Scarred for Life. How conditions in early life affect socioeconomic status, reproduction and mortality in Southern Sweden, 1813-1968

Quaranta, Luciana

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Luciana Quaranta

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To the memory of My Mother

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List of Abbreviations

GDP	Gross domestic product
GNP	Gross national product
HISCO	Historical international standard classification of occupations
IMR	Infant mortality rate
SEDD	Scanian Economic Demographic Database
SES	Socioeconomic status
SOCPO	Social power scheme

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Lund, April 2013

Chapter 1

Introduction

1.1 Motivation for the thesis

Populations have experienced remarkable transformations in recent history. The modern mortality decline began in Europe in the middle of the 18th century (Fridlizius, 1984; Perrenoud, 1984) and some decades earlier in England (Wrigley et al., 1997) and North America (Fogel, 1994a). Death rates also continued to fall during the 19th and 20th centuries, as a consequence of which world life expectancy has doubled (Riley, 2001). In best practice countries, the rate of change has been linear and constant since the 1840s, increasing by approximately three months per year (Oeppen & Vaupel, 2002). In Sweden, for example, life expectancy was approximately 38 years in 1750, 45 years in 1850, and is approximately 82 years today (Human Mortality Database, 2012). These changes in mortality did not occur simultaneously across all age groups, but declines were generally first observed in death rates among infants and children, followed by adults and finally by the elderly.

Reductions in death rates across populations have been accompanied by improvements in height, health and economic growth. Between 1820 and 2000, world per capita income increased by more than eight times (Maddison, 2001). Average heights have also increased in much of Europe and North America. Children now grow more and reach maturity at an earlier age than they did in the past (Tanner, 1989). For example, in Sweden, soldiers born in the early 19th century were on average 1 cm taller than those born in the second half of the 18th century (Sandberg & Steckel, 1980), and except for a temporary decline in stature experienced by those born in the 1830s and 1840s (Sandberg & Steckel, 1988), average height increased continuously throughout most of the 19th century (Sandberg & Steckel, 1997).

These processes of transformation have not ceased, and life expectancy and 'healthy life expectancy', which corresponds to the number of years lived without disabilities, continue to increase today. The changes that have occurred in the size, shape and capability of the human body are a reflection of economic and demographic developments that have taken place throughout history (Floud et al., 2011). These include the agricultural and industrial revolutions and the

demographic transition, with a transition from regimes of high to low fertility and mortality. Such changes have been accompanied by long-term shifts in mortality and disease patterns, where the importance of pandemics and infectious diseases as the main causes of morbidity and death have been replaced by degenerative and man-made diseases. Omran (2005) has defined this process as the epidemiological transition.

There is a long-standing debate over which factors caused these improvements in health and declines in mortality and contributed to economic growth. The most substantial transformations occurred in Europe before 1900 and therefore prior to the development of the public health movement and the availability of antibiotics and other advances in medical technology (Floud et al., 2011; Fridlizius, 1984; McKeown, 1976; Perrenoud, 1984; Steckel, 2008). Some scholars have emphasised the importance of improvements in nutrition resulting from the agricultural revolution, while others have focused on the impact of the decline in the virulence of pathogens. The debate has also considered the significance of period effects, which simultaneously affect the entire population, and cohort explanations, which relate to characteristics that influence all those born in a specific year over the entire life course.

The importance of early life conditions for health in later life has been known for centuries and can be traced back at least to Francis Bacon, who in 1625 wrote, 'For strength of nature in youth, passeth over many excesses, which are owing a man till his age' (Bacon, 1833: 117). Thus, when the long-term mortality decline was first noticed in the 1920s and 1930s, it is no surprise that scholars of demography and epidemiology also emphasised the significance of early life factors (Derrick, 1927; Kermack, McKendrick, & McKinlay, 1934). Using data on age-specific mortality, Kermack, McKendrick and McKinley showed that the declines in mortality in England, Wales, Scotland and Sweden were influenced by an individual's year of birth rather than the year of death, therefore proposing the cohort or early life explanation (Kermack et al., 1934).

In the 1950s, scholarly interest in cohort factors declined, and emphasis was placed on a multi-factorial period explanation, which underlined the role of public health reforms, advances in medical knowledge, improvements in personal hygiene, and increases in income and standards of living (United Nations, 1953). McKeown questioned this multi-factorial explanation and instead believed that the decline in mortality experienced from the end of the 18th century was primarily related to improvements in nutrition (McKeown & Record, 1962; McKeown, 1976). Easterlin (1999) disputed the role of economic growth and emphasised the importance of technology (in a broad sense), stating that the decline in mortality from the late 19th century onward was due to the development of new institutions based on innovative knowledge of disease.

Interest in cohort factors was later revived, partly due to the work of Fridlizius (1989) in his studies of Sweden as well as work by Preston and van de Walle for urban France (1978). Several authors maintain that advances in health and reductions in age-specific mortality occurred spontaneously and are not related to economic factors. They focus on the role of disease and claim that such changes were caused by declines in the virulence of pathogens and the resulting shift in the balance between such pathogens and their human hosts (Fridlizius, 1984; Perrenoud, 1984; Schofield, 1984). According to Fridlizius, individuals who have been exposed to certain infectious diseases in the first five years of life have reduced immunity to other diseases over the life course and are therefore at greater risk of contracting infectious diseases at older ages (Fridlizius, 1989).

The emphasis on cohort explanations has continued to grow in recent decades in both medical and historical research. Fogel (1994b) claimed that the declines in mortality and gains in heights and life expectancy have been possible thanks to the increases in net nutrition that occurred as diets and the quality of nutrients improved and morbidity in early life declined. In several papers published in the late 1990s, Fogel and Costa (1997) proposed the theory of 'technophysio evolution', which was expanded further in Fogel's 2004 book *The Escape From Hunger and Premature Death 1700-2100* and in the 2011 book *The Changing Body: Health, Nutrition and Human Development in the Western World since 1700*, written by Floud, Fogel, Harris and Hong. The technophysio evolution is a 'simplified form of endogenous growth theory'. It states that the ability of humans to control their environment and create technological innovations has given rise to a unique form of physiological development that has been much more rapid than previously witnessed in history. The primary conclusions of their work are that the health of one generation contributes to the strength, health and longevity of the next through mothers and the experience of infants and children; moreover, improved health and longevity allow members of that generation to work harder and longer to be able to generate resources that can, in turn, produce prosperity in succeeding generations. One of the caveats of this theory, according to its authors, is that its circular nature does not make it possible to determine the stage at which these bodily improvements began.

The main source of evidence used to formulate technophysio evolution theory concerns heights, as heights represent a summary measure of an individual's level of net nutrition from conception until maturity. Since the era of the French doctor Villermé, who in the mid-19th century studied French army conscripts (Floud, Wachter, & Gregory, 1990), anthropometric measures have been widely used across different disciplines as indicators of human health and standards of living. Studies based on data obtained from records of conscripts, convicts, hospitals and even skeletons have made substantial contributions to our understanding of the

past and the important processes of transformation that have taken place (e.g., Engerman, 1976; 1997; Eveleth & Tanner, 1990; Floud et al., 1990; Komlos, 1985; Komlos & Baten, 1998; Steckel, 1995; Steckel, Floud, & Sandberg, 1997; Steckel, 2005).

The theories presented by Fogel and Floud were largely based on the work of Barker and his colleagues, who indicated that coronary heart disease, hypertension, stroke, diabetes and chronic thyroiditis originate from inadequate cellular development during the foetal stage and are manifested in adulthood (Barker et al., 1989; Barker, Osmond, & Golding, 1990; Barker, 1994; Barker, 1995). This is the so-called 'foetal origins hypothesis' or 'Barker hypothesis'. In recent decades, the findings and theories presented by, among others, Fogel, Barker and Fridlizius have encouraged many scholars from different disciplines to adopt a life course perspective to study later life health and well-being (see e.g., Elo & Preston, 1992; Kuh & Ben-Shlomo, 2004; and Lawlor & Leon, 2009 for a review).

The data used in studies conducted by Fogel, Floud et al., Fridlizius and McKeown that attempt to identify the factors leading to the great-mortality decline, as well as in some of the initial works by Barker, were at the macro-level. Although these works have made enormous contributions to our knowledge, they can only describe which characteristics were associated with changes that have taken place, without being able to identify possible causal mechanisms. Bengtsson and Lindström (2000; 2003) introduced the notion of combining longitudinal, individual-level data with local infant mortality rates (IMR) or grain prices to evaluate the causal impact of exogenous variations in early life conditions. Using data from four parishes in southern Sweden for the period 1766-1895, these authors observed a strong impact from the disease load experienced during the year of birth on mortality later in life. At the macro-level, associations between a cohort's infant and old-age mortality were also found for Sweden, France, Switzerland and England by Finch and Crimmins (2006; 2004). The ideas of Bengtsson and Lindström (2000; 2003) and Finch and Crimmins (2006; 2004) have further developed the 'infancy inflammation hypothesis', which contends that exposure to disease in early life can lead to chronic disease in old age through inflammatory mechanisms.

In recent decades, scholars have continued to conduct numerous studies to evaluate the long-term effects of early life conditions using micro-level data. Associations have been shown between exposures sustained during the foetal stage and infancy and later life cognitive ability (Case & Paxson, 2008), educational attainment (Almond, 2006; Case & Paxson, 2010; Palloni et al., 2009), height (Bozzoli, Deaton, & Quintana-Domeque, 2009; Steckel, 2008), socioeconomic status (Almond, 2006; Bengtsson & Broström, 2009) and the development of chronic diseases in old age (Bengtsson & Lindström, 2000; Bengtsson & Mineau,

2009; Bengtsson & Broström, 2009; Lindeboom, Portrait, & van den Berg, 2010; van den Berg, Lindeboom, & Portrait, 2006; van den Berg, Doblhammer, & Christensen, 2009). When focusing on the long-term effects of early life conditions, the use of micro-level data and a life course approach has also made it possible to further elaborate on the concepts of 'selection' and 'scarring', which were introduced by Preston and co-authors (1998). Individuals who resist adverse early life conditions may be genetically or congenitally stronger and enjoy greater probabilities of survival at older ages (i.e., selection), but conditions of stress in early life can also damage the body permanently, causing increases in death rates later in life (i.e., scarring).

The existing literature has made remarkable contributions to our understanding of the factors that have led to the great mortality decline and influenced and are influencing the length and quality of our lives today. Nevertheless, there is still much knowledge to be obtained, and many questions remain unanswered. The theories presented by Fogel (Fogel & Costa, 1997; Fogel, 2004), Floud et al. (2011) and the works of many scholars utilising heights have substantially enhanced our knowledge, but they do not allow us to reach distinct conclusions regarding what consequences are attributable to diet and which are the result of disease. Moreover, much of the evidence on nutrition employed by Fogel and Floud et al. is fragmentary, and many of the theories they present were not tested empirically. Few studies have adopted a micro-level approach and exogenous measures of diet and disease to evaluate and compare the long-term impacts on health of such exposures, particularly during the period that connects the historical and modern epochs. In addition, when specifically focusing on the role of infection, few works contrast the effects of different diseases. Analyses of this sort are essential to identify the causal mechanisms linking early life conditions to later life health.

Understanding the mechanisms responsible for the long-term effects of early life exposures also requires an evaluation of these impacts throughout the life course, without having to condition on survival until specific ages. The majority of existing works have this far only focused on what occurs between birth and early adulthood or from early adulthood until old age and death, as they are often limited by the suitability of the data. Moreover, to identify causal mechanisms, it is also important that separate studies are conducted for males and females, something rarely done in the literature. The impacts could differ with respect to sex as a result of different vulnerabilities to exposures in early life and later life variations in the demands made to the body, for example in relation to childbearing or intense labour.

One of the claims advanced by Fogel (Fogel & Costa, 1997; Fogel, 2004) and Floud et al. (2011) is that the improvements experienced over time were largely related to transfers of health and prosperity across generations. As do

many other scholars, they discuss the impact of the conditions faced by mothers during gestation on later life health. However, they present little evidence on the effects of exposures during the mother's early life on their reproductive health and transfers of these impacts to their offspring. The existing literature linking early life exposures to female reproductive health is scant and inconclusive and only considers the impact of diet, disregarding the potential long-term influences of disease.

The aim of this thesis is to contribute to the debates on which factors influenced the mortality decline and the general literature on the long-term effects of early life conditions by evaluating the effects of exposure to inadequate nutrition during the foetal stage or a high disease load in infancy on health and wellbeing over the full life course. The consequences of these exposures are first measured on mortality, capturing changes in these impacts across age and sex. The effects on female health during adulthood are also estimated, using SES attainment and reproductive health as outcome measures. Transfers across generations are also assessed in this manner.

