Perspectives on Mortality Forecasting

V. Cohort factors: How conditions in early life influence mortality later in life

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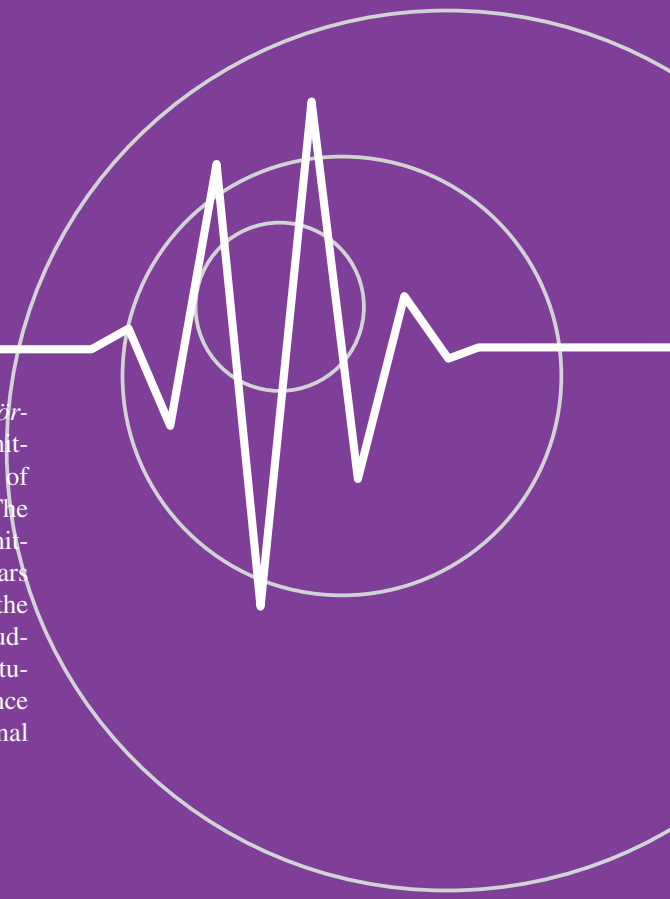

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Preface

Mortality projections are an essential input for projections of the financial development of pension schemes. Governments and insurance companies all over the world rely on good mortality projections for efficient administration of their pension commitments. Ideally, the expected value of the difference between outcomes and projections would be close to zero. In practise, during recent decades, demographers have continually underestimated improvements in life expectancy for persons 60 and older. The demographic models used in projecting mortality are usually based on statistical modelling of historical data. The question is whether it is possible to bring the results of mortality modelling closer to the ideal, and if so, what do demographers need to do to achieve this result?

This question provided the impetus for forming the Stockholm Committee on Mortality Forecasting. The Swedish Social Insurance Agency (formerly National Social Insurance Board, RFV) is the national agency in Sweden responsible for providing a financial picture of Sweden's public pension system. The Swedish Social Insurance Agency has a long-standing interest in the development of modelling of pension schemes and participates actively in the international dialogue among experts in this area. The Stockholm Committee on Mortality Forecasting was created by RFV to bring together scholars from different disciplines working on issues in projecting mortality. The aim of the Committee is to survey the state of the art and to provide incentives for the advancement of knowledge and better practice in forecasting mortality.

This is the fifth volume in a series presenting papers from workshops on mortality organized by the Stockholm Committee on Mortality Forecasting. It addresses the question of how cohort factors such as nutrition and diseases in early life affect health and mortality in later life and how information on cohort effects best can be used to improve mortality forecasting. The idea that conditions both in infancy and early childhood and during the fetal stage have an impact on adult health dates far back in time, at least to the 17th century. It was advocated again in the 1930s, when demographers and epidemiologists became aware of the great mortality decline that started in the West around 1800. While cohort factors were of substantial importance up until the 1920s, it seems that period factors, such as improved water supply, sanitation, and antibiotics – in other words factors that influence health status of all age groups at the same time – gained importance thereafter. Cohort factors were revitalised again in the 1990s by the work of David Barker and his group and from that time on, there has been an upsurge in the number of studies on this topic. While many give support to the idea that early life conditions present in the fetal stage and the first years of life are important for health later in

life, others question this conclusion. The question posed here is, if children very early in life are "programmed" for a certain health status, due to their mother's health and prevailing living conditions, can this information be used to improve mortality forecasting? To approach this issue, this volume gives an overview of findings and criticism of how conditions in early life influence adult and old age mortality, as well as some examples of recent studies.

The first chapter, by Martin Lindström and George Davey Smith, provides an overview of recent research in this area, with special emphasis on Sweden. In doing so they not only give a summary of empirical findings, historical and contemporary, but also of the various mechanisms that have been attributed to the link between health in early life and later in life. The mortality decline in three specific diseases, respiratory tuberculosis, haemorrhagic stroke, and bronchitis, which have accounted for two-thirds of the total decline in mortality in ages 15–64 years from the mid-nineteenth century to the first decade of the 20th century in Britain, have all demonstrable influences from infancy and childhood. The timing of improvements of conditions during infancy and childhood and health improvements later in life is precisely as expected for this period. Such a high degree of specificity and timing, however, is often lacking in analyses of contemporary data. Thus, while cohort factors were partly important for the decline from high to low mortality, their importance today needs to be verified further.

Kaare Christensen, in the second chapter, evaluates Barker's "fetal origins hypothesis" using data on twins and famines. Considerable evidence exists of the significant association between fetal growth and later life health outcomes, such as blood pressure and cardiovascular mortality. Firstly, the question is how large is this effect? Secondly, is the effect causal, or do other factors, such as genes or socioeconomic conditions, lie behind the association? Christensen begins by pointing out that the association between retardation of fetal growth and health in later life is not corroborated without exception, referring to several studies of famines. He then turns to twin studies, which are particularly interesting in this respect since twins usually experience retarded fetal growth and on average are 900 g lighter at birth than single children. Using the Danish twin register, which includes a large population with a long follow-up period, Christensen and his colleagues find no differences between twins and singles with regard to all-cause or cardiovascular mortality, and a similar study for Sweden confirms this result. Twins often differ in birth weight, which means that it is possible to control for genetic factors. Christenson and colleagues also use data for the US and find a very modest impact of birth weight on blood pressure, confirming previous analyses using twin data. Taken together, the effect of birth weight on blood pressure, after controlling for genetic factors, is too weak to justify intervention.

In the third chapter, Gabriele Doblhammer focuses on how factors related to season of birth influence mortality in later life comparing the United States, Austria, Denmark, and Australia. In all four populations, significant differences in lifespan exist by month of birth. Those born in the spring generally face lower life expectancy, likely due to nutritional factors, possibly also due to a lower disease load. The difference diminishes over time, which is consistent with improved diets but also a decline in morbidity in infectious diseases. Taken together, improvements in diet and reduction of infectious diseases in the beginning of life gave improved health later in life and contributed to the overall increase in life expectancy.

The fourth and final chapter, by Tommy Bengtsson and George Alter, analyses how conditions of nutrition and diseases in the first year of life affect old age mortality in historical populations in Belgium and Sweden. They make use of longitudinal individual level demographic data with information on socioeconomic factors at household level combined with data on food prices. They find that children born in years of excess infant mortality, generally due to outbreaks of epidemic diseases, face higher mortality in older ages. For Belgium, high food prices also have a similar effect.

To summarize, there is a considerable amount of detailed evidence as regards the ways health incidents in early life influence health later in life and mortality in certain causes of death. There is also detailed evidence as regards its timing for England during the mortality decline from the mid-nineteenth century up to the 1920s and possibly also for Sweden and some other western countries. For the period afterwards, the results are less conclusive. While many studies show significant associations between conditions in early life and health later in life, others do not. Whether this association is causal has also been questioned, as has its overall impact on the mortality decline.

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Contents

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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Early Life Events and Later Life Health: Twin and Famine Studies

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Introduction

During more than a decade, the relation between early life conditions and late life health has been one of the major topics in the epidemiological literature. The interest for the connection between early life conditions and later life health is by no means new. As early as in the 16th century, Francis Bacon suggested that the nutrition in the womb and the first year of life is very important for later life health. In more recent times, especially the classical paper from 1934 by Kermack et al., and Forsdahl's work in the 1970s, have been important contributions. However, since the early 1990s, one of the main advocates for the importance of early life conditions for later life health has been David Barker and his group in Southhampton. They revitalized the so-called "fetal origins hypothesis" and have produced an impressive series of papers on the topic. The studies were motivated by this intriguing hypothesis proposed by Barker and co-workers which asserts that a baby's nourishment before and during infancy programmes its susceptibility to cardiovascular diseases as well as several other diseases and adverse outcomes, ranging from diabetes mellitus to cancer and suicide. There is evidence that an association exists between fetal growth and later life health outcomes such as blood pressure and cardiovascular mortality. The key question is, however, whether it is fetal nourishment or other factors such as genes or socioeconomic conditions that cause the association. Some studies suggest that socioeconomic confounding cannot explain the association between fetal growth and cardiovascular mortality (Leon et al. 1998), but they are few, and even fewer studies have evaluated the influence of genetic confounding.

