the inclusion of country of birth affects the hazard ratios for our measures of early life conditions, in particular for IMR at birth. The effect of IMR at birth on cancer mortality is significantly positive for both men and women. For cardiovascular disease and other causes of death, our measures of early life conditions are insignificant. Regarding current socio-economic conditions, however, hazard ratios are only marginally affected by the inclusion of birth country indicators.

In sum, our estimation results show that the effects of early life conditions on mortality disappear when we control for current socio-economic conditions. Our largest model shows that a high level of infant mortality in the year of birth is associated with higher risk of death from cancer, significant for both men and women. Otherwise, there are no significant effects of our measures of early life conditions. The effects of current socio-economic conditions, on the other are clear and straightforward. A higher education implies lower risk of death, individuals who receive social welfare payments display significantly higher risk of death and individuals with high incomes have lower risk of death compared to those with low incomes, with only a few exceptions, e.g., income level is not significantly associated with cancer mortality for men.

Table 4. Estimation of mortality risk, Sweden 1980–2001, for immigrants and native Swedes, born 1921–1939. Mortality by cause of death, men and women analysed separately.

	Cardiovascular		Cancer		Other causes	
Model 6[a]	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Men $n = 18{,}673$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	1.30**	1.10–1.54	1.01	0.84–1.23	1.31**	1.05–1.63
IMR at birth	0.98	0.54–1.80	2.07**	1.06–4.07	0.60	0.29–1.26
GDP at birth	0.90	0.67–1.22	0.90	0.65–1.25	0.87	0.60–1.25
Age 41–45	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Age 46–50	2.78**	1.26–6.15	2.07*	0.92–4.64	1.71*	0.97–3.03
Age 51–55	5.09**	2.35–11.0	3.02**	1.37–6.64	1.41	0.79–2.50
Age 56–60	6.47**	2.97–14.1	5.08**	2.30–11.2	1.58	0.87–2.86
Age 61–65	10.50**	4.76–23.4	7.65**	3.39–17.3	2.23**	1.19–4.18
Age 66–70	14.40**	6.34–32.6	10.80**	4.64–25.1	2.58**	1.32–5.07
Age 71–75	19.30**	8.25–45.2	13.80**	5.69–33.5	3.91**	1.88–8.15
Age 76–79	36.80**	15.1–89.3	17.50**	6.79–45.3	6.18**	2.75–13.9
Single	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Married	0.88*	0.77–1.00	1.05	0.90–1.22	0.74**	0.62–0.88
Divorced	1.32**	1.14–1.51	1.09	0.92–1.30	1.56**	1.31–1.86
Widowed	1.23*	0.99–1.53	1.22	0.93–1.59	1.04	0.77–1.42
Income level 1	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Income level 2	1.30**	1.13–1.51	1.19*	0.99–1.43	1.03	0.87–1.22
Income level 3	1.04	0.89–1.22	0.99	0.82–1.20	0.65**	0.54–0.79
Income level 4	0.85*	0.71–1.02	1.00	0.81–1.23	0.54**	0.43–0.68
Income level 5	0.66**	0.52–0.84	0.91	0.70–1.18	0.32**	0.23–0.46
Income level 6	0.58**	0.46–0.72	0.91	0.72–1.15	0.39**	0.29–0.52
Higher education	0.74**	0.61–0.90	0.73**	0.59–0.89	0.78**	0.61–0.99
Welfare recipient	1.74**	1.45–2.09	1.43**	1.13–1.80	1.64**	1.32–2.03
Sweden	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Chile	0.54	0.16–1.79	0.22**	0.06–0.86	2.40	0.57–10.2
Czechoslovakia	1.18	0.65–2.14	0.71	0.37–1.36	2.12**	1.03–4.34
Denmark	1.26**	1.02–1.56	1.12	0.87–1.43	1.30*	0.98–1.73
Finland	1.69**	1.35–2.12	0.93	0.71–1.22	1.88**	1.42–2.48
Germany	0.93	0.65–1.33	0.77	0.52–1.14	1.23	0.80–1.91
Greece	0.63**	0.41–0.99	0.43**	0.26–0.73	0.85	0.48–1.49
Italy	1.01	0.63–1.61	0.81	0.48–1.34	1.03	0.55–1.94
Norway	1.29**	1.06–1.56	1.24*	0.99–1.56	1.22	0.94–1.58
USA	0.85	0.52–1.39	0.93	0.57–1.51	1.53	0.90–2.58
f. Yugoslavia	0.84	0.46–1.54	0.47**	0.24–0.93	2.73**	1.33–5.63
Women $n = 16{,}022$						
Cohort 1930s	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Cohort 1920s	1.71**	1.26–2.33	1.05	0.83–1.34	1.29	0.95–1.74
IMR at birth	1.10	0.42–2.86	2.19*	0.99–4.86	0.95	0.36–2.54
GDP at birth	0.81	0.47–1.39	0.87	0.60–1.26	0.69	0.41–1.15
Age 41–45	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Age 46–50	0.97	0.30–3.07	1.32	0.65–2.68	1.73	0.70–4.25
Age 51–55	1.42	0.48–4.21	1.78	0.89–3.56	1.74	0.71–4.27
Age 56–60	1.96	0.66–5.82	2.23**	1.10–4.54	1.81	0.72–4.55
Age 61–65	3.17**	1.03–9.78	2.98**	1.41–6.30	2.52*	0.96–6.64

Table 4 (*Continued*)

	Cardiovascular		Cancer		Other causes	
Model 6[a]	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*	*Haz. R.*	*Conf. int.*
Age 66–70	5.40**	1.66–17.5	3.09**	1.39–6.88	3.55**	1.27–9.94
Age 71–75	7.74**	2.25–26.6	3.74**	1.56–8.95	4.56**	1.51–13.8
Age 76–79	11.67**	3.17–42.9	4.01**	1.52–10.6	8.36**	2.55–27.4
Single	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Married	0.86	0.68–1.09	0.96	0.79–1.16	0.95	0.73–1.24
Divorced	1.08	0.83–1.39	1.02	0.83–1.27	1.66**	1.27–2.16
Widowed	1.13	0.87–1.46	1.12	0.88–1.41	1.40**	1.04–1.87
Income level 1	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Income level 2	1.24**	1.03–1.50	0.98	0.83–1.16	0.99	0.81–1.21
Income level 3	0.85	0.65–1.12	0.85	0.69–1.04	0.75**	0.57–0.98
Income level 4	0.66*	0.43–1.02	0.78*	0.58–1.04	0.64**	0.43–0.95
Income level 5	0.69	0.38–1.26	0.69*	0.45–1.05	0.55**	0.30–0.98
Income level 6	0.52*	0.26–1.03	0.79	0.52–1.18	0.44**	0.23–0.85
Higher education	0.64**	0.44–0.93	0.77**	0.59–1.00	0.80	0.56–1.14
Welfare recipient	1.52**	1.06–2.18	1.58**	1.18–2.11	2.56**	1.88–3.48
Sweden	*1.00*	*reference*	*1.00*	*reference*	*1.00*	*reference*
Chile	0.39	0.06–2.59	0.16**	0.03–0.75	0.37	0.05–2.62
Czechoslovakia	1.08	0.40–2.92	0.68	0.31–1.49	0.89	0.32–2.48
Denmark	1.22	0.83–1.79	1.11	0.82–1.51	1.30	0.88–1.90
Finland	1.63**	1.12–2.37	0.73*	0.53–1.01	1.12	0.76–1.65
Germany	1.30	0.75–2.25	0.84	0.54–1.29	0.89	0.50–1.58
Greece	0.37**	0.16–0.86	0.27**	0.14–0.54	0.99	0.50–1.97
Italy	0.89	0.37–2.15	0.92	0.48–1.74	0.97	0.39–2.40
Norway	1.25	0.91–1.72	1.11	0.84–1.46	1.25	0.90–1.72
USA	0.17*	0.02–1.20	1.13	0.64–1.97	0.80	0.31–2.01
f. Yugoslavia	1.06	0.42–2.68	0.35**	0.16–0.78	1.14	0.44–2.96

Note: Cox proportional hazards regression, results displayed as hazard ratios.
**Indicates statistical significance at 5% level, *Indicates statistical significance at 10% level.
[a]Model 6 adjusted for IMR at birth, GDP at birth, birth cohort, age, civil status, income, education, welfare and birth country.
Source: Swedish Longitudinal Immigrant Database (SLI).