Adopting the methodology introduced by Bengtsson and Lindström (2000; 2003), we combine longitudinal, individual-level data with local IMR of the year of birth and grain prices of the year of conception to evaluate the long-term effects of short-term variations in early life conditions. These were considered, respectively, as exogenous indicators of the disease load experienced in infancy and the level of nutrition encountered during the foetal stage. In addition to testing the impact of general exposure to disease, we also measure and compare the effects of specific exposure to measles, scarlet fever and whooping cough, which were the most common epidemics in the area and period studied. Individuals born in years with high IMR, or specifically in years with one of these epidemics, are compared to those born in years with a low-medium disease load to study the effect of disease. Individuals conceived in years with high prices are compared to those conceived in years with low-medium prices to measure the potential impacts of nutrition. The long-term consequences of exposure to disease in infancy are compared to those of being of low socioeconomic status (SES) at birth.

This thesis is divided into four independent articles that share a common theme, data and methods, the findings of which support one another. The first two analytical studies attempt to establish possible associations between adverse early life exposures and mortality. In Chapter 2, early life conditions are measured by considering price levels of the year of conception and IMR of the year of birth, while Chapter 3 specifically evaluates the impacts of exposure measles, scarlet fever or whooping cough in infancy. Both of these chapters consider the full life course and study males and females separately. This allows us to identify stages where selection dominates scarring and *vice-versa*. The final two chapters focus

on female health during adulthood. They measure the effects of exposure to high prices during the foetal stage or high IMR generally or whooping cough epidemics specifically during infancy. The outcome variables considered are SES attainment, fertility, offspring sex ratio at birth and offspring neonatal mortality. A summary of the findings of these four articles and a discussion are presented in this chapter after providing an overview of the main theories considered in this thesis, the context of study and the data and methods used.

The context studied in this thesis is five rural parishes in the region of Scania, located in Southern Sweden, for the years 1813 to 1968. The parishes were confined in their geography and presented differences in terms of size, topography and socioeconomic conditions that were common to peasant societies at the time, making this area representative of a typical rural population during the period considered. These parishes exhibited substantial changes and declines in mortality throughout the period and changes in life expectancy that were very similar to the pattern for Sweden as a whole.

The micro-level data used to conduct these studies were obtained from the Scanian Economic Demographic Database. The richness of these data allowed us to follow 86 cohorts from birth until old age, knowing at all times the size of the population at risk and their SES. We consider individuals born from 1813 to 1898 and study them until age 70. Few other databases have micro-level data with this level of detail so far back in time and also track such a large number of cohorts over the full life course[1].

This thesis expands on the studies conducted by Bengtsson and Lindström (2000; 2003) in various ways. First, a longer period is considered in this thesis, linking historical epochs to eras following modernisation, the introduction of sanitation and the spread of penicillin and modern medicine. It is therefore very interesting to determine whether the long-term effects of early life conditions can be found across this extensive number of years. Moreover, whereas the work by Bengtsson and Lindström (2000; 2003) focused on the impact of early life exposures on mortality in old age, here we consider the full life course and are therefore able to measure both selection and scarring. Finally, we not only focus on

1 A full life course approach can be adopted, for example, in studies conducted using data from the Helsinki Birth Cohort Study (see e.g., Räikkönen et al., 2009) or the Uppsala Birth Cohort Multigeneration Study (see e.g., Koupil, Leon, & Lithell, 2005; McCormack et al., 2005). However, the Helsinki Birth Cohort Study is based on individuals born in the period 1934-1944 and the Uppsala Birth Cohort Multigeneration Study on individuals born in the period 1915-1929. Therefore, these studies make it possible to follow a maximum of 15 cohorts. In addition, they only contain information on individuals born in more contemporary periods, while other databases such as POPUM (see e.g., Edvinsson, 2001) only have data from the 18th until the mid-19th century. Such databases therefore do not allow scholars to link historical epochs to modern periods to study the factors affecting the processes of transformation that occurred in populations during these years.

mortality but also on other indicators of health during adulthood also evaluating transfers across generations.

1.2 The long-term development of mortality and wellbeing and the influence of early life conditions

1.2.1 The influence of diet and disease in the historical decline in mortality

The work of McKeown (1976) has provided seminal contributions to the debate over the causes of the great mortality decline, even if his findings have been widely questioned. By ruling out other factors, he claimed that improvements in food supplies were the main cause of the declines in mortality and increases in population that occurred from the beginning of the 18th century through the middle of the 19th century. The declines in mortality were primarily related to reductions in the number of deaths from infectious diseases, and according to McKeown, nutrition determined the frequency and the outcomes of infections. McKeown also argued that improvements in food hygiene and environmental conditions contributed substantially to reducing mortality from water and foodborne diseases during the second half of the 19th century, but these factors were not responsible for the declines in deaths from airborne infectious diseases. He also showed that advances in medicine did not have substantial effects before the discovery of sulphonamides and penicillin, and prior to 1838, inoculation and vaccination for smallpox did not have a considerable role in reducing mortality.

Focusing on similar notions, Fogel (1994b; 2004) and Floud et al. (2011) used the term technophysio evolution to describe the process of transformation that occurred in many parts of the world from 1700 to 2000, through which humankind has gained an 'unprecedented degree of control' over its environment by developing and using technology, which has led to changes in the size, shape and longevity of the human body. These authors stated that such changes have been more rapid and substantial than ever before in history and cannot therefore be explained by the traditional concepts of variation and selection that are the core of Darwinian theories of evolution.

The primary assertion of Fogel (1994b; 2004) and Floud et al. (2011) is that these changes occurred because populations were able to 'escape from hunger and disease'. The most important debates of the technophysio evolution are, in fact, centred on the concept of 'nutritional status'. Nutritional status, or net nutrition,

is the balance between the quantity of food consumed (diet) and the claims made on such energy and nutrients for basic bodily maintenance, fighting diseases, and performing work and other activities. These authors argued that advancements in nutritional status were related to increases in the amount of food available and to gains in the nutritional content of diets. Improvements in clothing and shelter have also enhanced the way in which energy consumed is converted into work output by reducing the amount of calories necessary to maintain the body's temperature (Dasgupta, 1993).

Floud et al. (2011) link the nutritional status of individuals and populations to changes in body measures, longevity and economic growth using five principles that discuss how growth and prosperity is produced and transferred across generations through the adaptation and control of the environment. These five principles form the backbone of the book *The Changing Body* (Floud et al., 2011, pp. 3-4):

1. The nutritional status of a generation – shown by the size and shape of their bodies – determines how long that generation will live and how much work its members will be able to do.
2. The work of a generation, measured both in hours, days, and weeks of work and in work intensity, when combined with the available technology, determines the output of that generation in terms of goods and services.
3. The output of a generation is partly determined by its inheritance from past generations; it also determines its standard of living and its distribution of income and wealth, together with the investment it makes in technology.
4. The standard of living of a generation determines, through its fertility and the distribution of income and wealth, the nutritional status of the next generation.
5. And so on *ad infinitum*.

Whereas Malthus (1798/1986) believed that populations adapted to resource limitations through increases in death rates (positive checks) or reductions in birth rates (preventive checks), Fogel (2004) and Floud et al. (2011) state that chronically malnourished populations in the past reacted to such constraints by changing their body size. By 'shrinking people', the energy required for basal metabolism is reduced. The basic metabolic rate, which is the amount of energy required to maintain body temperature and organ functions while at rest, depends on age, sex and body size. This is one of the points where Fogel (2004) and Floud et al. (2011) introduce a cohort explanation. Whereas weight can vary in the short-term, height is a long-term measure, determined by the level of net nutrition received in infancy and childhood. Height cannot be altered after maturity to meet cyclical fluctuations in food availability. According to these

authors, populations consequently anticipated future constraints by exposing children to the level of nutrition that they were likely to encounter at older ages. They also dispute Malthus' beliefs by claiming that there is not one single level of subsistence that results in 'demographic disaster' if it is not met but, rather, that there are numerous possible levels of subsistence at which a population can be in equilibrium with food supply. Some of these equilibria will result in higher levels of mortality and others in smaller average body size. Malthus (1798/1986) assumed the link between a specific number of individuals and a given caloric requirement as static; Fogel (2004) and Floud et al. (2011) instead claim that such needs can be changed by altering body size.

According to Floud et al. (2011) the declines in mortality that occurred in different countries beginning in the 18th century were accompanied by improvements in anthropometric measures and are therefore likely to be caused by the same factors. They claim that heights represent a summary measure of an individual's 'capacities' and 'constraints', therefore again adopting a cohort explanation. Most of the evidence used to formulate the technophysio evolution hypothesis is based on heights. Height is determined by complex interactions among genetic and environmental factors (Thoday, 1965). Genotypes define an individual's potential height, while environmental conditions influence the degree to which that potential is achieved. The difference between mean height when the full genetic potential is met and an individual's stature determine his/her risk of morbidity and mortality (Floud et al., 2011). Height is highly dependent on net nutrition from conception until maturity. Low levels of net nutrition place a biological constraint on individuals that limits the extent to which their height or weight can increase, and even if they have higher levels of resources in the future, such constraints cannot be eluded. Inadequate growth causes children to be stunted (short in comparison to normal standards) or wasted (light in comparison to normal standards). Children who are stunted or wasted at early ages cannot fully catch up at later stages.

Fogel (2004) and Floud et al. (2011) present an illuminating explanation that links improvements in nutritional status to increases in individual capabilities and consequently to economic growth. They state that gains in the amount of calories available have resulted in economic growth by affecting the labour force participation rate, intensity of work, and reproductive capacity of females. According to these authors, improvements in nutrition account for between 20 to 30% of the increases in per capita income that occurred in Britain over the past two centuries. They also argue that such changes have allowed individuals to dedicate a continuously increasing share of energy to leisure and that the effects are not only limited to the health and wellbeing of one generation but are transferred

across generations in the form of technological levels, the income and wealth distributions, fertility, and reproductive health.

One of the case studies presented in *The Changing Body* to explain these principles is a description of changes taking place in Britain. Floud et al. (2011) state that increases in food availability during the last half of the 19th century made it possible to eliminate the class of paupers and beggars, who represented the bottom two deciles of consumption and whose energy availability up to that point had only been sufficient for basic bodily maintenance and a few hours of strolling. The resulting effect was an increase in the size of the workforce. Increases in caloric consumption have, in addition, expanded the capabilities of those who already participated in the labour force, thereby further increasing productivity. Improvements in health have also meant increases in life expectancy, allowing a greater portion of the population to survive until they could begin labour, and even up to retirement, and more females to reach physical maturity and to remain alive until the end of their childbearing years. Such changes have expanded the reproductive and work capacities of individuals, resulting in further sources of population and economic growth. Moreover, citing the work of Case and Paxson (2008; 2009), Floud et al. (2011) report that productivity is also influenced by cognitive ability, another characteristic that is determined by exposures early in life. According to these authors, through increases in the size of the workforce across generations and gains in the intensity of labour, improved nutrition has resulted in greater productivity and food production and economic growth, allowing current and future generations to live healthier and longer lives. Such changes have also given rise to advancements in standards of living; people were no longer only able cover their basic needs but could also afford leisure.

The cohort explanation employed to formulate the technophysio evolution is, to a large extent, based on existing research showing that adverse conditions in early life predispose individuals to develop chronic diseases in adulthood. Fogel (1994b; 2004) describes three mechanisms through which malnutrition *in-utero* or during the first years of life relate to chronic diseases in later life: malnutrition that causes permanent damage that is evidenced directly; malnutrition that causes inadequate cellular development and the degradation of organ function in early life and leads to the development of degenerative diseases in old age; the degradation of the tissue structures of vital organs such as the lungs, heart, and gastrointestinal tract, which in principle could be reversed but in fact persist because the cause of the malnutrition remains. According to this author there are relationships between variations in body height and weight and the chemical composition of the tissues of the organs of the body, the quality of the electrical transmission between membranes and the functioning of the endocrine, immune and nervous systems and the capacity of the lungs.