Figure 1 **The fetal origins hypothesis states that the observed negative correlation between birth weight and cardiovascular disease risk is due to early life nutrition**

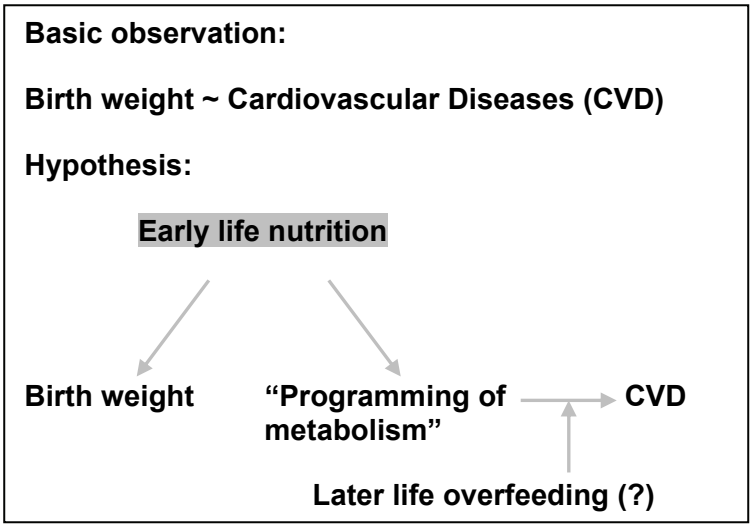
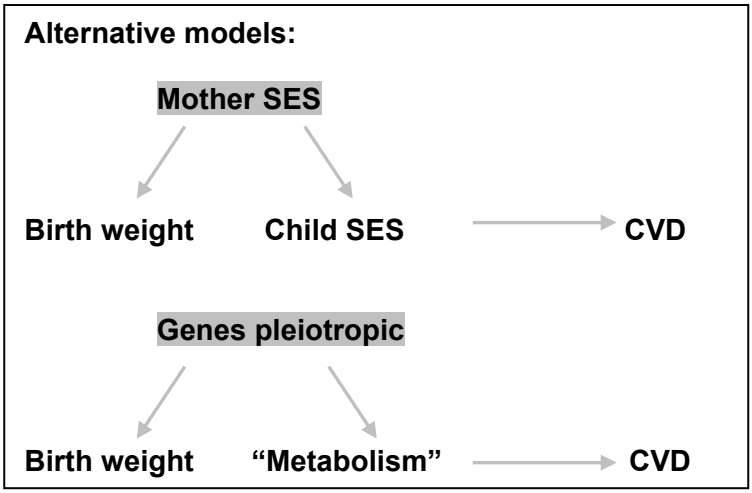


Figure 2 **Alternative explanations for the observed negative correlation between birth weight and cardiovascular disease risk**



A major concern about the work on the fetal origins hypothesis has been the wide range of exposure proxies and outcomes. Among the exposure proxies measured are birth weight, birth length, ponderal index, abdominal circum-

ference, and corresponding measurements have been performed at age 1 year. The measurements have been related to outcomes such as survival, cardiovascular diseases, hypertension, diabetes, suicide, and even to getting married (Barker 1994, 1998). Furthermore, these relations have been investigated in hundreds of data sets and very often in subtypes like obese mothers or children with rapid catch-up growth etc. This increases the risk of type 1-errors, i.e. statistically significant random findings, considerably, and has therefore created a certain amount of scepticism (Kramer and Joseph 1996). To avoid some of these problems, in our group at the University of Southern Denmark, we have focused on famine and twin studies which are dealing with extreme conditions in early life, and we have examined how these conditions affect later life health.

Famine Early in Life and Later Life Health

During the late 1990s, three reports have addressed the influence of prenatal exposure to famine on health in later life. We studied 161,744 individuals born during the 1866–68 Finnish famine and found, on the basis of a comparison with more than 600,000 individuals born before and after the famine, that nutritional deprivation in utero has no effect on survival in adult life (Kannisto et al. 1997). Stanner and colleagues (1997) investigated a broad range of coronary heart disease and diabetes mellitus risk factors among 169 people exposed to malnutrition in utero during the siege of Leningrad in 1941–42 and nearly 400 born before or outside the area of the siege. They found no association between intrauterine malnutrition and glucose intolerance, dyslipidaemia, hypertension, or cardiovascular disease in adulthood. Finally, Ravelli and colleagues (1998), studied 279 individuals who were exposed to malnutrition in utero during the Dutch hunger winter 1944–45 and nearly 425 controls born before and after. They found an association between intrauterine exposure to famine and decreased glucose tolerance in adults aged around 50 years. However, it was disappointing that Ravelli and colleagues, among all the suggested outcomes related to fetal nourishment, initially only reported glucose tolerance. Later reports showed that, for example, blood pressure showed no association with blood pressure in the Dutch famine study (Roseboom et al. 1999).

Later Life Health for Twins

Twin studies are especially interesting because twins experience severe growth retardation in the uterus, especially in the third trimester and, furthermore, studies of twins can control for the influence of the mother's socioeconomic status and for the effect of genes. Twins experience considerable

retardation in intrauterine growth – for example, they are on average more than 900 g lighter than single children at birth (MacGillivray et al. 1988; Kline et al. 1989). Phillips (1993) has argued that even small birth weight differences in twins could reflect important differences in intrauterine conditions important for programming of diseases later in life, because the mean birth weight among twins is already considerably lower than in singletons. Therefore, birth weight differences in twins offer a unique opportunity to test the "fetal origins hypothesis".

This also raises a question important to twin researchers: Does the reduced growth pattern in the last trimester make twins more vulnerable in adult life with an increased risk of cardiovascular diseases, diabetes mellitus and other assumingly "programmed" diseases? If so, then twin studies may be a poor model for studying these diseases because the causal field of the diseases could be different from that of singletons.

If twins are "programmed" due to the considerable growth retardation during the third trimester, one could expect an increased mortality and especially an increased cardiovascular mortality in adulthood for twins compared to the general population. Both a Swedish and our earlier Danish twin study found similar mortality patterns among twins and singletons in adulthood (Vågerö and Leon 1994; Christensen et al. 1995). However, the Swedish twin study (Vågerö and Leon 1994) had a limited follow-up period with no distinction between monozygotic (MZ) and dizygotic (DZ) twins (the latter having slightly higher birth weights on average), and our Danish twin study (Christensen et al. 1995) did not include causes of death.

Therefore we studied cause-specific mortality of 19,986 Danish twin individuals from the birth cohorts 1870–1930 followed from 1952 through 1993 (Christensen et al. 2001). Despite the large sample size and follow-up period, we were not able to detect any difference between twins and the general population with regard to all-cause mortality or cardiovascular mortality. Hence, the intrauterine growth retardation experienced by twins does not result in any "fetal programming" of cardiovascular diseases.

Twins and Genetic Confounding

The potential for genetic confounding in relation to the fetal origins hypothesis has been illustrated by Dunger et al. (1998), who showed that variation in the insulin gene (INS VNTR) is associated with fetal growth. Based on studies of fetal insulin secretion and monogenic diseases, Hattersley and Tooke (1999) proposed that genetically determined insulin resistance con-

tributes substantially to the association of low birth weight with diabetes, hypertension and vascular diseases and named this hypothesis "the fetal insulin hypothesis".

We used the Minnesota Twin Family study (Iacono et al. 1999) to test the potential influence of genetic confounding on the association between birth weight and systolic blood pressure, which is the best documented association between fetal growth and later life health outcome (Barker 1998; Kuh and Ben-Shlomo 1997; Law and Shiell 1996; Taylor et al. 1997). The effect of genetic confounding was evaluated by analysing individual twin data as well as intrapair differences in birth weight and systolic blood pressure. This approach enables controlling for the effect of all genetic factors in monozygotic pairs and on average half of the genetic factors in dizygotic pairs as well as environmental maternal effects. Two recent twin studies (Poulter et al. 1999; Dwyer et al. 1999) using a similar design did not find evidence for a genetic component to the association, but as pointed out in the accompanying editorial (Leon 1999), the number of monozygotic twin pairs in these studies was sparse.

We used the following statistical analysis:

As in Hopper and Seeman (1994), for each twin, i, of a pair (i = 1,2) let Y_i be systolic blood pressure and X_{1i} = birth weight and X_{2i} = current weight.

Let

$$Y_i = a_0 + a_1X_{1i} + a_2X_{2i} + E_i \qquad (1)$$

where E_i represents measurement error and effects specific to twin *i*. Each of the coefficients a_1 and a_2 represents the strength of a linear association between the blood pressure and a corresponding variable. The intrapair difference is

$$D = Y_1 - Y_2 = a_1D_1 + a_2D_2 + E \qquad (2)$$

where $D_j = X_{j1} - X_{j2}$ (j = 1,2) and $E = E_1 - E_2$. From (2) it can be seen that the same coefficients a_1, a_2 can be estimated by regressing D against D_1, D_2, and constraining the fitted line to pass through the origin (because (2) does not have an intercept term). This second regression approach controls for age, sex and genetic factors (all in monozygotic twins and on average half in dizygotic twins).

From the Minnesota Twin Family Study (Iacono et al. 1999) we included 1,311 pairs of adolescent twins, and we found a negative association between birth weight and systolic blood pressure in the overall sample. The regression coefficient after controlling for current weight was –1.88 mm Hg/kg (SE 0.61), which corresponds to results from previous studies of singleton adolescents. The regression coefficient fell to –0.64 mm Hg/kg (SE 0.86) when the intrapair analyses were used. The largest reduction was observed among monozygotic twins: from –2.44 mm Hg/kg (SE 0.75) in the overall monozygotic twin sample to –1.06 mm Hg/kg (SE 1.14) in the analyses of the within monozygotic pair differences.

Overview

In 2002, Huxley and co-workers published an overview of the available data on the relation between birth weight and later life blood pressure. This relation has been put forward as one of the most consistent and strong evidence of the association between birth weight and later life health. This overview found a clear indication of publication bias as smaller studies reported a large effect while larger studies reported a small effect. Furhermore, it was somewhat disturbing to see that the hypothesis-generating group consistently reported a larger effect than other research groups.

Huxley et al. (2002) also summarized the available interpair comparison studies in twins and found, based on the above-mentioned study of the Minnesota twins and on other studies, that the confidence interval for the effect estimated by intrapair differences in twins was not different from zero. Even if the largest estimate of the relation between birth weight and blood pressure is accepted, that is to say a 2mm Hg increase in blood pressure for every increase in birth weight by *1 kilo*, this is clearly not an important factor on the individual level. Theoretically, it might be an important finding for understanding the etiology of blood pressure, but from a public health perspective, the change of 2mm Hg per one kilo difference in birth weight would not call for intervention. This view is underlined by the observation by Huxley and colleagues who draw attention to the fact that increase in birth weight also correlates with an increase in weight which might have an even stronger effect on the adult blood pressure than the inverse relation between birth weight and blood pressure, when current weight is controlled for. At present, therefore, too little is known about the effect, and the evidence of the correlation between early life growth and later life health and survival is not strong enough to have any practical importance for forecasting models.