Discussion

Most effects of early life conditions on mortality disappear after adjustments for current socio-economic conditions. The largest model including demographic factors, early life exposures, socio-economic factors and country of birth show that a high infant mortality rate (IMR) in the year of birth in the country of birth is significantly associated with cancer mortality among men and (at 5.4% significance level) among women. Otherwise, we find no significant effects of the two early life variables IMR at birth and GDP at birth on total, CVD or all other diagnoses mortality. In contrast, the effects of current socio-economic conditions in Sweden are significant and robust. Higher education and high income are associated with lower mortality, while being a welfare recipient is associated with higher mortality. A few exceptions may be observed such as, for instance, the fact that income is not significantly associated with cancer mortality among men.

Men born in Denmark, Finland and Norway as well as women born in Denmark and Norway display significantly higher hazard rate ratios of total mortality than men and women born in Sweden, respectively, in the final models including both the early life factors and current socio-economic position. Even more persistent results have been observed for second and third generation men and women of Irish descent living in the United Kingdom who had higher total mortality rates than the UK population (Harding and Balarajan 1996, 2001). These results were hard to explain (Haskey 1996). In contrast, our study also shows that men born in Greece as well as women born in Greece and Chile display significantly lower hazard rate ratios of total mortality than men and women born in Sweden, respectively.

In the final models with all variables included, men born in Denmark, Finland and Norway have significantly higher (at the 5% significance level) CVD mortality than men born in Sweden. Women born in Finland also have significantly higher CVD mortality than women born in Sweden. In contrast, men born in Greece as well as women born in Greece have significantly lower CVD mortality. Men born in Chile as well as women born in Chile and Greece have significantly lower cancer mortality than men and women born in Sweden, respectively. Men who were born in Czechoslovakia and Finland display higher all other cause mortality than men born in Sweden.

As hypothesised, we find significant positive effects of infant mortality rate at birth in country of birth on cancer mortality; a higher infant mortality rate in the year and country of birth is associated with higher cancer mortality later in life. In contrast, no significant association is observed between GDP at birth in country of birth and cancer mortality. We find no significant effects of either IMR at birth or GDP at birth in country of birth on CVD mortality. Furthermore, we find no significant effects of either IMR at birth or GDP at birth in country of birth on all other causes mortality. However, although other diseases such as respiratory and allergic diseases (Strachan and Sheikh 2004) and some neuropsychiatric outcomes (Factor-Litvak and Susser 2004) are associated with early life conditions, all the other causes of death group are very heterogeneous.

Infant mortality rate in the year of birth in the country of birth seems to have an unclear association with CVD mortality in our study. This result is clearly discordant with findings in the previous literature (Barker 1995, Lawlor *et al.* 2004, Potischman *et al.* 2004). Both CVD mortality and cancer mortality are well established in the literature as later life diseases with early life determinants and risk factors (Lawlor *et al.* 2004, Potischman *et al.* 2004). Furthermore, a previous study of immigrants from West Africa and the Caribbean has shown higher mortality rates from cerebrovascular diseases prior as well as persistently after migration to the United Kingdom, which in that study was attributed to genetic factors (Wild and McKeigue 1997). The absence of an effect of IMR on cardiovascular mortality in our study may be due to a healthy migrant selection effect or, alternatively, to other selection effects, such as selective return migration. For instance, one US study showed that Mexican return migrants from the United States were shorter than those who stayed, height being associated with CVD as well as with early life conditions (Crimmins *et al.* 2005). However, such selection would probably also counteract the effect on cancer mortality. Actually, we find no evidence of an overall healthy migrant effect in Sweden. Greek and Chilean immigrants seem to be somewhat healthier than native

Swedes, whereas most other groups seem to be similar to native Swedes and, in particular, Nordic immigrants seem to be less healthy compared with Swedes.

Current socio-economic conditions appear to have a clear effect on mortality in the expected direction, with the exception of cancer mortality in most income levels. In this study socio-economic status is measured using educational level and disposable income. Socio-economic status is often also measured according to occupational status (Lynch and Kaplan 2000). However, this third option was not possible to include in the analyses of this study. In addition, occupational status is highly correlated with levels of income and education.

The data-set analysed in this study did not include diet, smoking and other health-related lifestyle factors. Mediterranean diet, which would be presumed to be more prevalent among participants born in Greece and Chile but also among participants born in Italy and Yugoslavia, would for instance be a lifestyle factor protecting against both CVD (Bendinelli *et al.* 2011) and cancer (Couto *et al.* 2011) mortality. Other studies have documented earlier migrants to be more obese, to have greater levels of cholesterol, to be less physically active, and to smoke more cigarettes than those with a shorter duration of residence (Goel *et al.* 2004, Gadd, *et al.* 2005, Wilkinson *et al.* 2005).

The most obvious health policy implication from this study is that health policy should focus on the reduction of the effects of current socio-economic risk factors in the country of immigration, i.e., in our study Sweden. This may include measures to increase the level of education that would in the next step widen labour market opportunities for immigrants, but it also includes direct policy measures to increase immigrants' access to employment. Further epidemiological studies of early life risk factors are needed in order to infer any health policy recommendation, mostly because of the restrictions on interpretation imposed by the aggregate nature of IMR and GDP per capita. Still, some of the findings, particularly the significant hazard rate ratio 2.07 (1.06–4.04) for men and almost significant hazard rate ratio 2.19 (0.99–4.86) for women for the association between IMR at birth and cancer mortality suggest that policy-makers should set goals for health policy that take into account early life experiences.

Strengths and limitations

Selection bias is less likely because the study population is a random sample from register data. In addition, we have reduced the problem of under-registration of return migration, i.e., the fact that some immigrants in Sweden may have return migrated to their countries of birth without this event of migration being registered, through the elimination of individuals who have no registered income at all and who can be assumed to have left Sweden.

Indicators of early life conditions at the micro-/individual level are simply not available for data on large immigrant populations. The use of aggregate country level data such as IMR and GDP per capita at birth, as in this study, is mostly the only option available, and even studies using this kind of aggregate data are still scarce.

Misclassification according to country of birth is not likely. Misclassifications of diagnoses are also less likely due to the high aggregation level of diagnoses. The GDP per capita and IMR, both at birth, may be very crude measures of early life conditions, mostly due to the variety of development and economic prosperity *within*

countries, especially large countries, in the year of birth. However, they are the best internationally comparable measures we have. Many important confounders have been taken into account in the multiple Cox regression survival analyses, although other important confounders, most importantly lifestyle factors such as for instance smoking, exercise and diet, have not been taken into account due to lack of these variables in the data material.