This line of debate is principally based on the works of Barker and his colleagues (1994; 1995; 1997; 2001). Barker formulated the 'foetal origins hypothesis', which states that 'disproportionate' retardation in growth caused by the lack of sufficient nutrition during the second and third trimesters of pregnancy leads to low birth weight, increasing systolic blood pressure in adulthood and the risk of heart disease later in life. During the foetal stage, cell division is very rapid, but it may be reduced as an adaptive mechanism to insufficient supplies of nutrients or oxygen, affecting the tissues that are undergoing 'critical' development when the undernutrition occurs (Barker, 1995). These permanent changes in the body's structure and function 'programme' disease in later life. There are also other mechanisms that seem to be involved in these early preconditions for later life disease, which include imbalances between cell types and alterations in gene expression, the structure of organs, the patterns of hormonal release and the establishment of hormonal responses (Sultan, 1994). The foetal origins hypothesis has received support from many scholars but has also been amply criticised (for recent reviews of the literature see e.g., Gluckman et al., 2008; Currie & Vogl, 2012; Almond & Currie, 2011). Huxley et al. (2002) and Christensen (2007) have, for example, shown that although birth weight has a significant effect on blood pressure, it is rather small.

When explaining the concept of net nutrition, Fogel (2004) and Floud et al. (2011) not only focus on the role of diet but also discuss possible impacts from disease exposure. Whereas McKeown (1976) claimed that there is a link between nutrition and infection by arguing that inadequate nutrition debilitates individuals and makes them more susceptible to disease, Floud et al. (2011) also explained the effect that diseases have on net nutrition. When individuals are affected by infectious diseases, energy is required to activate the immune system, and moreover, the person loses appetite, has lower capacity to absorb ingested nutrients and experiences an increasing metabolic loss of nutrients (Bellagio conference authors, 1983; Dasgupta, 1993).

Within the concept of technophysio evolution, the potential implications of diseases are only discussed in terms of the reductions they cause in the net amount of calories available for growth, work and other activities, and on the effects that such reductions may have on short- and long-term health. Other scholars have shown that exposure to disease in early life can affect later life health through mechanisms that are not strictly related to energy but to immunity, inflammatory processes, or direct damage to organs.

In his studies of Swedish mortality, Fridlizius (1984) has expressed doubt regarding the nutritional thesis advanced by McKeown because, according to this author, the development of consumption that has taken place and the patterns through which age-specific mortality declined cannot be reconciled with

these views. He showed that in the same period when infant mortality began to decline, old-age mortality was rising and only began to fall 50 years after infant mortality did and, moreover, such changes occurred simultaneously across different socioeconomic groups. Fridlizius (1984) also noted that improvements in nutrition did not take place until the 1850s, while mortality began to decline a century earlier. This author believed, instead, that the underlying factor behind the changes in mortality was disease. He stated that individuals infected in early life with diseases such as smallpox suffer from reduced immunity and are therefore more susceptible to other diseases throughout the life course (Fridlizius, 1989). This author also claimed that exposures to smallpox or scarlet fever affect age-specific mortality rates and that signs of these exposures could be observed throughout the lifetimes of the exposed cohorts.

Fridlizius agreed with McKeown that sanitary improvements and advances in personal hygiene could not have influenced the decline in mortality until the second half of the 19th century (Fridlizius, 1984). He also states that changes in climate, if any, only had a marginal effect in the decline in mortality after 1810 and that improved breastfeeding practices could not have been the cause of the declines in infant mortality in the first phase of the decline. This claim is based on the fact that declines in infant mortality occurred simultaneously across different socioeconomic groups and that changes in crop-rotation and increased proletarianisation led women to work outside of the household, reducing the possibilities for breastfeeding (Fridlizius, 1984). Moreover, Fridlizius (1984) also contends that reductions in smallpox mortality could not be related to inoculation, which was introduced in the 1780s ineffectively and at a small scale, or to vaccination, which was also introduced at a small scale and only in 1801, therefore after mortality from this disease had already begun to decline. He argues that the decline in mortality that took place leading up to the mid-19th century was a result of a long-term change in the immunological balance between infectious agents and the human host, caused by a reduction in the virulence of microorganisms. These changes were related to the end of something old rather than the start of something new (Fridlizius, 1984).

Fridlizius (1989) also showed that period effects can shift cohort mortality patterns. For example, the declines in mortality observed in late 19th-century Sweden present five 'deformations': increases in mortality between 1820 and 1850 among males of working ages as a result of high levels of alcoholism; increases in mortality from tuberculosis for men and women aged 10-30 years during the late-19th century and early-20th century; improvements in social conditions in Stockholm during the second half of the 19th century; further deformations in the cohorts of the 1850s and 1860s caused by a deformation of the initial group rather

than by period effects; and nicotine-induced higher mortality among males during the 20th century.

Perrenoud (1984) stated that economic and social factors were not responsible for the initial stages of the great mortality decline, as similar patterns of decline were observed in regions that had different social and economic structures. Moreover, these declines did not take place at the same time among children and adults. This scholar also supports Fridlizius' beliefs that reductions in mortality were a result of changes in the long-term relationship between infectious organisms and the human host.

Within the early life literature, links have been established between infection and disease later in life in connection to immunity, damage to organs, and inflammatory mechanisms. Exposure to a certain disease in early life could, for example, provide lifelong immunity to this pathology (Preston et al., 1998). Infections could also cause direct damages to the body's organs and cells. Associations have been found, for instance, between respiratory infections in early life and lung impairments at older ages (Barker et al., 1991; Bengtsson & Lindström, 2003; Shaheen et al., 1994) and between streptococcal infections and rheumatic heart disease (Jones, 1956).

Bengtsson and Lindström (2000; 2003), using micro-level data, and Finch and Crimmins (2006; 2004), using macro-level data, observed relationships between the infant and old-age mortality of a cohort. Finch and Crimmins (2006; 2004) stated that there is a positive relationship between decreases in mortality from cardiovascular diseases in old age and reductions in the exposure to infectious diseases in early life and subsequent declines in infant and child mortality related to these causes. They used the term 'cohort mortality phenotype' to denote this relationship. The works of Bengtsson and Lindström (2000; 2003) and Finch and Crimmins (2006; 2004) further expanded and discussed in detail the hypothesis of 'inflammatory exposure', which contends that short-term adaptive responses to infections or injury in infancy can become maladaptive in the long-run through inflammatory mechanisms. Serum levels of C-reactive protein (CRP, an acute-phase protein) rise in response to inflammation, increasing the risk of cardiovascular disease and hypertension (Willerson & Ridker, 2004; Zhu et al., 2000). Infections in early life may also cause arterial structure dysfunction (Liuba, 2003). The long-term role of infectious diseases in the change in mortality has also been considered by other authors (Elo & Preston, 1992; Leon & Davey Smith, 2000) and has inspired research that adopts a life course perspective within the field of epidemiology (e.g., Ben-Shlomo & Kuh, 2002; Kuh & Hardy, 2002; Kuh & Ben-Shlomo, 2004).

The link between adverse early life exposures and health in later life has also been studied within the field of epigenetics. It has been shown that when

environmental experiences are altered, a given genotype can give rise to different phenotypes through developmental plasticity and subsequently be expressed in diverse physiological or morphological states without modifications to the DNA sequence (Bateson et al., 2004; Jablonka & Raz, 2009). Such epigenetic changes can programme disease in later life (Lucas, 2007). Epigenetic inheritance can also occur, in which case any alterations to the parents' gene expressions that originated from conditions experienced during their development may be transferred to the next generation (Jablonka & Raz, 2009; Lummaa & Clutton-Brock, 2002).

1.2.2 The influence of medical advances and changes in standards of living on the decline in mortality

McKeown (1976), Fridlizius (1984), Perrenoud (1984) and Floud et al. (2011) asserted that the decline in mortality from infectious diseases occurred before medical measures to address them became available and prior to the introduction of hygiene and sanitary improvements. Although the role of these factors was more limited in the epochs these authors studied, these factors were very important in the transformations that have taken place from nearly the second half of the 19th century until today.

In his discussion of the factors that led to the first phase of the demographic transition in Sweden, as illustrated above, Fridlizius (1984) stated that nutrition, climate and changes in medicine were not responsible for the great mortality decline. However, he also noted that after the mid-19th century, new epidemics emerged, but the strength and duration of such epidemics were mitigated by hygiene, improved medical care, and sanitary improvements. In the 1840s and 1850s, advances in sanitary and hygienic conditions were primarily related to the construction of water supply and sewage systems, the wide distribution of soap and the breakthrough of easily washed cotton clothes. Fridlizius (1984) also believed that the increased propaganda and information activities led by the state to promote breastfeeding could not have been responsible for the substantial historical declines in infant mortality, but in the second half of the 19th century, the improved dissemination of information, also facilitated by an improved medical care system with more physicians and midwives, likely accelerated this decline. Moreover, he also stated that inoculation against smallpox was introduced in the 1780s and vaccination in 1801, but the decline from this disease had started earlier.

Even if they were not responsible for the great decline in mortality from infectious diseases, immunisation and modern medical advances have made important contributions to health and longevity in the last two centuries (see Floud et al., 2011 and the sources cited, pp. 178-180). The development of

bacteriological tests in the 19th and early 20th centuries led to the introduction of mass immunisation campaigns in Europe and America, which resulted in important reductions in morbidity from diphtheria, tetanus, tuberculosis, poliomyelitis, whooping cough, measles, mumps, rubella and more recently chicken pox. As a result of mass vaccination, the health of both children and adults has improved. Advancements in health were also achieved by the introduction of other drugs. The first sulphonamide drug, Prontosil, was discovered in 1932, and it was used to treat puerperal fever, leading to powerful reductions in maternal mortality. Penicillin and other antibiotics began to be manufactured in large quantities during the 1940s and were used against anthrax, tetanus, syphilis, diphtheria and pneumonia. The discovery of insulin therapy led to important reductions in mortality from diabetes. The therapeutic revolution and modern improvements in biomedical technology have achieved important reductions in mortality from cancer and heart disease and in prolonging the survival of those individuals affected by these pathologies.

The theory of the technophysio evolution contended that physiological improvements have been a cornerstone for economic growth over the centuries (Floud et al., 2011; Fogel, 2004). However, the authors of this work also note that the influence of economic factors on physiology has not always been positive. In fact, the rapid rates of urbanisation that occurred in the early stages of industrialisation led to the deterioration of health during part of the 19th century in many countries (Floud et al., 2011). Some of these changes were related to overcrowding and the worsening of housing conditions and of the quality and quantity of water supply, which increased the spread of airborne infectious diseases. When measuring economic growth, it is therefore important to account for the interaction between technological change and variations in human physiology (Engerman, 1997; Steckel, 1995).

Beginning in the latter parts of the 19th century and much of the 20th century, increases in real wages have led to improvements in housing conditions and reductions in the number of people per room and per dwelling (Floud et al., 2011). Sanitary and public health reforms, the provision of medical healthcare, increased public health investments and the expansion of medical education also made significant contributions. In addition, the introduction and extension of social welfare has allowed the poorest segments of the population to meet their basic needs.

1.2.3 Long-term effects of measles, scarlet fever and whooping cough

To determine the causal mechanisms responsible for the long-term consequences of infection in early life, it is necessary to measure the effects of exposure to

different types of diseases separately and specifically. Chapter 3 studies the impact of early life exposure to measles, scarlet fever and whooping cough on mortality by age and sex. In Chapters 4 and 5, the effects of general exposure to disease and specific exposure to whooping cough epidemics on female SES attainment in adulthood and reproductive health are measured. Emphasis is placed on these epidemics because they were the most diffused causes of death in the region and period studied. Nevertheless, the interest in these diseases is also more general. They are highly contagious, and transmission generally occurs through direct contact with nose or throat secretions of infected individuals or from airborne droplets of these secretions. Although measles, scarlet fever and whooping cough were not as important as smallpox in past populations, they nevertheless caused the deaths of a significant number of individuals. These diseases are also important because they have not been completely eradicated but continue to affect our health today. Outbreaks of whooping cough, for example, still occur in many nations.

Measles is caused by a virus in the genus Morbillivirus of the family Paramyoxoviridae, and its greatest incidence in areas with little or no vaccination coverage is among children under the age of 2 (Kim-Farley, 1993). Infection results in life-long immunity, and there is also transplacental immunity (Mortimer, 1994). It has been shown that girls lose maternal measles antibodies more rapidly than boys (Martins et al., 2009). Vitamin A levels are reduced during infections, and this depression is also associated with higher morbidity and mortality (Mortimer, 1994). Ear infections, pneumonia, hepatitis, meningitis and encephalitis are other possible complications. Individuals infected with measles are very likely to die from pneumonia (Mortimer, 1994).