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The Month of Birth: Evidence for Declining but Persistent Cohort Effects in Lifespan

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Introduction

In the second half of the 19th century, mortality started to decline and this decline seemed to follow a cohort pattern. A cohort pattern is direct evidence for the effect of early-life circumstances on adult mortality: improvements in the living environment early in life lead to reduced mortality during the whole life course. Early studies for England, Wales and Scotland (Kermack et al. 1934, 2001) suggest that, as far as mortality up to the year 1925 is concerned, the year of birth had more predictive power than the year of death. Around 1925, the responsible factors for the mortality decline changed and the year of birth lost its predictive power. Period factors became more and more important. In a recent study, Davey Smith and Kuh (2001) updated the table of relative death rates for England and Wales from the Kermack paper. They showed that from 1925 onwards at younger ages, death rates fell faster than predicted based on birth cohort regularities, whereas at older ages, mortality declined at a much slower rate than predicted.

Elo and Preston (1992) point out that the early studies were probably so successful in demonstrating cohort effects because they were based on mortality data from a time period before the process of mortality decline on a period level had begun. Once both cohorts and periods began to show mortality improvements, it became more difficult to separate the two.

The cohort decline at the beginning of the epidemiological transition is not without contest either. In their study of the Swedish mortality decline, Kermack et al. (1934, 2001) admitted that the cohort effect is not as clear as it was for England and Wales. The authors argue that a rectangular block dating from 1855 onwards and affecting the age groups 10 to 30 years was the primary cause of disturbances in the cohort decline. If the block is omitted, a cohort decline is observed. This result could not be replicated, however, in a

study of Swedish mortality between 1778 and 1993 by Vaupel et al. (1997). The conclusion according to Vaupel et al. is that "the pattern is clearly more complex than a pure cohort-effect model would suggest" (Vaupel et al. 1997: 63).

As a result of the loss of the predictive power of cohort factors around 1925, the emphasis turned towards period factors such as advances in medical technology, life-style, smoking, physical activity and diet. In the 1970s, however, Forsdahl (1973, 1977, 1978) observed that regional differences in adult lung cancer and heart disease were not related to contemporary differences in lifestyle, smoking behaviour, or socioeconomic status but rather to differences in regional infant mortality during childhood and youth of the cohorts under study. His study is now considered the starting point of a large and productive area of research that tries to link early-life conditions to the manifestation of chronic disease later in life. The discussion about early-life effects on health at adult ages gained momentum with studies conducted by the Southampton group of Barker and colleagues (Barker 1994; Barker and Osmond 1986a, 1986b, 1987). The group developed the fetal-origins hypothesis of adult disease (also known as the 'Barker hypothesis'), which suggests that coronary heart disease at adult ages results from poor conditions in utero caused by inadequate nutrition on the part of the mother and infectious diseases she suffered during pregnancy. Since inadequate nutrition of the fetus is reflected in low birth weight, the Barker hypothesis claims that growth retardation in utero leads to low birth weight and to an increased risk of chronic disease later in life. It seems that the main connection between birth weight and heart disease later in life is systolic blood pressure – infants with a low birth weight experience increased systolic blood pressure at adult ages.

The fetal-origins hypothesis has led to a large amount of research that generally concludes that low birth weight is associated with an increased risk of heart disease at adult ages and that low-birth weight infants suffer from increased systolic blood pressure later in life. The interpretation of these outcomes has been repeatedly challenged, however. The main idea underlying the fetal-origins hypothesis is that a critical period exists early in life and that negative effects during this period cannot be reversed later in life. Critics of the hypothesis frequently bring forward the argument that birth weight is confounded with socioeconomic status. Negative social factors in the early-life environment may set people onto life trajectories that negatively affect their health over the whole life course. Therefore, the almost universally observed relationship between birth weight and the risk of chronic disease later in life may be an outcome of the whole life course rather than the result of a critical period early in life (Joseph and Kramer 1996; Kramer 2000).

This criticism leads to the question whether one can find an indicator for the prenatal and early postnatal environment that is not related to the life-course. Birth weight certainly does not fulfil this criterion and, in addition, it is not widely available. Studies that use birth weight or other direct indicators of early-life circumstances are usually based on hospital data, which are invariable subject to selection bias. Moreover, their sample sizes tend to be modest.

The fetal-origins hypothesis suggests that nutrition and infectious diseases during the pregnancy of the mother are responsible for growth retardation in the infant, which leads to an increased risk of heart disease at adult ages. Both nutrition and infectious diseases are highly seasonal: respiratory infections peak in the autumn and winter, and gastrointestinal infections peak during warm periods of the summer months. The availability of fresh fruits and vegetables – and thus of micronutrients – tends to change according to the seasons of the year. An indicator that reflects the seasonally changing environment during the prenatal and early postnatal period is month of birth.

Epidemiological research on the underlying factors of schizophrenia has long used month of birth as an indicator for early-life circumstances that affect the risk of schizophrenia later in life. This line of research dates back to Ellsworth Huntington, who in 1938 published his book about seasonality (Huntington 1938), in which he describes the relationship between the seasons of the year and social, psychological, and demographic phenomena. By 1997, more than 250 studies about the month-of-birth effect in schizophrenia had appeared and many more are still being published (Torrey et al. 1997). Most of the research on the relationship between month of birth and the incidence of diseases has been conducted for mental disorders, in particular schizophrenia and bipolar disorders. The season-of-birth effect has also been studied for autistic disorder, Alzheimer patients, anorexia nervosa patients, and for diseases of the nervous system such as Parkinson's disease, multiple sclerosis and epilepsy. Recently much attention was for example given to the month-of-birth effect in insulin dependent childhood diabetes. For a review of studies about the relationship between month of birth and certain diseases, see Doblhammer (2004). Many of these studies suggest that virus infections in utero or in the first few months of life are responsible for the increased risk of developing a certain disease. None of these studies, however, provides concrete evidence for a specific causal mechanism.

Although widespread evidence exists concerning the month-of-birth effect for certain diseases, little attention has been given to the question whether there is a correlation between the month of birth and lifespan and whether this relationship has changed over cohorts. If the month-of-birth effect decreases in younger cohorts then this suggests that the influence of the very

first period of life on adult lifespan has reduced over time. Two recently published studies point in this direction. A study of young adults in rural Gambia found a significant difference in survival to age 45 by month of birth (Moore et al. 1997). When the authors repeated their study on a rural Bangladeshi population, they could not detect an effect of season of birth on survival (Moore et al. 2004). Furthermore, a study of early adult death in rural Senegal also failed to find any influence between month of birth and survival at young adult ages (Simondon et al. 2004). Both Moore and colleagues and Simondon and colleagues suggest that the negative findings in the Bangladeshi and Senegal population are due to cohort effects. While the data for Gambia are based on births during the 1950s and 1960s, the Bangladeshi and Senegal data include individuals born between 1974 and 2000 (Bangladesh), and 1962 and 2000 (Senegal).

This article takes up the question whether the season-of-birth effect in lifespan has changed over time and whether it is less important for more recent than for older cohorts. To answer this question the article first describes the month-of-birth pattern in lifespan for selected countries of the Northern (Austria, Denmark, and United States) and Southern Hemisphere (Australia). Second, a cohort analysis is performed based on the Danish register data and of consecutive US census rounds that include information about the season of birth. Third, the underlying causal mechanisms behind the month-of-birth effect are reviewed and finally, outcomes are discussed in the light of mortality forecasting.

Data

The optimal data to test for differences in lifespan by season of birth are longitudinal data. Birth cohorts born in a specific season are followed from birth to death and life expectancy can be calculated using simple life-table methods. Such data rarely exist however. The data that are closest to this requirement are register data from the Scandinavian countries. The Danish data used in this study consist of a mortality follow-up of all Danes who were at least 50 years old on 1 April 1968. This totals 1,371,003 people, who were followed up to week 32 of 1998. The study excludes 1,994 people who were lost to the registry during the observation period. Among those who are included in the study, 86% (1,176,383 individuals) died before week 32 of 1998; 14% (192,626 individuals) were still alive at the end of the follow-up.

Population registers do not exist for Austria, Australia and the US, where only individual death records are available. Exact dates of birth and death are known for in all 681,677 Austrians who died between 1988 and 1996 and for

219,820 native-born Australians who died between 1993 and 1997 at ages 50+. Two data sources are used for the United States. First, US death records for the years 1989 to 1997, which include place of birth, are the basis for the analysis of the month-of-birth pattern in lifespan. Second, the three US census rounds 1960, 1970, and 1980 are used to study cohort patterns. These three census rounds are the only rounds that include information about the quarter of birth. Data are extracted from the "Public Use Microdata Samples", which are accessible under http://usa.ipums.org/usa/. The extract is restricted to the native-born white US population aged 0 to 100. For whites, this gives a sample size of 1,490,444 in 1960, 1,672,107 in 1970, and 1,812,839 in 1980.

Methods

For Denmark, both the risk population and the number of deaths are known which means that it is possible to estimate remaining life expectancy at age 50 based on life tables that were corrected for left truncation. This was achieved by calculating occurrence and exposure matrices that take into account an individual's age on 1 April 1968. For example, a person who was 70 at the beginning of the study and who died at age 80 enters the exposures for ages 70 to 80 but is not included in the exposures for ages 50 to 69. The central age-specific death rate is based on the occurrence-exposure matrix. The corresponding life-table death rate is derived by means of the Greville Method (Greville 1943).