The longitudinal study design using Cox regression survival analyses may be considered a strength of this study.

Conclusions

Socioeconomic conditions in Sweden are more strongly associated with mortality than early life indicators IMR and GDP per capita in the year of birth in the country of origin. This finding has health policy and other policy implications.

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Appendix A. Descriptive statistics, men

	Chile		Czechoslovakia		Denmark		Finland		Germany		Greece	
Covariates	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.
Cohort 1920s	0.30	0.46	0.39	0.49	0.45	0.50	0.35	0.48	0.31	0.46	0.25	0.44
IMR at birth	242	16.0	131	18.0	741	8.1	78	11.1	831	19.0	110	14.1
GDP at birth	60	3510	121	1871	870	2120	520	1480	−41	3451	971	2171
Age 41–45	0.05	0.21	0.04	0.20	0.04	0.18	0.05	0.23	0.06	0.24	0.06	0.24
Age 46–50	0.12	0.33	0.12	0.32	0.10	0.31	0.13	0.34	0.14	0.35	0.16	0.37
Age 51–55	0.19	0.39	0.20	0.40	0.18	0.38	0.20	0.40	0.21	0.40	0.23	0.42
Age 56–60	0.24	0.43	0.25	0.43	0.24	0.43	0.25	0.43	0.24	0.43	0.25	0.43
Age 61–65	0.22	0.41	0.21	0.41	0.22	0.42	0.21	0.40	0.20	0.40	0.19	0.39
Age 66–70	0.12	0.33	0.13	0.34	0.14	0.35	0.11	0.31	0.10	0.31	0.08	0.28
Age 71–75	0.05	0.22	0.05	0.22	0.07	0.25	0.04	0.20	0.04	0.20	0.02	0.15
Age 76–79	0.01	0.09	0.01	0.09	0.01	0.11	0.01	0.08	0.01	0.08	0.00	0.05
Single	0.05	0.21	0.08	0.28	0.13	0.34	0.13	0.34	0.17	0.37	0.07	0.25
Married	0.74	0.44	0.74	0.44	0.61	0.49	0.59	0.49	0.63	0.48	0.84	0.37
Divorced	0.18	0.38	0.15	0.36	0.22	0.41	0.25	0.43	0.16	0.37	0.08	0.27
Widowed	0.04	0.19	0.02	0.15	0.04	0.20	0.03	0.18	0.04	0.19	0.02	0.14
Income level 1	0.25	0.43	0.11	0.31	0.17	0.38	0.18	0.38	0.15	0.36	0.21	0.41
Income level 2	0.23	0.42	0.17	0.38	0.20	0.40	0.23	0.42	0.12	0.32	0.30	0.46
Income level 3	0.26	0.44	0.19	0.39	0.26	0.44	0.29	0.45	0.23	0.42	0.31	0.46
Income level 4	0.14	0.35	0.16	0.37	0.16	0.37	0.16	0.37	0.19	0.39	0.12	0.32
Income level 5	0.07	0.25	0.10	0.30	0.08	0.28	0.07	0.26	0.13	0.33	0.04	0.19
Income level 6	0.06	0.23	0.27	0.44	0.12	0.33	0.06	0.24	0.19	0.39	0.02	0.15
Higher education	0.16	0.36	0.39	0.49	0.10	0.30	0.04	0.20	0.15	0.36	0.04	0.20
Welfare recipient	0.32	0.47	0.19	0.40	0.20	0.40	0.23	0.42	0.17	0.38	0.20	0.40
N individuals	746		503		1608		2177		899		1095	
Number of deaths	109		119		393		608		147		46	
Cardiovascular	34		47		175		297		59		46	
Cancers	42		42		131		144		52		37	
Other causes	746		30		87		167		36		27	

Appendix A. (*Continued*)

	Italy		Norway		USA		Yugoslavia		Sweden	
Covariates	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.
Cohort 1920s	0.34	0.47	0.43	0.50	0.38	0.49	0.25	0.44	0.34	0.47
IMR at birth	110	10.1	46	5.1	76	10.0	146	9.1	50	7.0
GDP at birth	261	1660	451	1731	−1620	5750	−20	720	290	1540
Age 41–45	0.06	0.23	0.04	0.19	0.04	0.21	0.06	0.23	0.06	0.24
Age 46–50	0.13	0.34	0.10	0.30	0.11	0.32	0.15	0.35	0.14	0.34
Age 51–55	0.20	0.40	0.17	0.38	0.19	0.39	0.21	0.41	0.19	0.40
Age 56–60	0.25	0.43	0.24	0.43	0.24	0.43	0.24	0.43	0.24	0.42
Age 61–65	0.20	0.40	0.22	0.42	0.21	0.41	0.20	0.40	0.20	0.40
Age 66–70	0.11	0.31	0.14	0.35	0.13	0.34	0.10	0.30	0.11	0.31
Age 71–75	0.05	0.21	0.07	0.25	0.06	0.24	0.03	0.18	0.05	0.22
Age 76–79	0.01	0.08	0.01	0.12	0.01	0.11	0.01	0.07	0.01	0.11
Single	0.19	0.39	0.15	0.36	0.13	0.34	0.08	0.27	0.33	0.47
Married	0.64	0.48	0.60	0.49	0.68	0.47	0.70	0.46	0.40	0.49
Divorced	0.14	0.35	0.21	0.41	0.16	0.37	0.19	0.40	0.24	0.43
Widowed	0.02	0.14	0.03	0.18	0.03	0.16	0.03	0.16	0.03	0.17
Income level 1	0.14	0.35	0.16	0.37	0.26	0.44	0.17	0.37	0.09	0.28
Income level 2	0.18	0.38	0.19	0.39	0.14	0.34	0.30	0.46	0.14	0.35
Income level 3	0.31	0.46	0.20	0.40	0.14	0.34	0.30	0.46	0.24	0.43
Income level 4	0.18	0.39	0.15	0.35	0.13	0.34	0.15	0.36	0.20	0.40
Income level 5	0.09	0.29	0.10	0.29	0.09	0.29	0.05	0.22	0.12	0.33
Income level 6	0.10	0.30	0.21	0.41	0.24	0.43	0.03	0.18	0.20	0.40
Higher education	0.07	0.26	0.16	0.37	0.44	0.50	0.04	0.20	0.16	0.37
Welfare recipient	0.19	0.39	0.18	0.38	0.17	0.38	0.23	0.42	0.18	0.39
N individuals	620		1417		404		1736		7468	
Number of deaths	116		305		56		386		1682	
Cardiovascular	49		139		19		128		731	
Cancers	47		94		20		106		540	
Other causes	20		72		17		152		411	