Scarlet fever is an infectious disease caused by certain types of bacteria from group A hemolytic streptococci (Hardy, 1993a). There is no lifelong immunity from previous infections. Possible complications include rheumatic fever, which is an inflammation of the heart and joints, and glomerulonephritis, which is an inflammation of the urine-producing structures of the kidney (Encyclopædia Britannica, 2012).

Whooping cough is caused by the bacteria *bordetella pertussis*, which affects the respiratory tract (Hardy, 1993b). Infection nearly always occurs during childhood and particularly in infancy, as there is no effective transplacental immunity (Mortimer, 1994). In the absence of a previous vaccination or infection, contagion across siblings is very likely to arise after one child becomes infected. Even today, despite high rates of vaccination, whooping cough is resurging in many industrialised countries (Warfel, Beren, & Merkel, 2012). Outbreaks occur every 2-5 years (Cherry, 2005), most likely because immunity wanes after approximately 4-20 years from infection and 4-12 years from vaccination (Wendelboe et al., 2005). Some of the possible complications of whooping cough include

bronchopneumonia and atelectasis, which are the main causes of mortality related to this disease, as well as encephalopathy[2], although less frequently, and in the past also exhaustion and malnutrition due to repeated vomiting (Mortimer, 1994). The bacteria *bordetella pertussis* attacks the mucus membrane of the respiratory tract, occasionally destroying it (Swansea Research Unit of the Royal College of General Practitioners, 1985). The lymphoid tissue of the adenoids can become hypertrophied if infection by these bacteria is prolonged, causing a permanent source of infection to the respiratory tract and middle ear (Swansea Research Unit of the Royal College of General Practitioners, 1985). Exposure to whooping cough can also lead to retarded infant weight gain (Barker et al., 1991).

Vaccination against measles became widespread in the 1960s. A vaccine for scarlet fever was developed in the 1920s, and it ceased to be used in the 1940s after the introduction of penicillin. Mass-vaccination against whooping cough was introduced in Sweden in the late 1940s (Claesson, 2009) and was halted in 1979 (Krantz et al., 1990). Vaccinations were therefore not available during the years in which the studied population was born. As these diseases spread very rapidly across populations, most children are likely to have been infected if they lacked prior exposure to this disease. Infants were therefore highly vulnerable.

Several works have shown that lower respiratory tract infections in early childhood, particularly during infancy, lead to airflow obstruction in later life, possibly through a failure to attain maximal potential lung function. Airflow obstruction can result in greater risks of death from chronic obstructive airway diseases (Peto et al., 1983) and lung cancer, coronary heart disease and other causes (Wiles & Hnizdo, 1991). Studies attempting to establish associations between lung diseases in early life and lung function at later ages face the difficulty of determining whether the effects demonstrate actual links between the two or are the result of other pre-existing obstructive airway diseases that may cause both respiratory infections in young ages and respiratory problems in adult life (von Mutius, 2001).

Much of the previous literature concerning the long-term effects of early life exposure to whooping cough has focused on respiratory function. Some works have found long-term consequences for children infected with whooping cough, including impaired lung function, additional respiratory symptoms, higher rates of hospital admittance, lower median intelligence quotient and worse educational attainment (Jedrychowski et al., 2002; Swansea Research Unit of the Royal College of General Practitioners, 1985; Swansea Research Unit of the Royal College of General Practitioners, 1987). In one study based on data for men born

2 Atelectasis is the partial or total collapse of a lung caused by a blockage of the air passages or external pressure on the lung (A.D.A.M. Medical Encyclopedia, 2012). Encephalopathy is a disease, damage or malfunction of the brain (MedicineNet, 2012).

in Hertfordshire between 1911 and 1930, greater reductions in lung function later in life were observed if infection to whooping cough had occurred in infancy rather than from ages 1 to 5, and these effects were independent of birth weight, smoking and social class (Barker et al., 1991). In another study conducted by Bengtsson and Linström (2003) based on data from four of the parishes considered in this work for the time period 1766-1894, children who were exposed to high IMR in their year of birth had greater risks of dying from airborne infectious diseases in old age. The authors of this work retrospectively showed that, in the studied area and period, years with high IMR were dominated by smallpox and whooping cough epidemics.

Links were also established between exposure to whooping cough in early life and later life impairments that were not related to the respiratory system. Associations were found between whooping cough infections in infancy and type 1 diabetes mellitus, with effects that were constant across socioeconomic groups (Montgomery et al., 2002). A delay between infection and the onset of diabetes was observed, from which the authors of this work concluded that infection in early life could cause the start of an autoimmune process or raise the hazard of delayed autoimmunity. Infections have been associated with the development of autoimmune diseases (Rose & Mackay, 2000). Type 1 diabetes can lead to numerous complications and can be fatal unless treated with insulin, as has been shown in many previous studies

The literature focusing on the long-term effects of exposure to measles in early life is more limited. In the study based on data from Hertfordshire where associations had been found between early life exposure to whooping cough and reduced lung function later in life, no long-term effects of measles were observed (Barker et al., 1991). This pattern, according to the authors of this work, was likely because measles infections generally occur later in infancy than whooping cough, at a stage when the lungs are growing less rapidly. In contrast, another work based on aggregate data from England and Wales found a correlation between infant mortality from measles and other infectious diseases and the rates of death from lung disease 70 years later for the same cohorts (Barker & Osmond, 1986).

The long-term effects of exposure in early life to scarlet fever have also not been very well studied. Streptococcal infections have been associated with two types of sequelae: acute rheumatic fever and acute glomerulonephritis (Bisno, 1991). Rheumatic fever is an inflammatory disease that is mediated by humoral and cellular autoimmune responses that occur some time after a streptococcus infection (Guilherme & Kalil, 2004). Approximately 30-45% of patients that have rheumatic fever suffer from carditis and have lesions of the mitral and aortic valves, which generate rheumatic heart disease (Guilherme & Kalil, 2004).

1.2.4 Life course approach and sex-specific patterns

This thesis adopts a full life course approach, studying individuals from birth until age 70. We selected this age boundary because it allowed us to completely follow as many as 86 cohorts, while still being able to observe ages when chronic diseases that are caused by these exposures are likely to appear. Much of the existing literature instead focuses exclusively on the elderly and must therefore condition on survival until old age, without understanding what occurs in the stages that precede it. Adopting a full life course approach makes it possible to distinguish stages where individuals are exposed to stress, or critical windows, and those where the impact of these exposures is measured. However, and most important, even if deaths related to conditions that originate during early development are more common in old age, it is important to identify phases where selection/immunisation dominate scarring or *vice-versa*. In Chapters 2 and 3, childhood, adolescence, childbearing/working ages and old age are studied separately, as each of these stages of life differs in terms of the development or functioning of the body. The findings of these chapters are considered as a point of departure for Chapters 4 and 5, which focus on adulthood by studying potential impacts on female reproductive health and SES attainment.

Organs have a pace of growth that changes with age. For example, growth in height declines from birth until age 4 or 5, increases slightly at around age 6 or 8 (referred to as mid-growth), and later declines again (Tanner, 1989). Adolescence is characterised by a growth spurt, where the rate of growth is nearly half of that during infancy, after which it declines rapidly until maturity (Steckel et al., 1997). Most skeletal and muscular dimensions of the body and internal organs such as the liver, spleen and kidney have growth curves similar to that of height, with the exception of the brain, skull and some other organs such as the reproductive system or the intestines, which have different rates of development (Tanner, 1989). The long-term effects of early life exposures could differ at various stages of the life course in relation to these fluctuations in development rates. Changes in these impacts may not necessarily only be connected to the velocity of growth, but they could also be linked to characteristics that are specific to different age groups. For example, childbearing and intense manual labour are both influenced by health, but they can simultaneously affect health and bodily function.

When conducting research evaluating the potential impacts of early life conditions on later life health and well-being, it is also important to adopt a sex-specific perspective. The underlying mechanisms determining the long-term effects of these conditions could differ between males and females as a result of factors occurring when these exposures take place or in relation to later life characteristics. A sex-specific dimension has only been considered in a few studies,

which have shown that in old age, men were more negatively affected by exposure to Dutch or Finnish famines or recessions during the year of birth than women (Doblhammer-Reiter, van den Berg, & Lumey, 2011; Lindeboom et al., 2010; van den Berg et al., 2009).

Sex differences in mortality have not been constant over time. Previous centuries were characterised by excess female mortality from late childhood until the childbearing years. In many urban areas, girls were more likely to contract infectious diseases, including tuberculosis (Tabutin & Willems, 1998). These differences have changed over time, benefiting females as mortality from infectious diseases declined, and penalising males as rates from other causes such as cardiovascular diseases increased (Preston, 1976). Throughout the 20th century, female mortality has fallen more rapidly than male mortality, increasing the advantage of females (Alter, Manfredini, & Nystedt, 2004).

Differences in mortality by gender result from interactions among biology, behaviour and environment (Alter et al., 2004). Females may be less vulnerable to stress in early life because X-linked immunoregulatory genes provide greater resistance to infectious diseases (Waldron, 1983) and because males are usually born at younger gestational ages (Hall & Carr-Hill, 1982) and, for a given gestational age, with less developed respiratory systems (Torday et al., 1981). Males are more susceptible to respiratory infections and accidents in childbirth, and they therefore experience greater perinatal mortality, a difference that diminishes within the first year of life (Waldron, 1986). Some diseases such as measles, however, cause higher death rates among girls because they lose maternal antibodies more rapidly than boys (Martins et al., 2009). At older ages, instead, females are more protected against cardiovascular diseases as a result of behavioural and biological factors (Matthews, 1989). Biological protection is likely to be linked to female reproductive hormones such as oestrogen.

Reproduction can also result in sex-differences in death rates. The widest excess in female mortality is often observed during childbearing ages and disappears after menopause (Alter et al., 2004). This pattern is not necessarily directly caused by complications of childbirth, in relation to which death rates are rather low (Schofield, 1986), but may be linked to maternal depletion from greater resource requirements during pregnancy and lactation, which makes women more susceptible to certain infectious diseases (Alter et al., 2004). In the past, many females also died in connection with the use of rudimentary and dangerous abortion methods.

Economic roles, behaviour and unequal distributions of resources also cause differences in mortality across sex. In historical populations, males were more likely to be involved in work in the fields and with the care of animals, making them more prone to accidents. Females, in contrast, were responsible for household

chores and rearing children. The greater amount of time spent in poorly ventilated rooms made them more susceptible to infectious diseases (Fridlizius, 1988), and their role in nursing the sick meant that they were more exposed to infectious pathogens (Alter et al., 2004). There could also be differences in mortality that relate to engagement in alcohol consumption, cigarette smoking and behaviours leading to death from accidents or violent causes (Waldron, 1983). In the past, the observed excess mortality of Swedish males relative to females in adult ages has been attributed to excessive alcohol consumption, which declined during the second half of the 19th century (Fridlizius, 1988; Willner, 1999). Greater death rates among females may also be caused by unequal distributions of resources within the household in relation to nutrition and health care, often favouring males because their tasks were believed to be more physically demanding (Alter et al., 2004). In Sweden, England and Germany, it has been shown that these differences declined as females became more involved in agriculture (Humphries, 1991; Johansson, 1984; Klasen, 1998).

Many of the patterns described above could have played an important role in the long-term effects of early life exposures. Males' greater vulnerability in early life could have made them more susceptible to complications during gestation and infections in infancy. The long-term effect of such exposures may have been counterbalanced by higher mortality during the first year of life and therefore by stronger selection. At older ages, behaviour could have interacted with the impacts of these exposures. Females, however, could have been less susceptible to adverse early life exposures, but due to childbearing, an unequal distribution of resources or greater exposure to pathogens at older ages, the negative long-term effect of these conditions could have been amplified. As a result of these possible differences, we believe that it is essential to analyse the long-term effects of early life exposures separately for males and females. When focusing on mortality in Chapters 2 and 3, sex-specific models are therefore estimated and interactions between early life exposures and sex are also considered. Chapters 4 and 5 focus specifically on females, studying SES attainment and reproductive health as outcomes.

1.2.5 Early life conditions and female health in adulthood

The conditions experienced in early life can affect health and wellbeing over the full life course. During early and mid-adulthood, impoverished health conditions may not only be manifested through morbidity and mortality, particularly because mortality is low at such ages. Other measures of health therefore need to be considered to improve our understanding of the long-term impacts of early life exposures. The final two chapters of this thesis evaluate the effect of exposure to

inadequate nutrition during the foetal stage or disease in infancy on female SES attainment and reproductive health, measured by considering fertility, offspring sex ratio at birth and neonatal mortality.