For Austria, Australia and the United States, the population at risk is unknown, which means that lifespan by month of birth cannot be estimated based on simple life-table techniques. For these three countries, remaining lifespan at age 50 was therefore estimated by calculating the average of the exact ages at death. It has been pointed out that using mean age at death as an approximation for life expectancy may lead to serious bias in the observed month-of-birth pattern (Gavrilov and Gavrilova 2003). It is well known that mean age at death does not correctly estimate life expectancy in non-stationary and non-extinct populations. The emphasis of this study, however, is not life expectancy per se but the month-of-birth pattern in life expectancy, which generally should not be affected. There is one exception, however. If the seasonal distribution of births has changed over time then not only life expectancy but also the month-of-birth pattern is biased when estimated based on mean ages at death. If more people proportionally are born in spring in younger cohorts than in older cohorts, then for a given time period the mean age at death will be biased downward for those born in spring. In the case of Austria and Denmark, the changes in the seasonal distribution of

births over time are minor, however, and the effect on the month-of-birth pattern is negligible (Doblhammer 2004).

The Danish register data consist of sufficiently large numbers of exposures and deaths to distinguish between age and cohort effects. Two ten-year birth cohorts are followed over an age-span of 20 years. The birth cohort April 1908 to March 1918 enters the study period between the ages of 50 and 59 and 11 months. They are followed from age 60 to age 79 in order, theoretically, to allow each member of the cohort to reach each age. The second cohort is aged 60 to 69 and 11 months at the 1968-baseline and is followed from age 70 to age 89. This specification allows the study of age-specific death rates at ages 70 to 79 for both cohorts. Conditional on surviving to age 70, all individuals are followed from age 70 to age 79. Those who survived age 79 are treated as censored. Mortality of the two cohorts between ages 70 and 79 is modelled by a proportional hazard model with the baseline hazard following a Gompertz function (1),

$$\mu\left(x|y_i\right) = ae^{b_0 x}e^{b_1 y_1 + b_2 y_2 + b_3 y_3} \qquad (1)$$

where $\mu\left(x|y_i\right)$ is the force of mortality at age x conditional on covariates y_i, a is the age-independent level of mortality and b_0 the increase in mortality over age. The three indicator-variables, y_1, y_2 and y_3, denote the quarter of birth and take the value one if a person is born in a specific quarter, and zero otherwise; the first quarter is defined as reference group. The parameters a, b_0, b_1, b_2, and b_3 are estimated by maximising the likelihood function. For each of the two cohorts, a separate model is estimated.

To estimate differences in survival according to the quarter of birth based on the US censuses for the year 1960, 1970, and 1980, a method called Survival-Attributes Assay (Christensen et al. 2001) is applied. This method uses cross-sectional data on "fixed-attributes" to estimate the effect of a fixed trait on survival.

Let N_x be the number of people at age x. Let p_x be the proportion of x-year-olds who have some fixed attribute such as the season of birth. Let p_{x+n} be the proportion at age $x+n$. Let s be the conditional survival probability from age x to age $x+n$ for the individuals who have the fixed attribute. Let S be the conditional survival probability from age x to $x+n$ for the entire cohort.

Then, because

$$p_x N_x s = N_x S p_{x+n} \qquad (2)$$

it follows that

$$s = S \frac{p_{x+n}}{p_x} \qquad (3)$$

Thus, the relative risk of surviving from age x to age $x+n$ for people born in a specific quarter is the ratio of their observed proportions in the two cross-sections. The proportion of the population within ten-year age groups that is born in a certain quarter of the year is followed over the three census rounds.

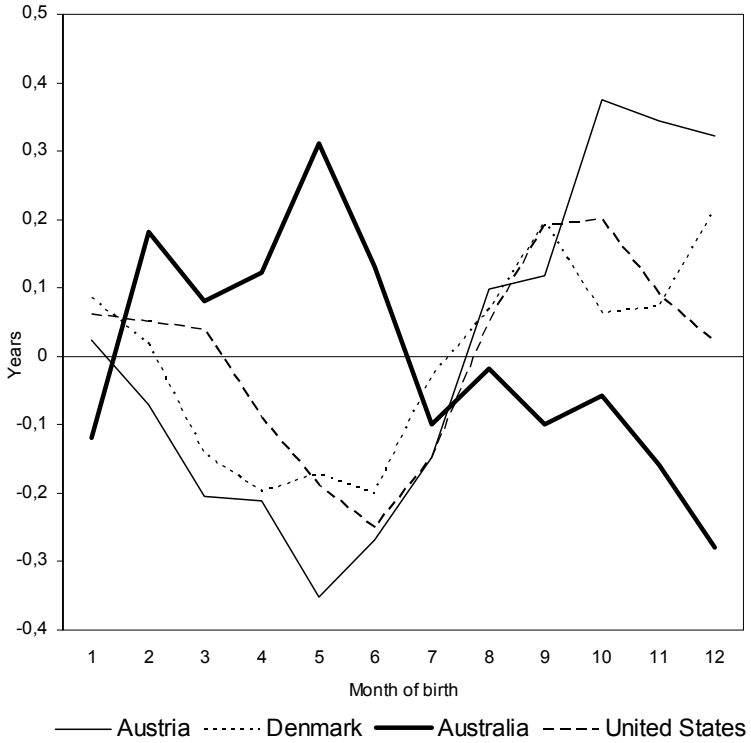
This method relies on the assumption that the x+20-year-olds in the third cross-section were similar to the x-year-olds in the first cross-section twenty years earlier; e.g. the 70-year-olds in 1980 are the survivors of the 60-year-olds in 1970 and the 50-year-olds in 1960. In other words, the change in the proportion of the fixed attribute over an age range of twenty years is solely due to age effects and not affected by cohort effects. Differences in the survival probability of ages that are further apart than twenty years can be both due to cohort and age effects. The method of Survival-Attributes Assays therefore, does not permit a clear distinction between age and cohort effects. The main advantages of the method are, however, that it does not require the calculation of death rates in order to verify the month-of-birth effect and that it can be used to study differences in survival at ages where death rates are low and therefore subject to random fluctuations. Thus, it can be used to study whether differences in survival by season of birth not only exists among today's elderly but also among more recent cohorts.

Results

Differences in lifespan in the United States, Austria, Denmark and Australia

A similar relationship between month of birth and lifespan exists in all of the Northern Hemisphere countries (Figure 1). Adults born in the autumn (October–December) live longer than do adults born in the spring (April–June). The difference in lifespan between the spring- and autumn-born is twice as large in Austria (0.6 years) as in Denmark (0.3 years).

Figure 1 **Deviation from average remaining lifespan at age 50 for people born in a specific month in Austria, Australia, Denmark and the United States**



In Denmark for those born in the second quarter, lifespans are 0.19 ± 0.05 years shorter than average; for those born in the fourth quarter they are 0.12 ± 0.04 years longer than average. This difference is statistically significant (Cox-Mantel statistic: $p<0.001$). Also in Austria the deviation in mean age at death is highly significant (Bonferroni test: $p<0.001$) for those born in the second and the fourth quarters. The lifespans of people born between weeks 14 and 26 are 0.28 ±0.03 years below average; lifespans of those born between weeks 40 and 52 are 0.32 ± 0.03 years above average. A highly significant difference in mean age at death by month of birth exists for US decedents who died between 1989 and 1997. Those born in June and July die about 0.44 years earlier than the October-born. The pattern in the Northern Hemisphere is mirrored in the Southern Hemisphere. The mean age at death of people born in Australia in the second quarter of the year is 78.0; those born in the fourth quarter die at a mean age of 77.65. The difference of 0.35 years is statistically significant (Bonferroni test: $p<0.001$).

Changes in the month-of-birth pattern over cohorts in Denmark

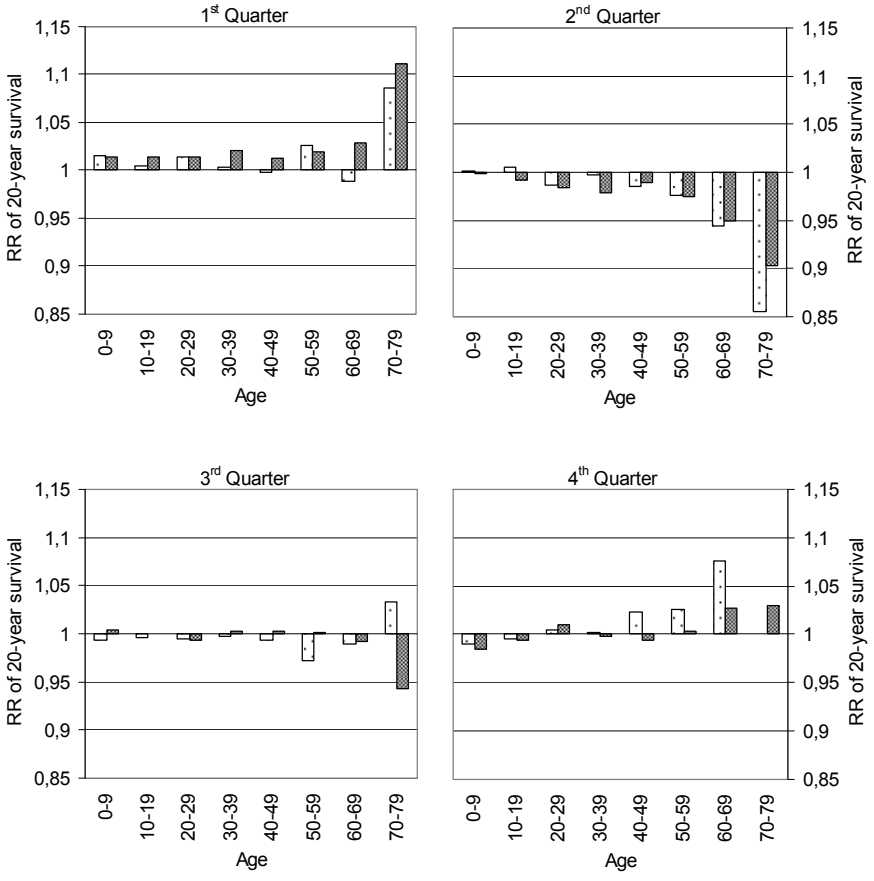
Table 1 contains the parameter estimates ln(*a)* and b_0 and the odds ratios of the Gompertz models for the two cohorts 1889 to 1908 and 1909 to 1918. In the older cohort (1889 to 1909), there exists a significant excess mortality of those born in the second quarter (+3% as compared to those born in the first quarter). People born in the fourth quarter experience the lowest mortality risk (–2 % compared to those born in the first quarter). In the younger cohort (1909 to 1918), the differences in mortality by quarter of birth become statistically not significant.