Appendix B. Descriptive statistics, women

	Chile		Czechoslovakia		Denmark		Finland		Germany		Greece	
Variable	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.
Cohort 1920s	0.36	0.48	0.42	0.49	0.37	0.48	0.34	0.47	0.34	0.47	0.28	0.45
IMR at birth	2430	170	1320	181	730	81	780	111	851	200	1100	150
GDP at birth	161	3480	121	1861	1081	2180	520	1480	−381	3311	770	2021
Age 41–45	0.03	0.17	0.04	0.20	0.05	0.21	0.05	0.22	0.05	0.21	0.06	0.23
Age 46–50	0.09	0.29	0.11	0.31	0.12	0.33	0.13	0.34	0.13	0.34	0.15	0.36
Age 51–55	0.17	0.37	0.18	0.39	0.19	0.39	0.20	0.40	0.20	0.40	0.22	0.42
Age 56–60	0.24	0.43	0.23	0.42	0.23	0.42	0.24	0.43	0.23	0.42	0.24	0.42
Age 61–65	0.24	0.43	0.22	0.41	0.21	0.41	0.21	0.41	0.21	0.40	0.19	0.40
Age 66–70	0.15	0.36	0.14	0.35	0.13	0.33	0.12	0.32	0.12	0.33	0.10	0.30
Age 71–75	0.07	0.25	0.07	0.25	0.06	0.24	0.05	0.22	0.05	0.23	0.03	0.18
Age 76–79	0.01	0.11	0.01	0.12	0.01	0.11	0.01	0.10	0.01	0.10	0.01	0.08
Single	0.10	0.30	0.03	0.18	0.10	0.30	0.11	0.31	0.15	0.35	0.03	0.18
Married	0.59	0.49	0.66	0.47	0.53	0.50	0.49	0.50	0.55	0.50	0.80	0.40
Divorced	0.15	0.35	0.19	0.39	0.23	0.42	0.29	0.45	0.20	0.40	0.05	0.22
Widowed	0.16	0.37	0.11	0.31	0.14	0.35	0.12	0.32	0.11	0.31	0.11	0.31
Income level 1	0.35	0.48	0.27	0.44	0.38	0.49	0.28	0.45	0.37	0.48	0.31	0.46
Income level 2	0.33	0.47	0.25	0.43	0.29	0.45	0.31	0.46	0.25	0.44	0.34	0.47
Income level 3	0.20	0.40	0.20	0.40	0.18	0.39	0.25	0.43	0.22	0.41	0.25	0.44
Income level 4	0.07	0.26	0.11	0.31	0.08	0.27	0.10	0.30	0.10	0.30	0.07	0.26
Income level 5	0.03	0.16	0.06	0.24	0.03	0.18	0.04	0.19	0.04	0.20	0.01	0.12
Income level 6	0.01	0.12	0.11	0.31	0.03	0.17	0.03	0.16	0.03	0.17	0.00	0.07
Higher education	0.08	0.27	0.34	0.47	0.10	0.30	0.07	0.25	0.14	0.35	0.01	0.11
Welfare recipient	0.38	0.48	0.19	0.39	0.18	0.39	0.19	0.39	0.16	0.37	0.19	0.40
N individuals	942		414		1218		2315		868		837	
Number of deaths	62		59		173		318		113		44	
Cardiovascular	15		17		47		123		37		8	
Cancers	35		30		78		111		52		16	
Other causes	12		12		48		84		24		20	

Appendix B. (*Continued*)

	Italy		Norway		USA		Yugoslavia		Sweden	
Variable	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.	Mean	St. dev.
Cohort 1920s	0.45	0.50	0.43	0.49	0.38	0.48	0.33	0.47	0.35	0.48
IMR at birth	1130	110	461	50	751	100	1460	90	501	71
GDP at birth	−90	1531	461	1710	−1380	6160	21	701	351	1541
Age 41–45	0.04	0.20	0.03	0.18	0.05	0.21	0.05	0.22	0.06	0.24
Age 46–50	0.11	0.31	0.10	0.30	0.12	0.32	0.12	0.33	0.13	0.34
Age 51–55	0.18	0.39	0.18	0.38	0.21	0.40	0.18	0.39	0.19	0.39
Age 56–60	0.24	0.43	0.23	0.42	0.24	0.42	0.23	0.42	0.23	0.42
Age 61–65	0.21	0.41	0.22	0.42	0.21	0.40	0.21	0.41	0.20	0.40
Age 66–70	0.14	0.34	0.15	0.36	0.13	0.34	0.13	0.34	0.12	0.32
Age 71–75	0.06	0.24	0.07	0.25	0.05	0.23	0.06	0.23	0.06	0.24
Age 76–79	0.01	0.11	0.01	0.12	0.01	0.09	0.01	0.11	0.02	0.12
Single	0.14	0.34	0.13	0.33	0.09	0.29	0.05	0.23	0.37	0.48
Married	0.64	0.48	0.50	0.50	0.62	0.49	0.61	0.49	0.29	0.45
Divorced	0.09	0.29	0.23	0.42	0.18	0.38	0.22	0.41	0.24	0.43
Widowed	0.13	0.34	0.14	0.34	0.11	0.31	0.12	0.32	0.10	0.30
Income level 1	0.33	0.47	0.37	0.48	0.38	0.49	0.33	0.47	0.28	0.45
Income level 2	0.30	0.46	0.29	0.46	0.18	0.38	0.37	0.48	0.25	0.44
Income level 3	0.24	0.43	0.19	0.39	0.18	0.39	0.21	0.41	0.22	0.42
Income level 4	0.08	0.27	0.08	0.27	0.11	0.32	0.06	0.23	0.13	0.33
Income level 5	0.02	0.15	0.04	0.19	0.06	0.23	0.02	0.12	0.06	0.24
Income level 6	0.02	0.13	0.03	0.18	0.09	0.28	0.01	0.10	0.06	0.23
Higher education	0.04	0.21	0.07	0.25	0.42	0.49	0.02	0.15	0.15	0.36
Welfare recipient	0.19	0.39	0.16	0.37	0.16	0.36	0.22	0.42	0.17	0.37
N individuals	311		1251		273		1521		6072	
Number of deaths	43		166		21		188		833	
Cardiovascular	10		52		1		63		238	
Cancers	24		65		15		63		369	
Other causes	9		49		5		62		226	

Paper V

Epidemic stress and socioeconomic stress in early life, and self-rated health in adulthood: A population-based study

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Abstract

Aims: To investigate associations between infant mortality rate (IMR) in the birth year and IMR in the year after birth, individual socioeconomic factors in childhood, and self-rated health (SRH) in adulthood.
Methods: The public health survey in Scania 2008 is a cross-sectional postal questionnaire study with 28,198 participants aged 18-80, of which 13,491 participants born in Sweden in 1927-1960 (63% participation in the sample in this age interval) were included. The associations between de-trended deviance in IMR, individual socioeconomic status of the father during childhood, economic stress in childhood and respondent's own education, and SRH were investigated in logistic regressions analyses. Calculations using logistic regression models including the same individual socioeconomic variables were also conducted with IMR after the year of birth in the models (one-year lag).
Results: Among men 33.0% reported poor health and among women 35.0%. The de-trended deviance in IMR was not significantly associated with SRH throughout the analyses. In the full final model, the individual socioeconomic variables were significantly associated with SRH. Interaction terms between IMR and father's socioeconomic position, economic stress in childhood and respondent's own education, respectively, were not significantly associated with SRH. Similar results were obtained when IMR in the year after birth (a one-year lag) was analyzed instead of IMR in the year of birth.
Conclusions: Only individual level variables depicting socioeconomic conditions in childhood such as father's socioeconomic status (occupation), education and economic stress in childhood, but not the aggregate level variable IMR, were associated with SRH in adulthood.