1.2.5.1 Possible impacts of early life conditions on SES attainment

When conducting studies based on historical populations, occupations are good indicators of social position. In industrialising societies, occupation was influenced by mobility taking place across generations, through marriage or within an individual's career (van Leeuwen & Maas, 2010). Early life conditions could have affected SES attainment by affecting the chances of experiencing intergenerational mobility, the probability of contracting marriage and partner selection, and the ability to experience career mobility.

Several studies have previously shown associations between early life conditions and SES attainment in adulthood. Exposure to diseases or inadequate nutrition in early life affects SES attainment at older ages through individual capabilities, which influence labour force participation and work intensity (Floud et al., 2011; Fogel & Costa, 1997). Early life exposures can also affect individual capabilities through cognitive ability (Case, Fertig, & Paxson, 2005; Case & Paxson, 2008). Using data for the period 1813 to 1894 for the same parishes studied in this work, Bengtsson and Broström observed that exposure to disease in infancy influenced an individual's probability of belonging to the landed class at age 50 but that socioeconomic position at age 50 did not have any effect on old-age mortality (Bengtsson & Broström, 2009). Other studies based on data from Britain and the United States have also found associations between early life health and adult SES (Palloni et al., 2009) and between earning and heights (Case & Paxson, 2008), both of which were related to cognitive ability. Works conducted using contemporary or historical data from developed and developing countries have shown that health and nutrition in early life affects cognitive development, health and educational attainment in childhood and in adult ages height, SES attainment, earnings, economic productivity and labour market supply (Johnson & Schoeni, 2011; Lundberg, 1991; Smith, 2009; Victora et al., 2008).

In historical studies, the SES of females is primarily measured through the husband's occupation, which is therefore largely influenced by marriage mobility. Marriage partner selection can also be influenced by the conditions experienced in early life. Individuals choose their partners to improve their life chances, and in addition to romantic considerations and socioeconomic and cultural factors, this selection can also be influenced by health (van de Putte, Matthijs, & Vlietinck, 2008). Three types of health characteristics are possible: health conditions (physical or mental illnesses), physical qualities that relate to past or

current health (e.g., weight and height) and behaviours connected to health (e.g., smoking and drinking) (Fu & Goldman, 1996). In preindustrial populations, marriage partner selection was shown to be affected by physical attributes such as strength, weight, height or previous health experiences (Baten & Murray, 1998; Fu & Goldman, 1996; Sköld, 2003). Different historical studies have also shown that individuals exposed to adverse early life conditions were less likely to marry (Baten & Murray, 1998; Manfredini et al., In Press; van de Putte et al., 2008).

1.2.5.2 Possible impacts of early life conditions on female reproductive health

Chapters 4 and 5 of this thesis evaluate whether associations exist between early life conditions and female reproductive health. We measure the effect of exposure to high prices during the foetal stage and to a high disease load in infancy on fertility, the offspring sex ratio at birth and neonatal mortality. In addition to measuring the impact of general exposure to disease, we also specifically examine the impact of exposure to whooping cough.

Adverse early life exposures could compromise reproductive health through damages to the reproductive or hormonal systems. The reproductive system develops in stages, beginning with prenatal sex-specific organogenesis and continuing with further maturation in the perinatal period and at puberty (Lemasters et al., 2000). The hypothalamus-pituitary-gonadal axis, which in females connects the brain, the gonad (an endocrine hormone producing gland) and the ovaries, regulates development, reproduction and ageing in humans. Proper functioning of this axis is necessary to achieve regular ovulatory cycles (Elias et al., 2005). Female fecundity is strongly influenced by hormones, which determine the size of the ovum (Apter et al., 1987) and its fertilisability (Yoshimura & Wallach, 1987) as well as the success of implantation and the maintenance of the pregnancy (Ellison, 1996). Moreover, girls born small for their gestational age have smaller uteruses and reduced ovarian volumes (Ibanez et al., 2000). Malformations of the uterus can also compromise a female's ability to carry a pregnancy to term (Lumey & Stein, 1997). They can cause infertility, recurrent spontaneous abortions, or other complications that increase the risk of perinatal morbidity and mortality (Acién, 1993).

Adverse early life conditions could also result in compromised reproductive health due to damages to organs that are not part of the reproductive and hormonal systems, but that could nevertheless affect a woman's ability to conceive or carry a pregnancy to term or the health of her foetuses and offspring. Adverse early life conditions, for example, have been associated with diabetes, cardiovascular diseases and reduced lung function later in life (e.g., Barker et al., 1989; 1990; 1991; Barker, 1994; 1995; Bengtsson & Lindström, 2003; Montgomery et al.,

2002). In other studies, lower fertility, increased risks of experiencing pregnancy complications, preterm birth and giving birth to offspring with lower birth weights and congenital malformations were observed among women experiencing such problems (e.g., Bánhidy et al., 2008; Bhatia & Bhatia, 2000; Department of Health and Human Services, 2001; Felten, Mercier, & Benhamou, 1999; Greenberger & Patterson, 1988; Jonasson et al., 2007).

The conditions experienced by a woman in early life could also affect the health of her foetuses and offspring through epigenetic changes and epigenetic inheritance. Due to epigenetic changes, adverse early life conditions could result in worse reproductive health. Epigenetic inheritance can also occur, in which case any alterations of the parents' gene expressions that originated from conditions experienced during their development may be transferred to the next generation (Jablonka & Raz, 2009; Lummaa & Clutton-Brock, 2002).

One of the most important measures of reproductive health is fertility. Fertility is a complex phenomenon, determined by a mixture of biological and behavioural factors (Bongaarts, 1978; 1993). Behavioural factors include age at marriage, duration of post-partum infecundability due to breastfeeding and/or abstinence, frequency of intercourse, and, in post-decline populations, contraception. Biological factors relate to the age of the onset of sterility, intra-uterine mortality and the biological risk of conception failure. Exposures to adverse conditions in a woman's early life could impact reproduction through one or several of these determinants, but these different effects may not necessarily influence fertility in the same direction. For example, the length of breastfeeding could be affected by health, but women could also choose to actively prolong lactation to improve the survival prospects of previously born children or shorten it to replace previously deceased children.

Adverse early life exposures could affect fertility through the death of previously born children or SES. Fertility could increase after the death of an infant, unintentionally in relation to the premature interruption of breastfeeding, and therefore also to the restraining effect that lactation has on ovulation, or intentionally due to the desire to replace a deceased child (Tsuya, Campbell, & Feng, 2010). Alternatively, parents who expect that some of their children could die may adopt an anticipatory strategy and attempt to have more births before such deaths occur (Preston, 1978). Fertility could, however, be lower among women facing adverse early life conditions as a result of reduced probabilities of attaining high SES. Prior to the fertility decline, couples with higher SES had greater fertility (Bengtsson & Dribe, 2009).

Another important indicator of reproductive health is the offspring sex ratio at birth. The average sex ratio at birth for humans is approximately 105 males per 100 females, although variations occur both between and within populations

(Sieff et al., 1990). It depends on the sex ratio at conception – or primary sex ratio – and on sex-specific foetal mortality (Tremblay et al., 2003). The sex ratio at birth could be affected by adverse exposure in a woman's early life as a result of damages to the hormonal system and organs involved in ovulation, fertilisation and the maintenance of a pregnancy and through epigenetic changes that are transferred to the next generation.

The sex ratio at birth is partly determined by the sex ratio at conception, which may be affected by characteristics of both parents. The sperm carries the genetic material that defines the sex of the zygote, (Magnuson, Bodin, & Montgomery, 2007) but maternal conditions can affect whether X- or Y-bearing sperm remain viable in the cervical mucus, reach the fallopian tube and penetrate the egg to fertilise it (Byrne & Warburton, 1987; Hingorani & Shroff, 1995).

Foetal mortality also influences the sex ratio at birth. Approximately 10% of fertilised ova fail to be implanted, and approximately 50% of those that are implanted and become embryos are aborted spontaneously (Tanner, 1989). Most miscarriages occur within the first 3 weeks after conception (Nepomnaschy et al., 2006) and are due to abnormalities in the development of the embryo or of the protective and nutritive structures that surround it (Tanner, 1989), low body mass index, stress, low levels of progesterone (Arck et al., 2008), exposure to organic solvents, cigarette smoking, cocaine use, the consumption of alcohol or of excessive quantities of coffee (Regan & Rai, 2000) and congenital uterine malformations (Woelfer et al., 2001). Because there are sex-specific differences in foetal deaths, women who experience a greater incidence of spontaneous abortions are likely to have lower offspring sex ratio at birth. The primary sex ratio – or sex ratio at conception – is estimated to be at least 120 males per 100 females (McMillen, 1979), and reductions in this ratio throughout pregnancy are the result of the excess mortality of male embryos (Byrne & Warburton, 1987; Hassold, Quillen, & Yamane, 1983; Mizuno, 2000), in particular, during the phase of organogenesis in early gestation (Kellokumpu-Lehtinen & Pelliniemi, 1984). This excess mortality may be caused by the faster growth rates of males, which make them more vulnerable to abnormalities (Forchhammer, 2000).

Another important indicator of reproductive health is offspring neonatal mortality. Neonatal mortality can be subdivided into early and late neonatal deaths, which occur, respectively, in days 0-6 and 7-27 of life. The most common causes of early neonatal mortality are maternal health problems or malnutrition during gestation, pregnancy complications, obstetric problems during delivery, premature birth, low birth weight, malformations, a lack of adaptation of the newborn child to the extrauterine environment, and poor partum or post-birth hygiene (World Health Organization, 2006). Late neonatal deaths, however, are more frequently linked to infections and poor care after birth.

The previous literature focusing on the impact of early life conditions on reproduction and offspring viability is scant and inconclusive. Moreover, it only evaluates the role of exposure to inadequate nutrition, disregarding possible effects of disease. Some works have found associations between birth weight and age at first birth (Ekholm et al., 2005), time to achieve a pregnancy (Nohr et al., 2009) and fecundity (Ekholm et al., 2005). Short length at birth and reduced weight gain in the first year of life were also linked to an earlier onset of menopause (Cresswell et al., 1997). Another study showed that being underweight/overweight is related to the age at menarche (Frisch, 1994) and the likelihood of experiencing menstrual problems (Lake, Power, & Cole, 1997). Associations have also been found between season of birth and the probability of experiencing menstrual disorders, earlier menarche and early or late menopause, (Jongbloet et al., 1994) as well as fecundability (Nonaka et al., 1990), length of reproductive lifespans, number of live births and offspring survival to adulthood (Lummaa & Tremblay, 2003). There is only one study that examined the possible impacts of early life exposures on the offspring sex ratio at birth. For a historical French Canadian population, the sex ratio at birth was shown to be associated with season of birth of the offspring and even more strongly with that of the mother (Nonaka et al., 1999).

Scholars focusing on the impacts of famines have not all reached the same conclusions. Women exposed to the Dutch Hunger Winter gave birth to offspring of low weight and who experienced higher perinatal mortality (Lumey & Stein, 1997). Concerning the effects on fecundity, one study found no impacts on age at menarche, proportion remaining childless, age at first birth, the total number of children and inter-birth intervals (Lumey & Stein, 1997), while another work found that exposed women exhibited greater reproductive success (Painter et al., 2008). In another study, associations were found for landless individuals between crop yield in the year of birth and the probability of marrying, giving birth to at least one child, and offspring viability (Rickard et al., 2010).

1.2.6 Pathways linking early life conditions to later life health and wellbeing

The association between early life conditions and health in later life can be characterised by selection, immunisation or scarring (Preston et al., 1998). Selection can take place during periods of adverse exposures, where conception, the ability to carry a pregnancy to term and survival past the first birthday may be limited to couples or infants with better health and a wider availability of resources. It can also occur in the transition from childhood/adolescence/adulthood to the

following stage of the life course, and in this case, survival is also likely to be limited to those that have better health or material conditions. The number of individuals in a specific cohort that is still alive in a certain year depends on the initial size of that cohort and the number of deaths in preceding years. Exposure in early life to a specific disease could also provide lifelong immunity to this pathology (Preston et al., 1998). Alternatively, through a mechanism that has been termed scarring, adverse early life conditions can permanently damage in the body in a way that cannot be altered by later experiences and may lead to greater morbidity and mortality at older ages (Ben-Shlomo & Kuh, 2002; Preston et al., 1998).

When conducting studies that use individual level data to summarise the characteristics of a population, only the net of selection and scarring effects is observed. If individuals conceived in years with low food availability or born in years with a high disease load show lower levels of mortality or better reproductive health with respect to those conceived or born during more favourable periods, selection prevails over scarring. When the opposite is observed, scarring dominates selection. However, a lack of differences between these two groups could indicate that either no significant effects exist or that there may be both selective and scarring mechanisms, but both have similar magnitudes and therefore cancel one another out.