Table 1 Parameter estimates and 95% confidence intervals of the Gompertz models estimated for Danes born in a specific quarter for birth cohorts 1898–1909 and 1909–1918 at ages 70–79

	Parameter estimate	95% LCI	95% UCI
Cohort 1898–1909			
1st quarter	1.00		
2nd quarter	1.03	1.02	1.04
3rd quarter	1.00	0.99	1.02
4th quarter	0.98	0.96	0.99
ln(a)	–3.44	–3.45	–3.43
b0 x 102	8.59	8.42	8.76
Cohort 1909–1918			
1st quarter	1.00		
2nd quarter	1.08	0.96	1.21
3rd quarter	1.05	0.94	1.18
4th quarter	1.06	0.95	1.19
ln(a)	–3.51	–3.62	–3.39
b0 x 102	8.08	7.49	8.68

Source: The Office for National Statistics

Figure 2 **Relative risk of twenty-year survival by age in the 1960 US census by sex (males = white-dotted bars, females = grey bars) and quarter of birth**



Changes in the 20-year survival probability by quarter of birth in the United States

Figure 2 shows the relative risks of the 20-year survival probabilities conditional on age for people born in a specific quarter compared to the average population.

At younger ages, the mortality advantage of the autumn-born and the disadvantage of the spring-born is minor. For males, it is a maximum of one per cent over an age range of 20 years. In other words, up to the age of 40 the conditional survival probability of surviving the next 20 years is about one

per cent higher for the autumn-born than for the average population; it is one per cent lower for the spring-born. Differences in the 20-year survival start to accelerate from the age group 40–49 onwards, when those born in the fourth quarter have a higher chance of 2.4% to survive the next 20 years; this advantage increases to 7.8 % for ages 60–69. The disadvantage in the 20-year survival of people born in the second quarter starts at ages 50–59 and is about minus 2.8 per cent. It increases to minus 6.6 per cent for the age group 60–69. Similar trends emerge for women.

Discussion

In all four populations, Austria, Australia, Denmark and United States, significant differences in lifespan exist by month of birth. Those born is spring generally face a lower life expectancy than those born in autumn This finding is independent of the Hemisphere as is shown by the Australian result.

The US death data contain detailed information about the state of birth, education, marital status, and race of the deceased (Doblhammer 2004). Among the white US population, the age-standardised peak-to-trough difference in the month-of-birth pattern increases from the North to the South while the basic pattern remains unchanged. The difference is smallest in New England, with 0.31 years and largest in the East South Central Region, with 0.86 years. The differences in the West are intermediate. The age-standardised differences in lifespan by month of birth vary significantly according to education levels. The difference between the spring trough and the winter peak is 0.62 years for those with a low education and 0.38 years for the highly educated. There exists a highly significant difference in the month-of-birth pattern by marital status. The difference between the peak and the trough is largest for the never-married (0.62 of a year), and smallest for the married (0.40 of a year); the widowed (0.45 of a year) and the divorced (0.44 of a year) are intermediate. The month-of-birth pattern of the 1.7 million US African Americans differs significantly from that of the white population. It differs not only with respect to the number of years between the trough and the peak (0.57 years) but also with respect to the shape of the curve. The mean age at death is highest for those born between January and March. As in the case of the white population, the mean age at death for African Americans is lowest for decedents born in July.

In a multivariate analysis of ages at death in the United States (Doblhammer 2004), the main effects of sex, month of birth, education, race, region of birth, marital status and all the two-way interactions of the variables are highly significant. This implies that the regional differences in the month-of-

birth pattern are neither due to differences in education nor to differences in race but they exist independently of them. Overall, above factors explain 25 per cent of the variation in ages at death. About 86 percent of the model explanation is due to the effect of marital status and only 0.4 percent to the effect of month of birth. The large majority (70%) of this 0.4 percent result from the interactions of month of birth with region of birth and race.

What are the causal mechanisms behind the month-of-birth effect on life-span? One frequently raised concern is that the month-of-birth effect reflects the seasonal distribution of deaths rather than the seasonal changes in the early-life environment. More specifically, the concern is that the interaction between the seasonal distribution of deaths and the monthly increase in adult mortality causes a month-of-birth pattern. This hypothesis has been already widely discussed in the research about the month-of-birth effect in schizophrenia, whose incidence is seasonal and whose risk increases with age. Two studies (Doblhammer and Vaupel 2001; Doblhammer 2004) have shown that, although month of birth, age, and month of death influence mortality simultaneously, they are independent of each other.

A second, frequently raised concern is that the month-of-birth effect is caused by socioeconomic differences in the seasonal distribution of births. The number of births is distributed seasonally over the year with the exception of only a few populations. If the seasonality in births is partly driven by the preference of couples for giving birth in certain seasons of the year, then this preference may differ between social groups. In schizophrenia research, this explanation is generally known as the procreational habits theory. Individuals with schizophrenia may have a procreational pattern that differs from those of the non-schizophrenic population (Torrey et al. 1997). On basis of the 1981 census for Austria, it was possible to refute this hypothesis (Doblhammer 2004). This is also true for the deadline hypothesis. Starting school is usually tied to reaching a certain age before a certain deadline. Children who are born shortly after the deadline have to wait an additional year before the can start school and will therefore be among the oldest of their classmates. This may pose a special advantage compared to those who are born shortly before the deadline, who will thus always be among the youngest. However, since the mean age at death of the autumn-born is higher than that of the spring-born, the deadline hypothesis cannot explain the month-of-birth effect on the lifespan.

Public health experts at the beginning of the 20th century felt that the health status of mothers and whether mothers breastfed their babies were the two most important factors determining the survival of an infant, followed by housing, sanitation and general poverty (Preston and Haines 1991). The

health status of pregnant women depended largely on their diet and on the general disease load. Breastfeeding the infant is related primarily to a lower incidence of infectious diseases of the gastrointestinal tract, which historically is the major cause of infant mortality. Danish data on historical infant mortality between the years 1911 and 1915 show that it is the spring-born who experience higher mortality in their first year of life (Doblhammer 2004). The standardised death rate of the June-born infants is 30 per cent higher than the death rate of the December-born. This finding implies that those factors that contributed to the high infant mortality of the past are also the factors that cause the differences in lifespan by month of birth.

Nutrition is highly seasonal. Diet at the beginning of the 20th century did not much resemble contemporary dietary patterns. People ate less meat, fruits, and vegetables and more starchy staple food. The first vitamins were not discovered until 1911, and in the early 1900s, nutritionists were even opposed to greens, which were considered to require more bodily energy for digestion than they provided. Although severe malnourishment was not widespread, people had inadequate nutrition – particularly during the winter and early spring. Peak growth of the fetus in utero occurs during the third trimester. For infants born in spring, the third trimester coincides with a period of largely inadequate nutrition; for those born in the autumn it coincides with a period of plenty.

The effect of nutrition early in life on adult health is highly contested. Studies that looked at the old-age mortality of cohorts born shortly after periods of famine, which were thus presumably marked by severe malnutrition of the mother during the gestational period of their unborn, did not find any differences (Kannisto et al. 1997). Two studies about the long-term effects of severe starvation during the siege of Leningrad come to contrary results (Stanner et al. 1997; Sparén et al. 2003). The effect of the Dutch famine in 1944–1945 on later life disease and mortality is explored in a series of studies (Rosenboom et al. 2001, 2000a, 2000b). The authors find that mortality up to age 18 was higher for those born before the famine and those exposed to the famine in the third trimester. Between the ages of 18 and 50, however, no effect of prenatal exposure to the famine could be demonstrated. Thus, the evidence is weak concerning the effect of nutrition during gestational age on mortality later in life.

The incidence of infectious diseases depends on the climate and on the seasons of the year. The incidence of waterborne infectious diseases, which affect mainly the gastrointestinal tract, is correlated with warmer temperatures and flooding. Peak climatological temperatures coincide with the incidence of foodborne diseases. Many childhood diseases are highly seasonal;

airborne diseases affecting the respiratory tract usually peak in autumn and winter. Historically, people born in years with extremely high infant mortality caused primarily by whooping cough and smallpox tend to have higher mortality later in life (Bengtsson and Lindström 2003).

Infant mortality at the turn of the 20th century was mainly caused by exogenous factors, in particular infectious disease. Infants born in spring had an increased risk to die from infectious disease during their first year of life. The month-of-birth patter in adult lifespan suggests that those who survived were debilitated and suffered from higher mortality during adult ages.

Explanations other than nutrition and infectious disease have also been brought forward to explain the month-of-birth effect. One of the first to study the influence of the month of birth on the lifespan was Elsworth Huntington, who formulated the hypothesis in 1936 that high temperatures at the time of conception weaken the "germ plasma" of the parents, with negative effects on the development of the foetus. Recent research has shown that the sperm quality of men who work outdoors does indeed decrease during periods of high temperatures (Centola and Eberly 1999). A related hypothesis is that hot summers are the cause of protein deficiencies at the time of conception (Pasamanick 1986). This hypothesis is clearly ruled out on basis of the US death data. The United States consists of six major climatic zones with very different climatic conditions. Since the US death data contain the state of birth, it is possible to correlate the peak-to-trough difference in lifespan by month of birth for people born in a specific state with maximum and minimum temperature and with the maximum difference in temperature. It appears that no correlation exists between the peak-to-trough difference and the temperature variables, neither for total mortality nor for major causes of death (Doblhammer 2004).