Key Words: Self-rated health, infant mortality rate, early life, life course, socioeconomic status, Sweden

Introduction

A growing number of studies suggest that life conditions early in life are associated with health in adulthood. The notion that early life conditions may affect health in later life was empirically supported already in the 1930s (Kermack, McKendrick, & McKinlay, 1934). In recent decades, the life course approach in epidemiology has emerged as a new framework for the understanding of risk factor exposure and health effects (Kuh & Ben-Schlomo, 2004). This comparatively recent early life perspective was initiated by the work of Barker, who suggested that foetal preconditions in utero such as growth retardation in the third trimester condition risk factors for cardiovascular diseases and diabetes mellitus type 2, such as hypertension, high cholesterol, deranged serum lipids, overweight and obesity (Barker, 1995). The life course approach was later empirically investigated regarding a wide range of other diseases, disease groups and health conditions (Kuh & Ben-Schlomo, 2004). Risk factors in early life research for adult disease include not only Barker's "foetal origins hypothesis" but a wide variety of risk factors ranging from biological risk factors such as early life infection followed by chronic sub-clinical inflammation with chronically increased inflammation markers as risk factor markers for cardiovascular disease (Pearson et al., 2003), to social and economic circumstances, e.g. exposure to childhood economic stress as a risk factor for poor self-rated health (Lindström, Hansen, & Rosvall, 2012), and adverse health behaviours such as tobacco smoking (Lindström, Modén, & Rosvall, 2013) in adulthood.

It has also been suggested that cardiovascular diseases and some other chronic diseases in adult and old age may have infectious and chronic inflammatory causes originating in the external environment as common causes (Finch & Crimmins, 2004; Crimmins & Finch, 2006). Empirical results from earlier historical periods such as Scania in the southernmost part of Sweden in the 18th and 19th centuries, for which individual mortality and some other census data are available, indicate that peaks in some years in the infant mortality rate (IMR) due to epidemics of small pox, whooping cough (bordetella pertussis) and other airborne infectious diseases also resulted in increased old-age (55-80 years) mortality in four parishes in Scania for the specific birth cohorts affected by high IMR:s as infants (Bengtsson & Lindström, 2000; Bengtsson & Lindström 2003). Exposure to high post-early neonatal mortality

rate (PENMR) (8-364 days of life) was also positively associated with higher mortality in adult life among persons born in 1813-1898 followed until 1968 in the same area (Quaranta 2013, 2014). A number of studies have investigated cohort associations between IMR and mortality for the same birth cohort in adulthood in pre-industrial populations, using between-year IMR variations as a cohort indicator of epidemic infectious diseases. Some of these studies show significant associations (Bengtsson & Lindström, 2000; Bengtsson & Broström, 2009), while other studies show no significant associations (Gagnon & Mazan, 2009). Omran (1971) has suggested a dynamic and multi-causal approach to the secular mortality decline that has been ongoing in Sweden and some other western countries for more than 200 years and in other countries during a shorter time period. A long-term change in mortality and disease patterns occurred, by which pandemics of infectious diseases were gradually replaced by degenerative diseases connected with socioeconomic differences in health-related behaviours (Omran, 1971). IMR as an environmental measure of infectious diseases in infancy (0-1 years) was investigated in a Swedish immigrant study (persons born in 1932-1974 with observation period 1981-1991) which found a positive association with length of sick leave (Helgertz &Persson, 2014), but the native population was not in focus.

The individual health outcome in this study is self-rated health (SRH), which is internationally regarded as a valid and strong predictor of mortality (Idler & Kasl, 1991). Studies with individual level data have demonstrated that social and economic conditions in adulthood such as education, marital status, economic stress (not being able to pay bills), social support (emotional and instrumental) and social capital are associated with SRH in adulthood. In addition, individual level studies have also demonstrated positive associations between poor economic conditions in childhood and poor SRH in adulthood (Regidor et al., 2011), positive associations between poor maternal socioeconomic circumstances in early life and poor SRH (Power, Matthews, Manor, 1998), and positive associations between low childhood socioeconomic status (SES) and poor SRH in adulthood (Hagger-Johnson et al., 2011).

Individual socioeconomic status (SES) has for a long time mostly been measured according to occupation, education or income (Whitehead, 1982). In this study the individual SES variables will be restricted to SES factors during childhood which

temporally precede self- rated health in adulthood: father's SES (occupation) during the respondent's own childhood, the respondent's self-reported economic stress in childhood and the respondent's own education. Higher IMR in the birth year (and the year after birth), lower SES of father, the experience of economic stress in childhood and low education are hypothesized to be positively associated with poor SRH in adulthood. Models with lagged IMR, i.e. the association between the SRH of a birth cohort born a specific year and the specific IMR of the following year, will also be investigated, because IMR in the year of birth (t) measures exposure in utero for persons born very late in the year and exposure in infancy for those born early in the year, while IMR in the year after birth (t+1) measures exposure in early childhood.

The aim of this study is to investigate the associations between the aggregate measure IMR in the year of birth (and the year after birth) and individual socioeconomic factors in childhood such as father's SES (occupation), economic stress in childhood and education in logistic regression models, and self-rated health in adulthood, adjusting for age and sex.

Material and methods

Study population

The 2008 public health survey in Scania in the southernmost part of Sweden is a cross-sectional study. A total of 28,198 persons from a stratified random sample from the official population registers of people living in Scania born between 1927 and 1990 answered a postal questionnaire in August and September 2008 (approximately 55% response rate from the total sample). Two reminder letters were sent to those who had not responded initially. The present study encompasses a total of 13,491 respondents born in Sweden in 1927-1960. Among those born in 1927-1960, another 1,900 respondents were born abroad and 358 respondents had missing values concerning country of birth. The response rate in the age interval born 1927-1960 was 63%. Only the respondents born in Sweden were included in the present study because of the high number of countries of birth (approximately 180) and because most of these countries do not have data concerning IMR reaching back in time to 1927. The birth years 1927-1960 were chosen for reasons of statistical availability in

official publications from Statistics Sweden (Befolkningsrörelsen, 1927-1960). This research was approved by the Ethical Committee at Lund University (No. 2010/343).

Definitions

Dependent variable

Self-rated health (SRH) was obtained with the item "How do you rate your general health status?" with the five possible answers "very good", "good", "neither good nor poor", "poor" and "very poor". These were dichotomised into good (the two first alternatives) and poor (the three latter alternatives) SRH.

Independent variables

Birth cohorts according to specific *birth years* of participants born 1927-1960 were included. The *age* of the respondents thus included the age range 47-81 years.

Sex was stratified in table 1, but no stratification for sex was conducted in the multiple analyses in tables 3-4 because the distributions of both the outcome and exposure variables were very similar according to sex.

Socioeconomic status (SES) of the father by occupation was assessed with the SES categories higher non-manual employees, medium-level non-manual employees, lower non-manual employees, skilled manual workers, unskilled manual workers, self-employed and farmers according to the official coding system of socioeconomic status (SES) by occupation by Statistics Sweden (Statistics Sweden, 1985).

Economic stress in childhood was measured with the question "Did your family experience economic hardship when you grew up?" with the three optional answers "No, no significant problems", "Yes, less severe problems and/or problems during short time periods" and "Yes, severe problems and/or problems during long time periods".

Education was divided by length of education into the categories 13 years of education or more, 10-12 years of education and 9 years of education or less. The "other" group included individuals who answered the "other" alternative on the education item.