Early life conditions can also be linked to later life health and disease through different pathways. Kuh and Ben-Shlomo (2004) proposed a series of conceptual models to study such pathways. The first of these is the 'critical period model', which is also known as the 'biological programming model' and assumes that exposures in certain stages of development have a direct negative effect on health that lasts throughout the life course and cannot be reversed by later experiences. Critical periods are often considered to be the foetal stage and first year of life, which are of great importance to later life health because of the rapidity of the growth and development of organs and cells that takes place during such stages. The second type has been referred to as the 'critical period model with later effect modifiers'. It is an extension of the first model, and it takes into account that later life exposures can interact with experiences perceived in early life, enhancing or diminishing their negative impact on health. Instead, the 'accumulation of risk model' states that risks accumulate over the life course, although some exposures may occur at sensitive periods and their impacts may therefore have stronger negative long-term consequences. A special type of the accumulation model is the 'chain of risk' or 'path model', which states that there is a sequence of interconnected exposures, each causing some damage or debilitation, and leading to a successive negative experience or exposure and finally resulting in disease or other impairments.

Much of the literature measuring the impacts of early life conditions on later life health and wellbeing has been based on the 'critical period model' that forms the basis of the foetal origins hypothesis. However, currently different scholars are beginning to consider indirect effects. In fact, previous research has shown that associations exist between early life exposures and education (Almond, 2006; Case & Paxson, 2010; Palloni et al., 2009), height (Bozzoli et al., 2009; Steckel, 2008), socioeconomic status (Almond, 2006; Bengtsson & Broström, 2009) and the ability to accumulate wealth, (Bengtsson & Mineau, 2009) and these intermediate factors could affect later life health and wellbeing. Such pathways would form the basis of the chain of risk or path model.

A study conducted by Bengstsson and Broström (2009) using data from Scania for the period 1813 to 1894, found that individuals exposed to a high disease load in early life were less capable of accumulating wealth in adulthood, but they did not observe indirect effects of early life conditions on old-age mortality that were mediated through SES. Other works have shown that in pre-industrial agricultural societies, social differences in mortality were limited (Bengtsson & van Poppel, 2011; Bengtsson & Dribe, 2011). Based on these findings, Chapters 2 and 3 consider the critical period model and only measure the total impact of early life conditions on mortality. Both of these chapters evaluate possible differences in impacts for individuals born into families with different SES.

Although no significant indirect effects mediated through SES have been observed when considering mortality as the outcome of interest, such pathways are likely to appear when focusing on reproduction. Research conducted by Bengtsson and Dribe (2009) revealed that, in Scania, there were SES differences in fertility before the fertility decline and in the timing of the decline. Moreover, they showed that couples involved in higher-status occupations and farmers presented the highest level of fertility prior to the transition. As a result of such distinct childbearing patterns or of differences in the quality of housing and nutrition and the amount of workload carried by pregnant women, the impact of early life conditions on reproductive health could have been class dependent. In Chapter 4, SES is therefore considered as a possible modifier of this relationship, and high and low SES females are studied separately.

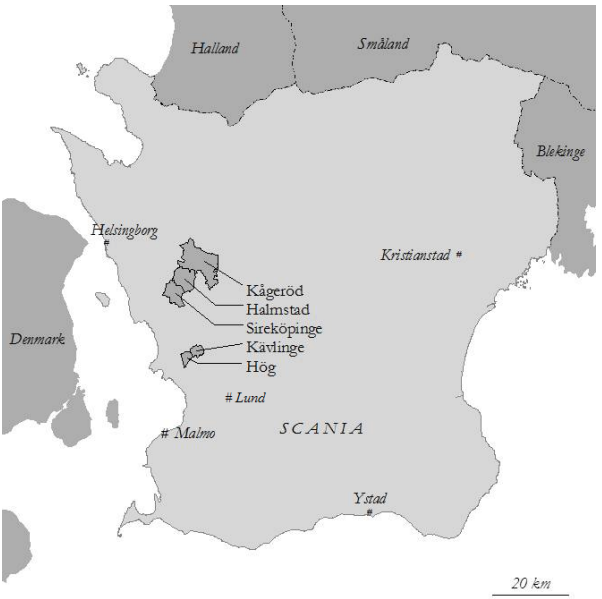
Chapter 5 is also based on the critical period model. When measuring the effects of early life conditions on fertility, it is also noted that direct effects are not the only possible relationship, but that impacts could also be indirect, mediated through SES attainment and the survival of a previously born child. In the case of early life exposures affecting fertility indirectly through intermediate variables, however, causality cannot be inferred.

1.3 Area

The area under study in this work comprises five rural parishes, Hög, Kävlinge, Halmstad, Sireköpinge and Kågeröd, located approximately 10 km from the coast in the western part of Scania, the southernmost province of Sweden. The most closely situated small towns (10 to 30 kilometres away) are Lund, Landskrona and Helsingborg. Kågeröd, Halmstad and Sireköpinge formed a continuous district, while Hög and Kävlinge were located approximately 10 kilometres to the south. A map of Scania and the five parishes is presented in Figure 1. The analysis was conducted for the years 1813 to 1968, and the choice of period and geographical setting was determined by data availability.

The five parishes studied are not representative of Sweden or Scania. However, they are compact in their geographical location and presented differences in terms of size, topography and socioeconomic conditions that were common to peasant societies (Bengtsson & Dribe, 1997). Consequently the life courses of people who lived and worked in these communities were similar to those of most families in rural settings (Bengtsson, 2004b). Furthermore, the geographical heterogeneity of these localities was limited.

Figure 1: Map of the area under study



1.3.1 Economic and social development in Sweden

The 19th and 20th centuries were periods of great transformation in Sweden. Of particular importance were the 1850s and 1860s, which marked the beginning of a new era in the country, with peaks in the transformation of agriculture, industrialisation, rapid economic growth and increases in exports (Schön, 2010). These changes were closely connected to the construction of railways. Real wages for workers also increased in the 1860s (Jörberg, 1972). The transformations that were taking place were initially limited to rural areas, and in the 1880s they also expanded to urban areas; these decades marked the breakthrough of industrialisation. This led to the development of a new working class and also to the internationalisation of the labour market, which resulted in large scale emigration in the 1860s, the 1880s and the first decade of the 20th century, particularly to North America, but also to Britain, Germany and Denmark. Growth was exponential in Sweden from the 1890s, primarily due to the transformation of industry, which changed its focus from sectors such as ironworks and sawmills to new sectors such as engineering, pulp and paper, and consumer goods. From 1930 to 1950 Sweden grew faster than any other country, and the period from 1950 to 1975 was also of very rapid growth (Schön, 2010).

In response to the development that took place between 1850 and 1890 and after 1890, there were many institutional changes in Sweden (Schön, 2010). These included the integration with European markets, market deregulation, the modernisation of the banking system and the decentralisation and expansion of the public sector. With the emergence of the market economy, the monitoring of literacy and poor relief were no longer the responsibility of the Church, but became part of the tasks of local authorities. After the Poor Relieve Act of 1847, unemployment was considered as a social phenomenon, and dealing with indigence became a political task. Many changes in the poor relief system were also introduced in the periods that followed, which made authorities responsible of different social services, including the care of the elderly, children's welfare, medical care of the poor and care of individuals who were mentally ill. The Compulsory Education Act of 1842 required all communities to have a school; schooling instead became compulsory in 1882 (Schön, 2010).

Different reforms were also made to deal with the changing demands of urbanisation (Schön, 2010). The first municipal gasworks were built in 1846 in Göteborg, the nation's second largest city, while the first waterworks were built in Stockholm in the early 1860s. Covered sewers were also built in these two cities in the mid-1860s, and refuse collection was organised in many municipalities, particularly after new public health regulations were adopted in 1875. The municipal structures and technology to deal with urbanisation were in place before

urban areas started to grow, since urbanisation occurred at a rather late stage in Sweden's industrialisation (Schön, 2010).

During the first decade of the 20th century new social and welfare reforms were also passed, which assigned a greater public responsibility to the welfare of individuals and to a social insurance system (Schön, 2010). The most important of these reforms was the National Pension Insurance Act of 1913, and although this system was largely connected to the old poor relief system, it made Sweden one of the most modern European countries in terms of social insurance. The Social Democrats introduced new economic and social policies in the 1930s, which promoted the role of the State in providing security to all citizens, this way steering towards the development of a welfare state centred on a strong government. These changes and the rapid growth experienced after 1950 also led to the emergence of the modern welfare society, although many of the contemporary welfare reforms were not introduced until after the 1970s (Schön, 2010).

These processes of transformation that occurred across Sweden's history were also accompanied by developments in sanitation. The first hospital was built in Stockholm in 1752, and about 100 years later the country had 50 hospitals (Hjortsberg & Ghatnekar, 2001). Because many of these hospitals were small and did not administer any outpatient care, most services were provided by physicians privately. The beginning of today's Swedish healthcare system structure began in 1862, with the establishment of county councils, which had health care as one of their main duties. However, the legal responsibility of the county councils to provide hospital care to all residents was not instituted until the Hospital Act was passed in 1928. The responsibilities of the councils increased gradually, and in the 1930s they also had to take charge of different types of non-hospital healthcare services such as maternity and paediatric care. A National Health Insurance Act was passed in 1946, but it was not implemented until 1955. This act introduced a universal cover for all citizens, primarily financed by the government from tax revenue (Hjortsberg & Ghatnekar, 2001).

1.3.2 Economic and social development in Scania

Scania is known as the granary of Sweden. As in the rest of the country, the agricultural sector in this region underwent substantial transformations over the course of the 18th and 19th centuries, primarily in relation to enclosures, breakups of the villages, reclamation of land and the introduction of new crops and tools (Bengtsson & Dribe, 2010). Grain production was more important than animal husbandry, and the dominant crops produced in this region were rye, barley and oats, and to a lesser extent, potatoes. Agriculture was highly commercialised, and

substantial quantities of agricultural products were sold in the European market. Enclosures primarily took place during the first half of the 19th century[3], and early signs of industrialisation started to appear. The breakthrough of industrialisation occurred in Scania during the last three decades of the 19th century, and the industrial sector expanded further in the first half of the 20th century, which caused relative declines in agriculture.

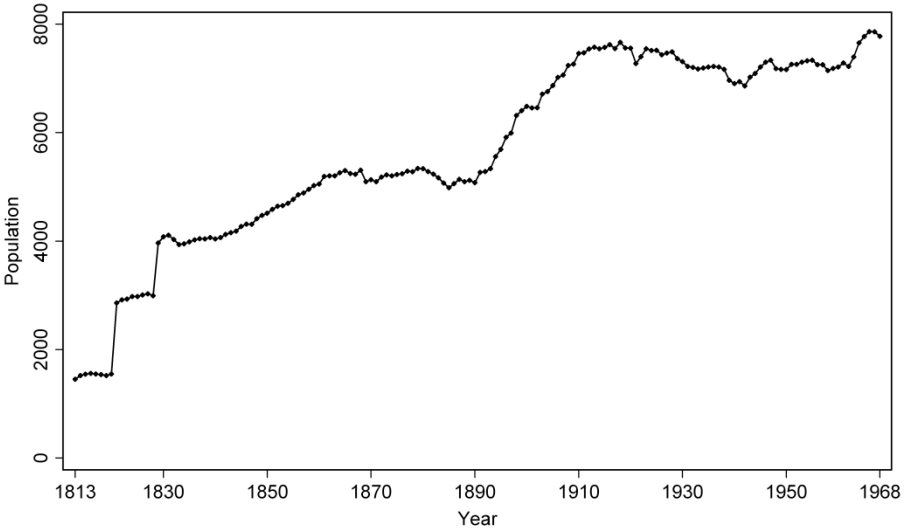
The area considered in this work was open farmland except for the northern part of Halmstad, which was more wooded. Hög, Halmstad, Sireköpinge and Kågeröd were similar in terms of economic structure and population growth, while Kävlinge experienced the most rapid change. Initially, this location had some mills and a leather industry. After a railway was constructed in 1886, it experienced an industrial expansion, for example within the food sector (Bengtsson & Dribe, 2011). Important establishments in this territory were a textile mill (1892 in Furulund), a leather and shoe factory (1896) and a sugar mill (1891) (Billing et al., 1983; Högs by skifteslag, 2000). The largest population growth occurred in Kävlinge. Hög remained rural for a longer period but due to its proximity to Kävlinge, it presented some urban characteristics; it was possible to reside in Hög and work at the sugar factory or one of the leather mills in Kävlinge (Dribe, Helgertz, & van de Putte, Forthcoming).