Another explanation is that seasonal changes in the hours of daylight influence the human endocrine functions and that the month-of-birth effect might be caused by variations in the internal chemistry or neural development brought about by the seasonal variations in light (Wehr 1998; Turnquist 1993; Quested 1991; Morgan 1978; Jongbloet 1975; Pallast et al. 1994).

Conclusion

The analysis of the Danish register data and the consecutive US census rounds shows that the differences in lifespan by month of birth have become smaller over time. This is consistent with the explanation of nutrition and infectious disease since both have considerably improved over time. Al-

though diet still differs between spring and fall, the difference in the nutritional value is much smaller than at the beginning of the 20th century. In addition, the epidemiological transition has reduced infectious disease to a minor cause of death.

Ample evidence exists that the health of today's elderly is scarred by negative events that they experienced during their pre-natal or early post-natal life. This study shows that already among the elderly, those born in more recent years are less affected by seasonal early life factors and that the month-of-birth effect has become smaller. This finding suggest that in more recent cohorts period factor as opposed to cohort factors have gained increased importance and that period factors may therefore predominantly determine future gains in life expectancy.

On the other hand, the US census rounds indicate that differences in the 20-year survival still exist at young ages between 1960 and 1980. In addition, a study of twins born in the 1970s in Minnesota (Doblhammer 2004) shows that the seasonal pattern in birth weight – a widely used indicator for growth retardation in utero – is positively correlated with the month-of-birth pattern in the mean age at death of decedents aged 50+ who were born in Minnesota. Thus, there exists evidence that the seasonal fluctuations in the early life environment of recent cohorts have still an effect on life expectancy.

Huge gains have been made in the health environment during the very first period of life during the last century. Infant mortality has fallen drastically during the last century. Since infant mortality in the early 20th century was primarily due to exogenous factors such as infectious disease, the decline in infant mortality points to a largely improved health environment of infants and children. However, in the 1980s and 1990s researchers have repeatedly pointed out that decreasing poverty among the elderly has led to increasing poverty in childhood (Preston 1984), particularly in the United States. A recent article by Komlos and Baur (2004) finds that in the most recent decades the height of Americans has been lagging behind that of Europeans while at the beginning of the 20th century they were the tallest of the world. The authors even present some evidence that heights have been stagnating among US men and might actually be decreasing among females born in the 1960s. Height primarily reflects the socioeconomic and epidemiological environment during childhood and adolescence. It is significantly correlated with health and longevity at adult ages. Height and life expectancy rises together.

In an ageing society with too few children and an ever increasing proportion of the old and very old the danger exists that resources in general and social

transfers in particular are channelled towards the elderly which may lead to increasing poverty among children. In his 1984 article, Preston wrote, "that the transfers from the working age population to the elderly are also transfers away from children [...]". Thus, childhood poverty may become an ever more widespread phenomenon leading to a deterioration of the social and epidemiological environment early in life. In this case, cohort factors may gain importance again in mortality forecasting.

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Early-Life Conditions and Old-Age Mortality in a Comparative Perspective: 19th Century Sweden and Belgium*

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Introduction

Kermack and colleagues (1934) proposed the cohort explanation in their analysis of the aggregated mortality decline in England, Wales, Scotland, and Sweden. Their conclusion was that reductions in the death rates of the various age groups attained at any particular time depended primarily on the individuals' date of birth, and only indirectly on the particular year under consideration. The essential effects on health and survival of adults and older persons were mainly caused by improvements and beneficial effects on their respective birth cohorts during childhood several decades earlier. Jones (1956) brought up the cohort approach anew and recently it has gained focus again through works in medicine but also in historical demography (Barker 1994; Elo and Preston 1992; Fogel 1994; Fridlizius 1989; Kuh and Ben-Shlomo 1997; Preston et al. 1998; Finch and Crimmins 2004). The plausible causal relationships between early-life experiences and old-age mortality have been discussed, with special attention to intrauterine cellular development and cellular development during early childhood. Robert Fogel (1994)

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has proposed several plausible causal mechanisms that connect malnutrition in utero and during early life to chronic diseases in later life. These propositions are also supported by the work of Barker (1994, 1995) 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. In contrast, Jones (1956), and later Fridlizius (1989), in his analysis of the aggregated mortality decline in Sweden, proposed that the genesis of disease in later life could be due to exposure to certain infectious diseases in the first years of life. Fridlizius argued that this was caused by life-long reduced immunity, which consequently gave higher general risk of other infectious diseases in later life. The knowledge of the medical mechanisms today seems to be more in favour of permanent retardation of organs due to infections rather than immunological mechanisms (Finch and Crimmins 2004). Either way, it implies that factors other than nutrition are important early-life determinants of mortality in later life, because the outcome of some other important infectious diseases, like smallpox, is almost completely unrelated to the nutritional status of the infected individual (Rotberg and Rabb 1985).

In two recent essays, Bengtsson and Lindström (2000, 2003) investigated the different cohort hypotheses using longitudinal data for individuals instead of aggregated data like Kermack et al., Fridlizius, and many others. Bengtsson and Lindström analysed demographic and economic data for individuals and households and combined with community data on food prices and disease load. The analyses included variables measuring conditions during the fetal stage and the first year of life, as well as the disease load and access to nutrition (food prices). Strong support was found for the hypothesis that the disease load experienced during the birth year had a consistent impact on mortality in later life (Bengtsson and Lindström 2003). This was particularly the case with the outcome of airborne infectious diseases during old age (Bengtsson and Lindström 2000). The hypotheses that access to nutrition and the disease load on mothers during the fetal stage had impacts on mortality in later life were not supported and neither was the hypothesis about the effects of access to nutrition during the first year of life.

Table 1 Estimation of effects of infant mortality rate at birth on mortality in ages 55–80 years in various diseases

Death cause	Deaths	Rel. risk	Wald P-value
Airborne infectious disease	343	4.65	0.00
Non-infectious diseases	208	3.41	0.05
Old-age mortality	339	1.46	0.45
All causes of death	1 400	1.80	0.03

Note: The model controls for sex, birth year, birthplace, socioeconomic status, time period, and logarithm of current rye prices in four Scanian parishes, 1766–1894. Number of deaths = 1,400.

Source: Bengtsson and Lindström (2000: table 5).

The influence of short-term variations in infant mortality on old-age mortality was due to both cycles in infant mortality and trend (Bengtsson and Lindström 2003). A test of potential nonlinearity of the cycle effect reveals that only years with particularly high disease load had an impact on mortality in later life (Bengtsson and Lindström 2003). Highly virulent infectious diseases, especially smallpox and whooping cough, dominated infant mortality in those years (Bengtsson and Lindström 2003). These diseases are so virulent that the outcome shows no social gradient, and they probably penetrated the entire population. Smallpox, which was mainly a childhood disease during the eighteenth century, was not only highly virulent but also equally mortal with an overall fatality rate of about 15 percent (Sköld 1996: 70–75; Riley 2001). The eighteenth-century pattern of total childhood dominance in smallpox mortality indicates that during this period the majority of the adult population had already been exposed to smallpox as children, and had survived. The fact that airborne infectious diseases in the first year of life particularly affected old-age mortality may imply that exposure to airborne infectious diseases during the first year of life may make individuals more vulnerable throughout life. Cohorts exposed during infancy to such infectious diseases may thus be much more susceptible to high morbidity and mortality rates in old age than cohorts exposed later in childhood to epidemics of smallpox and other infectious diseases. The causal biological mechanisms in early life that might explain these significant associations are only partly known (for further discussion, see Bengtsson and Lindström 2003; Lindström and Davey Smith 2008).

In another recent essay on the effect of different forms of community variables, Bengtsson et al. (2002), analyse early-life links in further detail. The essay supports the earlier conclusion that the functional form of the effect of exposure is nonlinear and includes valuable information about the causal link.

Furthermore, it shows that while both observed and unobserved characteristics at family level – whether the result of genetics or of shared experience – had a significant impact on mortality in later life, their inclusion in the models only marginally alters previous estimates.

The main question in this paper is whether these historical findings for rural Sweden are a local, or possibly a Nordic, phenomena, or if we find the same pattern outside Sweden. We have therefore replicated the study for southern Sweden with one for the rural parish of Sart in eastern Belgium. The population we analyze in Sart are born in the period 1799 to 1846 and followed until 1899. For southern Sweden, we analyze the population born between 1750 and 1840, followed to 1895. The longitudinal demographic data on individuals and household socioeconomic data from parish registers were combined with community data on food costs and disease load, using a Cox regression analysis for the mortality among ever-married persons in ages 55–80 years. In addition to trying to answer the main question, we will briefly discuss whether information about conditions early in life can be used to improve mortality forecasting

Models

We use a *proportional hazards model* (Cox 1972). This means that we assume that a relative effect on mortality of any covariate is constant over age. The model allows time-varying covariates. It is very important to check the assumptions behind this model, especially the proportionality assumption. We have therefore routinely tested all models for deviations from the proportionality assumption.[1] The test we have used is based on the correlation between log(t) and the Schoenfeld residuals for each covariate. A large correlation indicates that the corresponding coefficient varies with time, which means that the hazards are not proportional. We found no signs of nonproportionality for any of the covariates or globally.[2]

Data for Scania

The Swedish data come from the Scanian Demographic Database, which consists of records of births, marriages, deaths, and migrations for nine rural

[1] We used the function 'cox.zph' in the 'survival' package in R.

[2] For a more detailed description of the test, see Therneau and Grambsch (2000: chapter 6, 127–152).

parishes and one town situated in the southernmost part of Sweden. The material for two of the parishes dates back to 1646 and for the others to the 1680s. The publicly available records end in 1895. Four of the rural parishes – Hög, Kävlinge, Halmstad, and Sireköpinge – are included in this study. The parish register material is of high quality and shows few gaps for births, deaths and marriages. Migration records are less plentiful, but continuous series exist from the latter part of the eighteenth 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.