The *infant mortality rate (IMR)* for Scania stems from Statistics Sweden's regional data for the years 1927-1960 concerning Scania (Befolkningsrörelsen, 1927-1960). Three measures of IMR were included in the multiple analyses in tables 3-4; crude IMR, relative IMR measured as yearly deviance from the time trend in IMR over the 1927-1960 period, and the IMR trend. The IMR (deviance/relative) and IMR (trend) measures were calculated from the IMR (crude) measure with the STATA insert program hprescott with Hodrick Prescott filtering factor 6.25 used for annual data (https://ideas.repec.org/c/boc/bocode/s447001.html). The IMR (deviance/relative) was calculated to remove the trend component in IMR.

Statistics

Prevalences (%) of poor SRH, age, father's socioeconomic status (occupation), economic stress in childhood and education were calculated, stratified by sex (table 1). Infant Mortality Rate (IMR) as crude IMR, trend in IMR and IMR (deviance/relative) are given according to birth year (1927-1960) of birth cohorts included in this study (table 2). Odds ratios with 95% confidence intervals (OR:s, 95% CI) of poor SRH were calculated according to IMR, age, sex, father's socioeconomic status (occupation), economic stress in childhood and education (table 3). In a first model, crude IMR values were analyzed in relation to the outcome poor SRH adjusting only for age and sex (model 1). In the second model, IMR trend and IMR with relative values (deviance) were introduced instead of crude IMR with age and sex (model 2). In the third model, only relative values (deviance) of IMR were adjusted for age and sex (model 3). In the fourth model, father's socioeconomic status (occupation) was entered into the previous model 3 (model 4). In the fifth model, the respondent's economic stress in childhood and education were entered into model 4 (model 5). Finally, the interaction terms for IMR (relative)*socioeconomic status (father), IMR (relative)*economic stress in childhood and IMR (relative)*education were entered with the other variables in model 5 (model 6). All statistical analyses in

table 3 were conducted in logistic regression models. Models 1-6 were also calculated with a one-year lag for IMR in logistic regression models (table 4). All calculations in table 3 thus analyze birth year (t) and IMR at year (t), while all calculations in table 4 analyze IMR in year (t+1). The statistical analyses were performed with the PASW software package version 20.0.

Results

Table 1 illustrates that 33.0% of the men and 35.0% of the women had poor SRH. The age distribution was similar for men and women. Father's socioeconomic status (occupation) had approximately the same distribution among men and women with 7.3% non-manual employees in higher positions, 12.3% middle level non-manual employees, 8.7% lower level non-manual employees, 22.8% skilled manual workers, 25.8% unskilled manual workers, 6.1% self-employed and 17.0% farmers for the aggregate of men and women. Economic stress in childhood showed approximately the same distribution in both sexes with 62.9% with no, 27.6% with moderate and 9.5% with severe economic stress in childhood. The proportion with high education was 25.8% among men and 32.2% among women. In contrast, the proportion with low education (-9 years) was 37.9% among men and 31.9% among women.

Table 2 shows that IMR in Scania decreased throughout the 1927-1946 period from 63.03 per 1000 in 1927 to 18.99 per 1000 in 1960. The decrease in IMR was most dramatic both in absolute (per cent units) and relative terms in the 1927-1946 period, when IMR dropped from 63.03 per 1000 to 24.58 per 1000, less dramatic in both absolute and relative terms in the 1947-1960 period, in which IMR fell from 24.45 per 1000 to 18.99 per 1000.

Table 3 shows that the odds ratio for IMR in the year of birth remained statistically significant in models 1-2 when IMR was measured as IMR (crude) (model 1) and IMR (trend) (model 2). In contrast, relative IMR (de-trended deviance in IMR) remained statistically not significant at the 5% significance level throughout models 2-6. In model 4 father's socioeconomic status was statistically significant, p= 0.000, and the odds ratios of poor SRH among father non-manual employees in medium positions, 1.32 (1.09-1.60), non-manual employees in lower positions, 1.16 (0.95-

1.42), skilled manual workers, 1.58 (1.33-1.87), unskilled manual workers, 1.65 (1.39-1.96), self-employed, 1.33 (1.07-1.66), and farmers, 1.30 (1.09-1.56) were mostly (with the exception of non-manual employees in lower positions) significantly higher than the odds ratio 1.00 of poor SRH in the higher non-manual employee reference group. In model 5, father's socioeconomic status (occupation) was still statistically significant at the 5% significance level, p= 0.046, although with an attenuation to not significant odds ratios of poor SRH at the 5% significance level among all of the stratified father's socioeconomic status (occupation) groups compared to the non-manual employee reference group. The individual level childhood economic stress included introduced in model 5 was significantly associated with SRH, p=0.000. The odds ratios of poor SRH in model 5 were 1.47 (1.34-1.61) in the group with experience of moderate economic stress in childhood and 2.05 (1.78-2.36) in the group with severe economic stress in childhood compared to the no economic stress in childhood reference group. Individual education was also included in model 5 and its association was significant at the 5% significance level, p=0.000, with an odds ratio 1.47 (1.34-1.61) for the 10-12 years of education and an odds ratio 2.05 (1.78-2.36) in the -9 years of education groups compared to the 13 or more years of education group. Finally, the interaction terms IMR (relative)*father's SES, IMR (relative)*economic stress in childhood and IMR (relative)*education were not significant, p=0.330, p=0.910 and p=0.588, respectively, in model 6, and the main patterns for the other variables remained principally unchanged in this final model compared to model 5.

In the models with lagged IMR (t+1), relative IMR (de-trended deviance) remained not statistically significant throughout tables 2-6, just as in the un-lagged models in table 3. All other variables retained the same patterns as in table 3, and the interaction terms IMR (relative)*father's socioeconomic position, IMR (relative)*economic stress in childhood and IMR (relative)*education were also statistically not significant (table 4).

Discussion

The observation that de-trended deviance in IMR, either in the year of birth or with a one year lag, is not significantly associated with SRH is coherent with the fact that the

IMR patterns in the years of birth 1927-1960 were not subject to extreme mortality peaks in specific years caused by infectious disease epidemics such as those seen in historical time. IMR in this study was rather subject to a continuous decrease over the 1927-1960 period. Two earlier historical studies based on 18th and 19th century data from western Scania have shown that crude death rates in the age interval 0-1 years (infant mortality) significantly predicted old-age 55-80 year mortality in later life when birth cohorts were followed prospectively in 18th and 19th century data from western Scania (Bengtsson & Lindström, 2000, 2003), and these results were confirmed for a population born in 1813-1898 in approximately the same area followed until 1968 (Quaranta, 2013, 2014). In contrast, the present study based on modern survey (2008) and IMR (1927-1960) data from Scania find no significant cohort effects of IMR on SRH. Instead, individual level socioeconomic variables such as father's SES (occupation), economic stress in childhood and education are significantly associated with SRH in adulthood with rather strong effect measures. The odds ratios of poor SRH for father's SES (occupation) are much attenuated after the introduction of economic stress in childhood and education in model 5, which may reflect a close association between father's SES and respondent's own education. These findings may reflect the relative transition, outlined by Omran as "the epidemiologic transition", from a historical disease pattern dominated by pandemic infectious diseases to a pattern with a predominance of degenerative and man-made diseases such as cardiovascular diseases and cancers connected with risk factors such as socio-economically stratified health-related behaviours following the rapid industrialization, modernization and urbanization and later de-industrialization during the 20th century (Omran, 1971).