The population trend in the five parishes is presented in Figure 2. A noteworthy aspect is the steps in 1821 and 1829, which relate to data availability and expansions. The data from Kågeröd were first collected in 1813, in 1821 the registers from Halmstad and Sireköpinge were added and in 1829, Hög and Kävlinge were also included. The total population was 1,453 in 1813; 2,860 in 1821; 3,967 in 1829; and increased to 7,779 in 1968. This territory therefore exhibits rapid expansions, particularly during the last decade of the 19th century and the first decades of the 20th century. Much of this change occurred after 1890, partly due to the construction of one of Sweden's most important railway lines, which linked the city of Malmö, located in the south of Sweden, with Göteborg (Dribe et al., Forthcoming).

The changes observed in the occupational and class structure followed the contextual developments that took place in the parishes. Table 1 presents the occupational distributions of household heads at ages 20 and 50 during different periods. As can be observed in this table, there were important reductions in the proportion of farmers and increases among the higher occupations and skilled workers.

3 For further discussion on the behaviour of peasants during the agricultural transformation and the institutional and organisational changes that were taking place, including enclosures, see (Svensson, 2006).

Figure 2: Population in the five Scanian parishes, 1813-1968



Note: The data from Kågeröd was collected starting from 1813, in 1821 the registers from Halmstad and Sireköpinge were added and in 1829, Hög and Kävlinge were also included.

Table 1: Distribution of occupations among household heads, Scania 1813-1968

	1813-1839	1840-1869	1870-1899	1900-1929	1930-1968
Higher occupations	5.68	7.27	11.45	19.70	24.09
Skilled	6.26	7.96	12.20	14.28	18.98
Farmers	40.31	34.77	27.21	21.01	12.74
Lower skilled	29.17	24.26	16.67	19.52	26.91
Unskilled	15.22	23.60	24.48	18.31	14.17
N/A	3.37	2.14	7.99	7.20	3.11

Note: the percentages represent the percentage of individual time. They were calculated among household heads in the age groups 20-50.

1.3.3 Fertility and mortality in Sweden and Scania

The decline of mortality in Sweden, as in many other countries, did not occur simultaneously in all age-groups, but three different patterns can be distinguished, which concerned children, adults and the elderly. Infant mortality began to decline rapidly and continuously in the 18th century. The mortality of children aged 1-10 started to drop at the end of the 18th century but changed to an increasing pattern in the middle of the 19th century. Adult mortality, instead, did not decline until 1840. Finally, old-age mortality increased until the beginning of the 19th century

and only began to decline after 1850 (Fridlizius, 1984). The decline in mortality in Scania presents similarities to that of the rest of Sweden, although it was more pronounced in Scania in the latter parts of the 18th century than in the country as a whole (Bengtsson & Dribe, 1997). The evolution of mortality in Scania during the studied period is discussed further in Section 1.5 of this chapter.

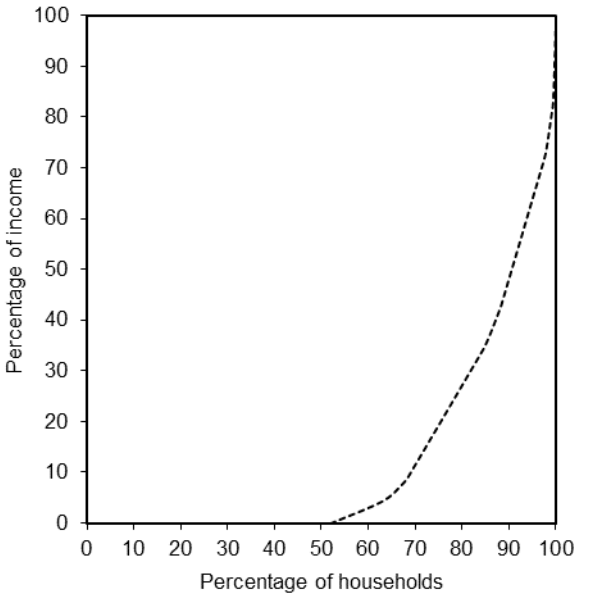
In the period that preceded the fertility decline, age-specific fertility was somewhat higher in Scania than in Sweden as a whole (Bengtsson & Dribe, 2010). Total fertility in Scania was slightly above 5, while the level for Sweden was slightly above 4. The decline in fertility in Sweden began in the 1880s and lasted for approximately 50 years, reaching an average of two children per woman (Dribe, 2009). The decline began slightly later in Scania, in the 1890s, and it continued without interruption until the 1930s (Bengtsson & Dribe, 2009). As in Sweden as a whole, in Scania reductions in fertility occurred over the full reproductive span, not only through stopping behaviours after desired parities were reached but also through prolonged birth intervals (Bengtsson & Ohlsson, 1994; Bengtsson & Dribe, 2009; Dribe, 2009).

Studies conducted at an aggregate level for Sweden as a whole and using macro- and micro-level data for Scania showed that throughout these processes of transformation, fertility, mortality and nuptiality were affected by short-term changes in food prices and real wages. In Sweden, it was observed that the response was similar for males and females but varied by age and was strongest among adults (Bengtsson & Ohlsson, 1985a). The response in fertility was stronger and more consistent than the response in mortality (Bengtsson & Ohlsson, 1978). The close response of crude birth rates to changes in real wages was not related to fluctuations in marriage but instead in marital fertility (Carlsson, 1970).

In Scania during the 19th century, the mortality response to short-term economic stress exhibited a social gradient, showing that the landless and semi-landless were more vulnerable than individuals belonging to other social groups (Bengtsson, 2000; Bengtsson, 2004b). During the same period, a similar gradient was also observed in variations in fertility in response to short-term economic stress. Evidence was found of deliberate decisions to control births if high prices were foreseen, as well as of reductions in fertility due to subfecundity or spontaneous abortions caused by severe malnutrition for landless and semi-landless families but not landed ones (Bengtsson & Dribe, 2006; 2010).

This social gradient was largely caused by the fact that wealth and land were not equally distributed in Scania. Figure 3 shows the distribution of landownership among families and farmers based on real estate and personal income tax records in 1800. As can be observed in this figure, the top 5% of families owned 36% of the land, and landless households accounted for 50% of all households.

Figure 3: Percentage of households paying real estate and personal income tax, Scania 1800



Source: Lee, Bengtsson et al. 2004

1.4 Source Material

The source material used for this work is the Scanian Economic Demographic Database (SEDD)[4], which currently includes information for the years 1813 to 1968. The family reconstitutions were performed using register type data from catechetical examination registers (*husförhörslängder*) together with information on births, marriages and deaths from church books maintained by the clergy. The reconstitutions were performed automatically using a computer programme, and the results have also been checked manually. The methods used have been described and evaluated thoroughly in a previous work by Bengtsson and Lundh (1991). The database contains information relating to all individuals born in the

4 The SEDD was created in a collaborative project between the Regional Archives in Lund and the Centre for Economic Demography at Lund University (Bengtsson, Dribe, & Svensson, 2012). The structure of the SEDD was programmed to follow the format suggested by the Intermediate Data Structure (Alter, Mandemakers, & Gutmann, 2009). The data were converted into spells using the code developed by Quaranta (2012).

parishes or who migrated to them, and they are followed from the time they were born or immigrate until they die or outmigrate.

Bengtsson and Dribe (2010) previously discussed the quality of the data. They state that, for the years 1766 to 1865, the percentage of stillbirths and the rates of infant and neonatal mortality give no indication of serious recording problems. If we make calculations for the years 1813 to 1898, the proportion of infant deaths taking place during the first month of life was 38%, which does not indicate the under-registration of deaths. For the same years, the sex ratio at birth for the five Scanian parishes is 107.6 males per 100 females, which is slightly higher than the value for Sweden as a whole (105.0) for births taking place between 1816 and 1895 (Statistics Sweden, 1999). Bengtsson and Dribe (2010) obtained a sex ratio at birth of 109 for the years 1766 to 1865, noting that this figure could indicate a small under-registration of female births, but that it is more likely that it is a result of random variation given the small size of the population.

The SEDD contains data on occupations obtained from different sources: church books, poll-tax registers (*manltaslängder*) and income registers (*inkomslängder*). In the church books, occupations were declared at birth and marriage events, while the information in the poll-tax and income registers was updated annually. Poll-tax registers were used for the collection of taxes and provide information on where families lived and whether they had access to land, among other things indicating the size of the landholding and thus approximately indicating the productive potential of farms (Dribe, 2000). They report information on the *mantal*, which was a measure of the wealth of the farm that also depended on the productivity of the land.

Occupations in the SEDD are available for individuals and household heads. There is also occupational data that relate to the head of the individual's family of origin. As this area was characterised by very high migration rates (Dribe, 2000; 2003), when constructing the SEDD, married individuals were traced back to their birth parish where possible to include information regarding the occupations of their fathers at the time of birth.

All occupations in the database where coded into HISCO (van Leeuwen, Maas, & Miles, 2002) and later classified according to HISCLASS and SOCPO. SOCPO is a classification scheme that comprises five categories, based on skill level, degree of supervision, whether an individual was self-employed, and pure status (van de Putte & Miles, 2005). In this work, we utilise the SOCPO classification, which is shown in Table 2.

We determine the SES of each individual/family using occupational data from all available sources, updating this measure each time a new occupation was declared. If different occupations were given on the same date in the different

Table 2: SOCPO classification scheme

Social power level	Commanders (authority)	Self-employed (business/property owners)	Skill	Pure status
Level 5	High commander: executive, general policy tasks	Macro-scale self-employed; supralocal businessman	Nonmanual superskilled	Nobility
Level 4	Medium commander: supervisor of skilled workers	Medium-scale self-employed: local businessman	Manual superskilled/ nonmanual skilled	
Level 3	Low commander: supervisor of semi- and unskilled workers		Manual skilled	
Level 2		Micro-scale self-employed: "penny capitalist"	Semi-skilled	
Level 1			Unskilled	

Source: van de Putte, Miles 2005

sources, the occupation with the highest status was used[5]. In Chapters 2, 4 and 5, the occupation of the family of origin of each individual is considered as an explanatory or control variable in the analysis. Current SES is considered in Chapter 4. All occupations refer to the head of the family. Current SES is therefore the occupation of the husband for married women or that of their fathers for single women living in their parental homes, while individual occupation is considered for single women forming their own households and life-cycle servants.

This work also employs data on rye prices. This cereal is considered because it was the most common grain in this part of the country (Bengtsson& Dribe, 1997). We use prices of the *födgeri* of Landskrona. A *födgeri* is a rural level below the county. In 1815, it was decided that prices in every parish should be used to determine the prices of the *födgeri*, and representatives of all parishes were therefore gathered to make this assessment. The *födgeri* prices were calculated as an average of the prices of the different parishes it comprised (Bengtsson & Dribe, 1997). It was not possible to use quarterly or monthly data because observations are only available for shorter periods. Nevertheless, seasonal fluctuations were rather limited, and variations in prices were dominated by year-to-year changes. Prices relate to a harvest year, which corresponds to the period between October 1st and September 30th of the successive calendar year.

5 The code developed by Dribe (2012) was used to assign SES.

1.5 Methods

To conduct this work, we follow the methods used by Bengtsson and Lindström (2000; 2003), which are an extension of the methods introduced by Bengtsson (1989) to combine longitudinal macro-demographic data with macroeconomic data using an event-history framework. To evaluate the long-term effects of early life conditions, we consider prices of the year of conception and the IMR of the year of birth. These are considered, respectively, as indicators of the level of nutrition experienced *in-utero* and the disease load during infancy. Prices were obtained from external sources, as described above, while IMR was calculated directly from the data. Instead of considering prices of the harvest year where the date of conception falls, each person is linked to the prices of the harvest year when at least half of the last two trimesters of their foetal stage occurred, as previous studies have shown that nutrition during these stages of gestation is the most influential in later life health (Barker, 1994; 1995; 1997; 2001).

In the past, mortality, nuptiality, fertility and migration were all affected by variations in food prices, not only during periods of famine but also in relation to smaller changes in food supply and prices (Bengtsson, 2004a). The price of grain is the most commonly used indicator of external stress related to access to food, as the largest fraction of individual incomes was spent on food, and grain was dominant in their diets (Bengtsson, 2004a). According to Myrdahl's estimates, among the lower social classes in 19th-century Sweden, foodstuffs accounted for 83% of individual budgets (Myrdahl, 1933), and according to the calculations made by Jörberg, 59% of total food expenditures were on grain (Jörberg, 1972). Grain prices can therefore serve as a good indicator to also measure long-term effects of nutrition during the foetal stage.