Our interest in life-course effects on later-life mortality further limits our dataset. We need information about socioeconomic conditions at birth not only for those born in the parish but also for in-migrants. Data needed to create information for the socioeconomic condition at birth of an in-migrant can be obtained from the birth parish, but is generally available only after 1829. We have therefore had to limit the period of our analyses to 1829–1894.

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, while freehold and crown land dominated in Kävlinge and Hög. The parishes each had 200–500 inhabitants in the latter half of the eighteenth century. The agricultural sector in Sweden, and Scania, became increasingly commercialised in the beginning of the nineteenth century. New crops and techniques were introduced. Enclosure reforms and other reforms in the agricultural sector influenced the population growth, in particular in Sireköpinge, which experienced rapid population growth. In Kävlinge, the establishment of several factories and railroad transportation led to rapid expansion from the 1870s onwards (see Bengtsson 2001 for more details).

The social structure of the agricultural sector is often difficult to analyse since differences of wealth between the various categories of farmers and occupations are unclear and subject to change with the passage of time. Land was the most important source of wealth in the societies we analyse. Data from land registers on types of tenure is limited and therefore must be combined with information from poll tax records concerning farm size in order to arrive at a better understanding of each household's access to land. The category *peasant* includes freeholders, tenants on crown land, and tenants on noble land as well as a few tenants on church land. We only include peasants

with farms larger than 1/16 *mantal* in this category since it has been argued that peasants with smaller farms were not self-supporting. *Mantal* was not a measure of the actual size of the farm but a tax-assessment unit based on potential productivity. The few persons belonging to the nobility are also included in this group. The second group includes farmers with land smaller than 1/16 *mantal,* crofters, and the landless workers, the latter being in majority (see Bengtsson and Lindström 2000 for more details). Thus, we are only differentiating between two social groups: those with land enough to feed a family and those who need to work for someone else to be able to support a family.

The nineteenth century was a period of considerable social change in the countryside. It has been described as a period of proletarianization and pauperization (see Lundh 1983 for an overview). The numbers of landless increased (Carlsson 1968). The downward mobility was significant since many children of farmers were unable to obtain a farm themselves. This was true both for Sweden in general and for the area we study (Lundh 1998). Downward mobility was also common among the elderly, since many either sold their farms or gave them to their children. However, they could still be rather well off since the new owner of their farm often had to look after them in accordance with special contracts (*undantagskontrakt*). Not only did social stratification increase at the beginning of the nineteenth century, the economic condition of the landless worsened. They were, for example, more vulnerable to short-term economic stress than they were both before and after this period (Bengtsson and Dribe 2005).

The nineteenth century was also a period of rapidly expanding population in Scania as well as in Sweden in general (see Bengtsson 2001). Fertility rates were rather stable and mortality fell, first among infants and children, later among adults and the elderly. During the period we study, the crude death rate for ages 55–80 years was declining in the four parishes, as in the rest of Sweden. Life expectancy of Swedish women was the highest in the world (about 45 years around 1830) and remaining life expectancy at age 55 was about 16 years. The figures for men were several years lower. The corresponding figures for our four parishes are slightly higher than for Sweden.

Mortality in ages 55–80 years varied markedly from one year to the next and showed a downward trend, as was the case nationally in Sweden (Jones 1956; Fridlizius 1989). The models that we apply include a number of variables: sex, whether a person has in-migrated to the parish or not, the parish of residence, birth year, current food prices, season of birth and four other variables as indicators of conditions in early life (see Bengtsson and Lindström 2000, 2003 for details). The infant mortality rate in the year of birth, a

time-varying community variable, is used as a fixed early-life covariate. It measures the disease load during first year of life. Here the variation from one year to the next is also large but diminished somewhat over time. The trend is upward for most of the eighteenth century and downward from the 1780s onwards. Thus, old-age mortality is preceded by a decline in infant mortality by about 70 years. In order to separate effects of the trend from the effects of occurring cycles in infant morality, we have constructed two variables: a trend variable, constructed using a Hodrick-Prescott filter and a variable designed to pick-up cycles, measured as deviations from the trend. We have then categorized the variable "infant mortality rate cycle" into five groups, the upper one at 0.12.[3]

The aggregated indicator of the food prices is included in the regressions as a time-varying communal covariate (Bengtsson 1989, 1993). We use the deviation from the log trend in rye prices as an indicator. This means that the aggregated economic information is used as a time-varying covariate common to all individuals in the risk set at each point in calendar time.[4] Both price at birth and price at the time of conception are included in the models. Thus, we estimate the effects of food availability both during pregnancy and during first year of life. We use local prices of rye, the most common crop, referring to the conditions in the fall, and we estimate the effects of food prices during the subsequent year (see Bengtsson 2001 for more details). Finally, we include mortality in ages 20–50 years as an indicator of the disease environment during pregnancy.

Data for Sart

Our Belgian data come from the municipality of Sart, located in the Ardennes region, close to the German border. Although the commune is geographically quite large compared to other Belgian communes, it has always been sparsely populated (42 inhabitants per square kilometer in 1846). The territory of Sart includes part of the area known as the "Hautes Fagnes," a high plateau of peat bogs and forest where agriculture has always been marginal. The population of Sart resided in a half dozen hamlets on the northern slopes of the Fagnes. Each one remains an island surrounded by forests. The area was very poor in the nineteenth century (Alter et al. 2004b).

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[3] For further discussion of the functional form, see Bengtsson et al. (2002).

[4] We use the free software R (Hornik 2002), and the R package eha, which can handle time-varying community covariates in a simple way (Broström 2002).

The rural population of the Ardennes was mostly composed of smallholders on middle-sized farms. At the beginning of the nineteenth century, much of the land in Sart was held in common, and recognized members of the community had a variety of rights on common lands and forests (Vliebergh and Ulens 1912). An 1847 law encouraged the sale of common land and the formation of larger holdings, but the few large estates that resulted were abandoned shortly thereafter (Vliebergh and Ulens 1912: 62). Agricultural techniques were primitive at the beginning of the century, and farmers depended heavily on forests for both wood and feeding livestock. The population of Sart grew from about 1,800 persons at the beginning of the nineteenth century to about 2,500 in 1850, and there are signs of increasing population pressure (Alter et al. 2004a). After 1850, the area was strongly affected by the rapid industrialization of the region. Sart is less than 20 km from Verviers and 40 km from Liège, two important centers of the Industrial Revolution. Out-migration to industrial centers increased rapidly after 1850 (Oris and Alter 2001). The combination of slow population decline and the introduction of new agricultural techniques raised incomes, which are reflected in rapidly rising property values.

Sart was chosen as a research site because we have exceptionally complete demographic records covering most of the nineteenth century. In 1811, the population of Sart was recorded in a register showing the names of all persons arranged in households. This register was updated to reflect changes due to births, marriages, deaths, and migration, and a new register was opened in 1843. After the national census of 1846, population registers were implemented in all of Belgium (Alter 1988). Since the population register records dates of in- and out-migration, we are able to reconstruct the population at risk at every point in time.

Previous studies have already revealed the patterns of mortality in Sart during the nineteenth century (Alter et al. 2004a; Alter and Oris 2000). The crude death rate remained approximately constant until 1870, when a sustained decline began. The influence of several major epidemics is readily apparent, including a typhus epidemic in 1816–17 following the Napoleonic Wars. Life expectancy remained stable around 42 years before 1850 and increased slowly in the second half of the century. Improvements in mortality began among children aged 1 to 10 in the period 1867–1880, and spread to adolescent and adult ages after 1880 (Alter et al. 2004a). Infant mortality, however, was largely unaffected until the last decade of the century. The infant mortality rates show no trend during the period examined. Mortality after age 55 did improve after 1850 as in Scania.

We use annual prices of oats as an indicator of economic stress in Sart[5]. Oats were by no means the preferred grain, because it could not be made into bread.[6] As the least expensive grain, however, oats were the last resort of the poor. Previous studies have shown that an increase in the price of rye was often associated with lower mortality in Sart (Oris et al. 2005). Prices were determined on international markets, and farmers benefited from high prices as long as they had substitutes for high-priced grains. An increase in the price of oats had a large impact on the poor, however, because they had nowhere else to turn. Prices of oats tended to be more stable than other grains, but there were large fluctuations in prices between 1800 and 1820. There were constant demands for men and supplies when Eastern Belgium was part of the Napoleonic Empire. A severe economic crisis accompanied by a typhus epidemic followed Napoleon's defeat.

Results

Table 2 shows the abridged results for a basic model with four early-life factors included as well as a number of control variables. The full results for Sart are shown in Appendix Table 1, and for Scania in Bengtsson and Lindström (2000). Our focus is whether the effect of the disease load in year at birth has a strong impact on mortality in later life both in Scania and in Sart. This, however, is not the case. Instead, we find that the impact of food prices in year of birth is important in Sart; a 10 percent decline in food prices reduces mortality in older ages by 14 percent. This is the average effect for the entire population and since we can safely assume that lower strata were most negatively affected by high food prices the effect must have been even larger among the poor (Bengtsson 2004; Alter et al. 2004a).

[5] We have done analyses with both oats and rye, and the response was more sensitive to oats in this case. Both grains were grown in Sart, but prices were determined on international markets. In some cases we find that the grains have opposite signs when they are both included in the regression equation. The reason, we believe, is that farmers in Sart had the choice of selling their rye in urban markets when the price rose. Even if this meant that they ate more oats (the cheaper grain), it would increase their welfare. When the price of oats went up, the poor in Sart were severely affected, because (as we say in the paper) oats was their last resort.

[6] Prices for 1798 to 1830 were derived from Deprez (1948). Prices after 1831 come from Gadisseur (1990).