It is very hard to infer causality from cross-sectional studies. However, the fact that only individual retrospective variables such as father's SES (occupation), economic stress in childhood and education, as well as the aggregate variable IMR are included as independent variables, while the dependent variable self-rated health depicts the current health status, at least facilitates some discussion concerning temporality, although some respondents may be influenced by recall bias. Most studies concerning the impact of early socioeconomic risk factors on health in later life based on modern data exclusively include individual level variables and no variables depicting disease environment (Tubeuf, Jusot, & Bricard, 2012). Our inclusion of IMR in the year of

birth (and one year lagged IMR) excludes some of the problem with endogeneity in the data. In addition, IMR measured as an aggregate reflects an aggregate, contextual risk exposure in terms of the possibility of epidemics afflicting a vast part of society. The individual SES in childhood variables reflect individual risk exposures which may indicate SES stratification of early life risk factors connected with adult risk factors such as economic stress and health-related behaviours.

Results from other studies indicate that the impact of childhood social and economic conditions on health in adulthood is mediated by adulthood social and economic conditions as well as lifestyles and health related behaviours (Elo, 2009; Yi, Gu, & Land, 2007). In this study the associations between childhood socioeconomic conditions at the individual level in childhood, IMR in childhood and SRH in adulthood are analyzed without the mediating factors in order to isolate the direct associations in order to restrict the study in accordance with the temporality criterion that cause should precede effect (Hill, 1965).

No statistical interactions between IMR and individual socioeconomic factors in early life are statistically significant.

Strengths and limitations

The approximately 63% (55%) participation rate may be considered normal in current western settings, but still moderately low. However, the demographic and socioeconomic composition according to age, sex, education and socioeconomic status correspond well with the distribution in official population registers for Scania, the substantial exception being underrepresentation of people born abroad (Lindström, Fridh, & Rosvall, 2014). The underrepresentation of respondents born abroad is a problem of no importance in this study, because the study population is restricted to persons born in Sweden for reasons of data availability. The risk of selection bias is thus comparatively small.

The covariates age and sex as well as the competing exposure variables father's SES (occupation), economic stress in childhood and respondent's own education were taken into account in the analyses of the associations between IMR in the year of birth

(and one year lag in table 4) and SRH in the logistic regression analyses. The same analyses as displayed in tables 3 and 4 were conducted with the variable age squared instead of age yielding similar results as those displayed in tables 3 and 4 (not shown in tables). Post-early neonatal mortality rate (PENMR) and its between-year variation may be a better indicator of early life epidemic stress than IMR (Quaranta, 2014), and the use of this measure of early life epidemic stress is a possibility for future studies.

Self-rated health is internationally regarded as a valid indicator of health because it is a strong predictor of for example cardiovascular disease mortality and total mortality (Idler & Kasl, 1991; Heistaro et al., 2001; Heistaro et al., 2001). The dichotomization of self-rated health into a binary variable follows the international definition and how it predicts CVD incidence and mortality as well as total mortality. This binary SRH outcome has also been validated regarding a previous public health questionnaire in Scania in 2000 (Mohseni, 2008), which is the rationale why ordered probit analysis analysing all five alternatives of the SRH variable was not conducted. The validity of Swedish aggregate statistics on IMR is very high. Infant mortality rates (IMRs) from Scania based on officially published data from Statistics Sweden have very high validity. The reason for the restriction to only include respondents born in Sweden is that many countries only have time series data concerning IMR from 1952. Some countries such as the Nordic countries have such aggregate data for the entire 1927-1990 time period, but the comparatively low number of respondents from these countries makes their inclusion virtually useless.

This study has a cross-sectional study design which renders all causal inference almost impossible, although structural pathway analyses may be conducted. However, the aggregate IMR in the year of birth measures are retrospective and the self-reported SES items retrospectively depict living conditions earlier in life prior to the current self-rated health status.

Conclusions

De-trended deviations in IMR are not significantly associated with individual self-rated health in adulthood throughout the analyses. In contrast, the individual level socioeconomic exposure variables father's socioeconomic position, economic stress

in childhood and education were significantly associated with self-rated health, with higher odds of poor self-rated health for lower socioeconomic status (father's), higher levels of economic stress in childhood and lower education. The results for father's SES were attenuated by the introduction of economic stress in childhood and education in the models, which may plausibly be a result of a strong association between father's SES and respondent's own education. The interaction terms IMR (deviance/relative)*father's socioeconomic position, IMR (deviance/relative)*economic stress in childhood and IMR (deviance/relative) were not statistically significant. The same patterns of results were obtained when IMR in the year after birth (t+1) was analyzed.

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Table 1. Distribution (%) of self-rated health, birth year (age), father's socioeconomic status (occupation), economic stress in childhood and respondent's education, stratified by sex. The public health questionnaire in Scania 2008. Born in Sweden in 1927-1960. Men (N= 6,314) and women (N= 7,177).

	Men	Women	Total
Self-rated health			
Good	67.0	65.0	65.9
Poor	33.0	35.0	34.1
(Missing)	(119)	(208)	(327)
Born (age)			
1927-1939 (age 68-81)	27.8	27.3	27.5
1940-1949 (age 58-68)	38.7	36.9	37.7
1950-1960 (age 47-58)	33.5	35.8	34.8
(Missing)	(0)	(0)	(0)
Father's socioeconomic status (occupation)			
Higher non-manual	7.2	7.4	7.3
Medium non-manual	12.4	12.2	12.3
Lower non-manual	8.5	8.8	8.7
Skilled manual	22.8	22.9	22.8
Unskilled manual	26.1	25.5	25.8
Self-employed	5.5	6.6	6.1
Farmer	17.4	16.5	17.0
(Missing)	(576)	(586)	(1162)
Economic stress in childhood			
No	63.1	62.6	62.9
Moderate	27.6	27.7	27.6
Severe	9.3	9.7	9.5
(Missing)	(63)	(64)	(127)
Education			
13- years	25.8	32.2	29.2
10-12 years	33.1	32.0	32.5
-9 years	37.9	31.9	34.8
Other	3.2	3.9	3.5
(Missing)	(310)	(710)	(1020)

Table 2. Infant mortality rate (IMR) (per thousand), IMR (trend) and IMR (deviance from trend/relative) in Scania, southern Sweden 1927-1960. (Source: Statistics Sweden, 1927-1960)

Birth year	IMR	IMR (trend)	IMR (deviance/relative)
1927	63.03	64.70	-2.58
1928	63.75	62.95	1.27
1929	62.64	60.93	2.81
1930	56.50	58.50	-3.41
1931	59.54	55.80	6.70
1932	53.99	52.65	2.55
1933	47.24	49.45	-4.48
1934	42.46	46.84	-9.36
1935	45,27	45.09	0.40
1936	46.22	43.77	5.61
1937	42.32	42.47	-0.36
1938	40.54	41.21	-1.62
1939	38.16	39.93	-4.44
1940	42.00	38.51	9.04
1941	39.71	36.54	8.67
1942	31.16	34.14	-8.71
1943	29.36	31.95	-8.10
1944	31.84	30.14	5.62
1945	30.26	28.48	6.26
1946	24.58	26.97	-8.86
1947	24.45	25.93	-5.71
1948	25.64	25.29	1.37
1949	26.61	24.74	7.56
1950	22.96	24.02	-4.39
1951	24.95	23.17	7.68
1952	22.77	22.07	3.15
1953	19.30	20.89	-7.61
1954	20.97	19.89	5.43
1955	16.69	19.09	-12.57
1956	19.40	18.68	3.86
1957	19.28	18.47	4.41
1958	17.40	18.37	-5.28
1959	18.68	18.44	1.29
1960	18.99	18.58	2.20

Table 3. Odds ratios with 95% confidence intervals and p-values of poor self-rated health according to IMR in the year of birth, age, sex, SES (father), economic stress in childhood, education, and interactions between IMR and each of the three individual early life socioeconomic variables. The public health questionnaire in Scania 2008. Born in Sweden in 1927-1960. Men (N= 6,314), women (N= 7,177) and total (N=13,491).

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
IMR(crude)	1.01 (1.00-1.02) p=0.007					
Age	1.02 (1.00-1.03) p=0.014	1.02 (1.00-1.03) p=0.060	1.04 (1.03-1.04) p=0.000	1.04 (1.03-1.04) p=0.000	1.03 (1.02-1.03) p=0.000	1.03 (1.02-1.03) p=0.000
Sex	1.11 (1.03-1.19) p=0.005	1.11 (1.03-1.20) p=0.005	1.11 (1.03-1.20) p=0.005	1.14 (1.06-1.24) p=0.001	1.18 (1.09-1.28) p=0.001	1.18 1.09-1.28) p=0.000
IMR(trend)		1.01 (1.00-1.03) p=0.033				
IMR (relative)		1.00 (0.997-1.009) p=0.401	1.003 (0.997-1.009) p=0.309	1.002 (0.996-1.009) p=0.445	1.004 (0.997-1.010) p=0.266	1.002 (0.976-1.030) p=0.874
SES (father)				p=0.000	p=0.046	p=0.049
Higher non-manual employees				1.00	1.00	1.00
Middle position non-manual employees				1.32 (1.09-1.60)	1.12 (0.92-1.36)	1.11 (0.91-1.36)
Lower position non-manual employees				1.16 (0.95-1.42)	0.88 (0.71-1.10)	0.88 (0.71-1.09)
Skilled manual workers				1.58 (1.33-1.87)	1.02 (0.85-1.24)	1.02 (0.85-1.24)
Unskilled manual workers				1.65 (1.39-1.96)	0.97 (0.80-1.17)	0.97 (0.80-1.17)
Self-employed				1.33 (1.07-1.66)	1.08 (0.86-1.36)	1.07 (0.85-1.35)
Farmer				1.30 (1.09-1.56)	0.89 (0.73-1.08)	0.88 (0.73-1.08)
Economic Stress (childhood)					p=0.000	p=0.000
No					1.00	1.00
Mild					1.47 (1.34-1.61)	1.47 (1.34-1.61)
Severe					2.05 (1.78-2.36)	2.05 (1.78-2.36)
Education					p=0.000	p=0.000
13- years					1.00	1.00
10-12 years					1.53 (1.37-1.70)	1.53 (1.37-1.71)
-9 years					2.16 (1.92-2.42)	2.16 (1.93-2.42)
Other					1.48 (1.18-1.85)	1.48 (1.18-1.85)

IMR(relative)* SES (father)	1.002 (0.998-1.006) p=0.330
IMR(relative)* Economic stress in childhood	1.001 (0.991-1.010) p=0.910
IMR(relative)* Education	0.998 (0.990-1.006) p=0.588

Table 4. Odds ratios with 95% confidence intervals and p-values of poor self-rated health according to IMR in the year *after* the year of birth, age. sex, SES (father), economic stress in childhood, education, and interactions between IMR and each of the three individual early life socioeconomic variables. The public health questionnaire in Scania 2008. Born in Sweden in 1927-1960. Men (N= 6,314), women (N= 7,177) and total (N=13,491).

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
IMR+1(crude)	1.016 (1.002-1.024) p=0.008					
Age	1.02 (1.00-1.03) p=0.024	1.01 (0.99-1.02) p=0.446	1.036 (1.03-1.04) p=0.000	1.035 (1.03-1.04) p=0.000	1.027 (1.02-1.03) p=0.000	1.027 (1.02-1.03) p=0.00
Sex	1.10 (1.02-1.19) p=0.011	1.10 (1.02-1.19) p=0.010	1.10 (1.03-1.19) p=0.008	1.14 (1.06-1.23) p=0.001	1.18 (1.09-1.28) p=0.000	1.18 (1.08-1.28) p=0.000
IMR+1(trend)		1.02 (1.01-1.03) p=0.001				
IMR+1 (relative)		1.00 (0.99-1.01) p=0.907	1.00 (0.99-1.01) p=0.787	1.00 (0.99-1.01) p=0.709	1.00 (0.99-1.01) p=0.704	1.00 (0.98-1.02) p=0.915
SES(father)				p=0.000	p=0.045	P=0.044
Higher non-manual employees				1.00	1.00	1.00
Middle position non-manual employees				1.33 (1.09-1.61)	1.12 (0.92-1.37)	1.12 (0.92-1.37)
Lower position non-manual employees				1.18 (0.96-1.44)	0.90 (0.72-1.11)	0.89 (0.72-1.11)
Skilled manual workers				1.59 (1.33-1.89)	1.03 (0.85-1.25)	1.03 (0.85-1.25)
Unskilled manual workers				1.66 (1.39-1.97)	0.97 (0.80-1.18)	0.97 (0.80-1.18)
Self-employed				1.34 (1.07-1.67)	1.09 (0.86-1.38)	1.08 0.86-1.37)
Farmer				1.30 (1.08-1.56)	0.88 (0.72-1.08)	0.88 (0.72-1.08)
Economic Stress (childhood)					p=0.000	p=0.000
No					1.00	1.00
Mild					1.48 (1.35-1.62)	1.48 (1.35-1.63)
Severe					2.06 (1.79-2.37)	2.07 (1.79-2.38)
Education					p=0.000	p=0.000
13- years					1.00	1.00
10-12 years					1.52 (1.36-1.70)	1.52 (1.36-1.70)
-9 years					2.14 (1.91-2.41)	2.14 (1.91-2.41)

Other	1.47 (1.18-1.85)	1.48 (1.18-1.86)
IMR (relative)*' SEI (father)		1.002 (0.998-1.006) p=0.239
IMR (relative)* Economic stress in childhood		0.997 (0.988-1.007) p=0.614
IMR (relative)* Education		1.003 (0.995-1.010) p=0.499

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Martin Lindström

All that's mine I carry with me

Early life disease and adult health in Sweden during 250 years

The aim of this doctoral thesis is to study early life exposures in relation to adult health in Sweden during 250 years. The early life exposures investigated are the foetal origins (nutrition) and the inflammation hypotheses. Longitudinal individual and household data are combined with local area data on food costs (rye prices) and disease load (infant mortality rate, IMR) using a Cox regression framework to analyse the 55-80 year mortality in four parishes in Scania, southern Sweden, in the 18th and 19th centuries. Register based cohort data on individuals in late 20th century Sweden born in eleven countries in 1921-1939 are analysed in Cox regressions of adult mortality, including IMR and GDP per capita in the year and country of birth. A survey (2008) in Scania is used to analyse self-reported early life socioeconomic data and IMR in the birth year in relation to adult self-rated health (SRH). Results from the historical studies suggest that cohorts exposed to high IMR have high mortality in ages 55-80 specifically from airborne infectious diseases and that a high disease load of airborne infectious diseases in infancy has a strong impact on later life mortality, while hypotheses concerning food costs (nutrition) and disease load during pregnancy are not supported. Essentially no adult socioeconomic mortality differences are observed. In the two modern time studies individual adult and early life socioeconomic conditions are associated with adult mortality and SRH, respectively, while IMR and GDP per capita are mostly not.

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