Table 2 **Estimation of effects of infant mortality rate at birth, crude death rate at ages 20–50 years 9 months prior to birth, and cycles in the logarithm of rye prices both 9 months prior to birth and at birth**

Covariate	Scania		Sart	
	Rel.risk	p-value	Rel.risk	p-value
Infant mortality rate				
at birth	2.93	0.00	1.00	0.33
Crude death rate in ages 20–50				
at conception	0.67	0.91	0.99	0.62
Food-prices up 10%				
at conception	0.65	0.60	0.86	0.43
at birth	0.19	0.86	1.39	0.09
No. of deaths		1 398		573

Note: The model controls for socioeconomic status, sex, birth year, birth season, birthplace, parish of residence, and logarithm of current rye prices in four Scanian parishes, 1766–1894, and in Sart, 1854–1899.

Sources: For Scania: Bengtsson and Lindström (2003: table 1). For Sart: Appendix Table 1.

Table 3 **Estimation of effects of cycles and trend in infant mortality rate (IMR) at birth**

Covariate	Scania		Sart	
	Rel.risk	p-value	Rel.risk	p-value
IMR at birth				
trend	4.85	0.01	1.01	0.36
cycle	2.35	0.01	1.00	0.97
No. of deaths		1 398		573

Note: The model controls for sex, birth year, birth season, birthplace, parish of residence, socioeconomic status, crude death rate at ages 20–50 years 9 months prior to birth, and cycles in the logarithm of rye prices 9 months prior to birth, at birth, and currently in four Scanian parishes, 1766–1894, and in Sart, 1854–1899.

Sources: For Scania: Bengtsson and Lindström (2003: table 2). For Sart: Appendix Table 2.

Table 3 shows the estimation results of a similar model in which the disease load in the first year of life is included as a single early-life variable but where it has been divided into a trend and a cycle component. We still find no support for the hypothesis that the disease load in first year of life has an impact on old age mortality in Sart, as it was in Scania[7]. This is, in fact, hardly surprising since the infant mortality rate shows almost no trend in Sart.

Turning to Table 4, showing possible nonlinear effects of the disease load in birth year on old age mortality, we find that children born in years of very high infant mortality in Sart also face higher mortality later in life. The result is precisely the same as for Scania, despite the fact that the study for Scania covers a much longer period, one in which infants often were exposed to a highly virulent disease – smallpox. Thus, normal variation in the disease environment at birth from one year to the next has no impact on old-age mortality in Sart, only the extreme years have an effect in later life.

Table 4 Estimation of nonlinear effects of cycles in infant mortality rate at birth

Covariate	Scania		Sart	
	Rel.risk	**p-value**	**Rel.risk**	**p-value**
IMR at birth				
very low	1.03	0.90	–	–
low	1.01	0.93	1.14	0.26
normal	1.00	–	1.00	–
high	0.91	0.28	0.89	0.28
very high	1.51	0.02	1.58	0.02
No. of deaths		1 398		573

Note: The model controls for sex, birth year, birth season, birthplace, parish of residence, socioeconomic status, crude death rate at ages 20–50 years 9 months prior to birth, and cycles in the logarithm of rye prices nine months prior to birth, at birth and currently in four Scanian parishes, 1766–1894, and in Sart, 1854–1899.

Sources: For Scania: Bengtsson and Lindström (2003: table 3). For Sart: Appendix Table 3.

[7] There were no smallpox epidemics in Sart because there was a strong vaccination campaign in the early 19th century. There were isolated cases of smallpox later in the century, including a small epidemic in 1871, because physicians did not realise that the immunity conveyed by vaccination is not permanent.

Discussion

In a large body of studies, the conclusion is that conditions very early in life, in the fetal stage and in the first year of life, have an impact on health and mortality in later life. Robert Fogel (1994) has proposed several plausible causal mechanisms that connect malnutrition in utero and during early life to chronic diseases in later life. Fogel's propositions have been supported by the work of Barker (1994, 1995) who has suggested that the preconditions for coronary heart disease, hypertension, stroke, diabetes, and chronic thyroiditis are initiated in utero but do not become clinically manifest until much later in life. To the extent that the damage caused by malnutrition in early life shows up later in life, we label it "permanent" damage. Recent reviews of the evidence are given by Finch and Crimmins (2004) and Lindström and Davey Smith in this volume.

For Scania, we have previously shown that the disease load in the birth year affected mortality in ages 55–80 years, while we have found no support for either the in utero or the diseases environment during pregnancy hypotheses (Bengtsson and Lindström 2000, 2003; Bengtsson et al. 2002). The question we raise in this paper is whether this is a "Swedish" phenomenon or if it can be found elsewhere. On the one hand, we find support for the hypothesis of disease load in year at birth also for nineteenth century Sart, a rural parish in eastern Belgium. On the other hand, not only the disease load but also the food availability in year at birth affected old age mortality in Sart. Neither in Sart nor in Scania have we found any in utero effects.

As regards the impact of the disease load during infancy, in Sart we find a threshold effect but no basic effect (linear) and no trend effect. When we analyze the period 1829–1894 in Scania, we find threshold effects almost identical to those in Sart (Bengtsson and Broström 2003). Over the longer period from 1766 to 1894 the results for Scania are driven both by the trend in infant mortality, which also appears in analyses of aggregated data (Jones 1956; Fridlizius 1989; Finch and Crimmins 2004), and by extreme values. In the eighteenth century, most years with very high infant mortality were years with high smallpox mortality (Bengtsson and Lindström 2003: table 4) but smallpox was much less important in nineteenth-century Sart – and the subperiod 1829–1894 for Scania. Thus, other epidemic diseases like whooping cough, for Scania, and typhus and cholera, for Sart, had effects in old age mortality similar to those of smallpox.

Another interesting finding is that food prices in the year of birth also affected later life mortality in Sart. Could it be that when highly virulent diseases (smallpox) disappear, socioeconomic conditions gain in importance, at

least relatively speaking but perhaps also in absolute terms? If this is the case, then it fits well with the observation that socioeconomic factors were gradually becoming more and more important for mortality levels during the course of the nineteenth century.

Finally, we turn to a brief discussion of the use of early-life indicators to improve mortality forecasting. Several studies have shown that the disease load early in life can cause permanent damage that shows up in increased mortality risks later in life. This was the case for Sweden, using aggregate level data, as well as for a rural population in the very south of Sweden, using micro level data. This was also the case for Sart in eastern Belgium, also using individual level data, as shown in this study. Several other recent studies show similar results for other parts of Europe, as well as for Canada (for an overview, see Beise et al. 2006; Schuster and Sunder 2005). Taken together, these findings suggest that the disease load early in life can be used to predict mortality later in life. Finch and Crimmins (2004), however, find that whereas mortality in the first year of life is of most importance for mortality risks at older ages in some countries, mortality in childhood is more important in other countries. This constitutes a problem since it implies different mechanisms. If the mechanism in play had been the same and remained stable across populations, its value as a predictor of future mortality would certainly be much higher.

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Appendix

Table 1 **Sart, 1855–1899. Estimation of effects of infant mortality rate at birth, crude death rate at ages 20–50 years 9 months prior to birth, and cycles in the logarithm of out prices both 9 months prior to birth and at birth, controlling for socioeconomic status, sex, birth year, birth season, birth place. The number of deaths is 573**

Subjects		658		
Deaths		573		
Time at risk		8770.889		
Log likelihood		–3070.84		
p		0		
		Rel.risk	**p-value**	**Mean**
Female		0.91	0.28	0.47
Year of birth		1.04	0.00	1821.42
Birth season:				
	Jan–Mar	1.00		27.21
	Apr–Jun	1.09	0.49	25.11
	Jul–Sep	0.94	0.61	21.64
	Oct–Dec	1.20	0.10	26.03
Wealth after age 55				
	None	1.00		36.63
	Low	1.19	0.07	43.47
	High	0.70	0.00	19.91
Born in Sart		1.13	0.24	0.70
IMR year of birth		1.00	0.33	169.86
Adult Death Rate year before birth (difference from trend)		0.99	0.62	0.12
Oats year of birth (difference from trend in logs)		1.39	0.09	0.00
Oats year before birth (difference from trend in logs)		0.86	0.43	0.00

Table 2 **Sart, 1855–1899. Estimation of effects of cycles and trend in infant mortality rate at birth controlling for socioeconomic status, sex, birth year, birth season, birth place. The number of deaths is 573**

Subjects		658		
Deaths		573		
Time at risk		8770.889		
Log likelihood		–3071.97		
P		0		
		Rel.risk	**p-value**	**Mean**
Female		0.90	0.24	0.47
Year of birth		1.04	0.00	1821.42
Birth season:				
	Jan–Mar	1.00		27.21
	Apr–Jun	1.07	0.58	25.11
	Jul–Sep	0.93	0.58	21.64
	Oct–Dec	1.21	0.09	26.03
Wealth after age 55				
	None	1.00		36.63
	Low	1.22	0.04	43.47
	High	0.70	0.00	19.91
Born in Sart		1.14	0.23	0.70
IMR Trend year of birth		1.01	0.36	161.80
IMR Cycle year of birth		1.00	0.97	8.07

Table 3 **Sart, 1855–1899. Estimation of threshold effects of infant mortality rate at birth controlling for socioeconomic status, sex, birth year, birth season, birth place. The number of deaths is 573**

Subjects		658		
Deaths		573		
Time at risk		8770.889		
Log likelihood		–3068.41		
P		0		
		Rel.risk	**p-value**	**Mean**
Female		0.90	0.21	0.47
Year of birth		1.04	0.00	1821.42
Birth season:				
	Jan–Mar	1.00		27.21
	Apr–Jun	1.07	0.56	25.11
	Jul–Sep	0.94	0.60	21.64
	Oct–Dec	1.21	0.09	26.03
Wealth after age 55				
	None	1.00		36.63
	Low	1.22	0.04	43.47
	High	0.72	0.01	19.91
Born in Sart		1.14	0.23	0.70
IMR in year of birth				
	Low	1.14	0.26	21.92
	Normal	1.00		47.49
	High	0.89	0.28	21.19
	Very high	1.58	0.02	9.41

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