Grain prices serve as a better representation of short-term changes in the level of nutrition received during the foetal stage for workers before 1870 compared to thereafter. During this period in southern Sweden, real wages for workers exhibit short-term fluctuations very similar to those of food prices, the reason being that while nominal wages change very little annually, food prices change significantly. Thus, if food prices increase by, say, 30%, real wages typically decline by the same amount. However, in the latter half of the 19th century, nominal wages began to increase faster than food prices and exhibited more annual variation. In addition, new commodities, such as the potato, appeared (Bengtsson, 2000). Aside from modelling the long-term effect of price exposures in early life for all individuals, in Chapter 2 calculations are therefore also made only for the sub-group of individuals born before 1870.

It was also shown previously that economic variations affected childhood deaths but not infant deaths (Bengtsson & Ohlsson, 1985b). During the first year of life,

the health of children was primarily influenced by the conditions and behaviours of their mothers and exposures to epidemic diseases, and childhood health was not vulnerable to short-term economic stress while children were breastfed (Bengtsson, 2004a). In the four analytical chapters that follow, we therefore do not consider price levels during an individual's infancy but concentrate exclusively on measuring the impact of price levels during the foetal stage. In some preliminary models estimated in this chapter, prices in the first year of life have been taken into account as well. It would have also been possible to consider the impact of diet at later stages of the development, for example during the periods of rapid growth in mid-childhood and adolescence. However, these stages are less clearly defined, as they are not likely to have occurred at the same ages for individuals of different cohorts or sexes. We therefore only focus on measuring the effect of diet during the foetal stage and leave the modelling of possible long-term impacts of diet in other stages of childhood for further research.

When studying the long-term effects of early life conditions, an important evaluation to make is whether to use the full values of IMR and prices, or their trend and cyclical components (or thresholds of deviation from the trend). Different choices have been made in the literature; some authors believe that the associations between the trends in early life conditions and later life health are informative (see e.g., Bozzoli et al., 2009), while others claim that it is important to assess the effect of short-term variations in early life exposures on later life health (see e.g., Bengtsson & Lindström, 2000; 2009). The arguments made in the latter case is that the trend components of early life conditions are highly correlated with other environmental characteristics that reflect, for example, the development of healthcare and the economy, and these different effects cannot be easily distinguished. We choose to model the long-term impacts of having been conceived in years with high prices or having been born in years with a high IMR, which we identify by decomposing the series of prices and IMR into their trend and cycle components. By considering cyclical fluctuations, it is possible to evaluate the impact of short-term variations in the disease environment and the level of nutrition, more specifically years of epidemics or severe malnutrition. The extensive length of the time period studied in this work serves as further motivation for removing the trend component from the two series, since IMR and prices have changed substantially. One possible option to use the full values of IMR and prices would have been to adopt a sibling approach. However, this would have limited the sample size substantially.

The series of local IMR and of the logarithms of rye prices were decomposed into trend and a cycle components using the Hodrick Prescott filter with a filtering factor of 6.25, which is the value typically selected for annual series. A very high correlation (0.7) was observed between IMR and its cyclical component, implying

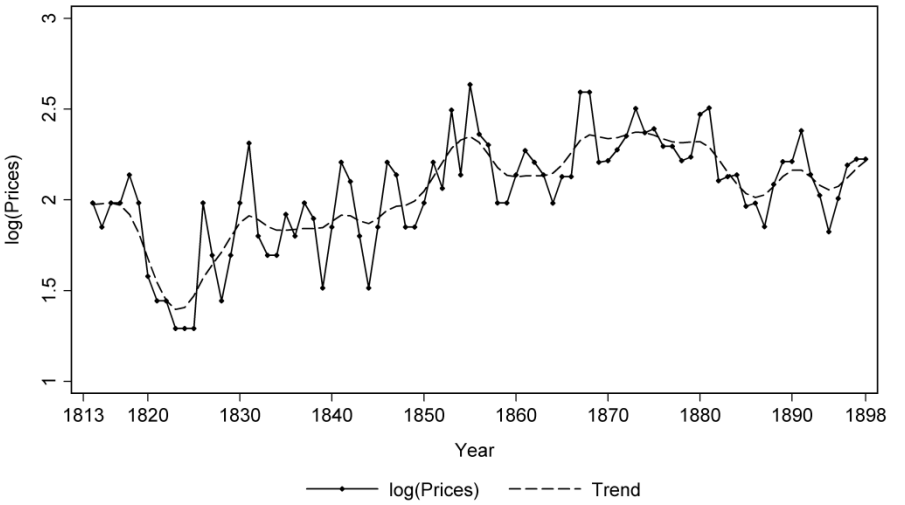
that short-term deviations were high mainly in years where the actual value of IMR was also high. Relative rather than absolute deviations were therefore considered to identify years with a high disease load, calculated by dividing the short-term component of IMR by its long-term trend. Logarithms, however, already represent relative values, and absolute deviations of prices were therefore taken into account. Years with a positive relative deviation from the IMR trend of at least 0.20 and with a positive deviation from the trend in the logarithm of rye prices of at least 0.12 were considered to be, respectively, years with a high disease load or low food availability. These threshold levels correspond to roughly the eightieth percentile in the distribution of relative deviations from the trend in IMR and of deviations from the trend in the logarithm of rye prices, which means that essentially one of every five years had high prices or a high disease load. Figures 4 and 5 present the series of rye prices, and Figures 6 and 7 the IMR series, including their trend and deviation components. In the different analyses performed in this thesis, males and females conceived in years with high prices or born in years with a high disease load are compared to those conceived or born in other years (i.e., those born in years with low-medium prices or IMR).

When evaluating the long-term impacts of exposure to high prices during the foetal stage in Chapter 2, the analysis is restricted to individuals whose families of origin could not support their subsistence from the land, while in Chapters 3-5, estimations are made for this subgroup and the entire population. It is important to make such a distinction because, as discussed earlier, grain prices only represent a measure of nutrition for individuals who were net consumers, particularly in historical societies, where a large fraction of income was spent on food. *Mantal* information, obtained from poll-tax registers, was used to identify this group[6]. Due to the small number of cases, in the final chapter, instead of focusing specifically on the landless, the group of net consumers was defined as those of low SES (SOCPO 1-2).

In Chapters 3-5, the effects of exposure in infancy to specific diseases are also evaluated. For each year where IMR was high, epidemics were specified by identifying the most common cause of death among children between the ages of 0 and 10 in the parishes studied. The three most diffused causes of death in

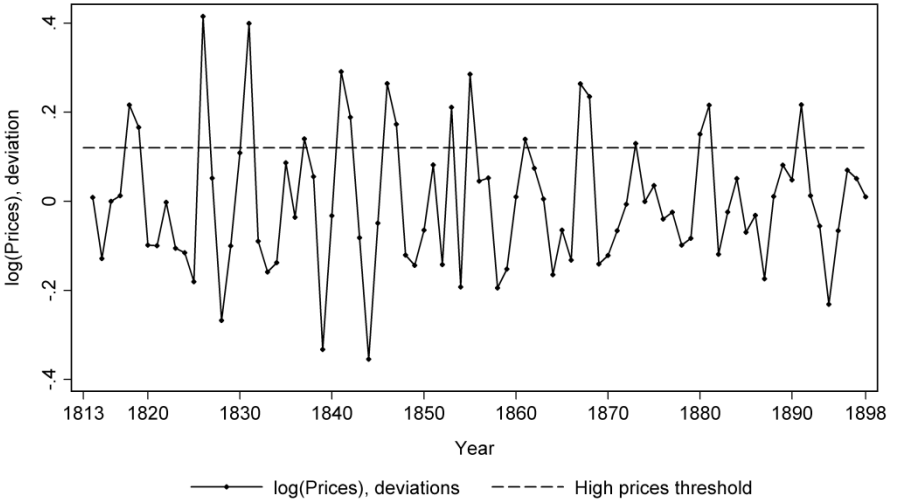
6 Previous works have shown that in the early decades of the 19th century, a mantal of 1/16 was sufficient for subsistence (Bengtsson & Dribe, 2006; Dribe, 2000). For the latter part of the century, there are no studies measuring farm productivity in this area. While a mantal of at least 1/16 was sufficient for subsistence in all years, due to improvements in farming in latter periods, it could have been possible to live off of smaller lands. To increase homogeneity, we consider as landless those with a mantal below 1/16 if they were born between 1813 and 1839, 1/32 if they were born between 1840 and 1869 and 1/64 if they were born between 1870 and 1898. Higher occupations and skilled workers were excluded from the landless group to increase homogeneity. To identify land ownership, we consider each individual's family of origin.

Figure 4: Log rye prices and Hodrick-Prescott trend , 1813-1898



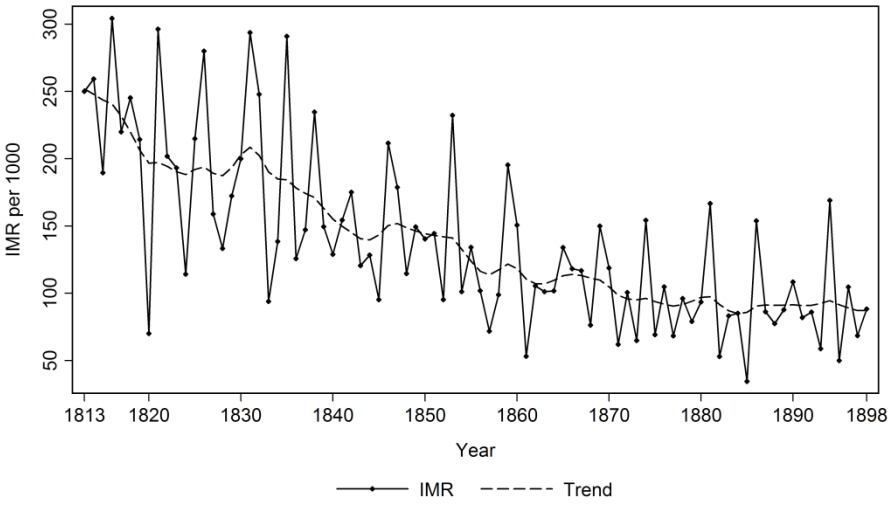
Source: Bengtsson, Dribe 1997

Figure 5: Cycles in log rye prices, 1813-1898. Deviation from a Hodrick-Prescott trend



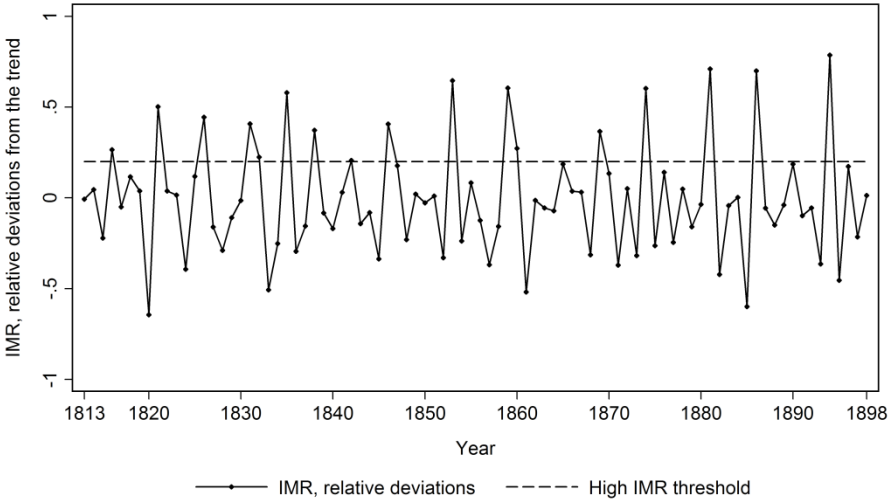
Source: Bengtsson, Dribe 1997

Figure 6: IMR and Hodrick-Prescott trend, 1813-1898



Source: Elaborations from SEDD

Figure 7: IMR cycles, 1813-1898. Deviation from a Hodrick-Prescott trend



Source: Elaborations from SEDD

the period considered were measles, scarlet fever and whooping cough. Chapter 3 compares the mortality impacts of these three epidemics, while in Chapters 4 and 5, only the effect of whooping cough is evaluated specifically (in addition to considering general exposure to high IMR).

This thesis was developed across a prolonged period, and the data extraction used in the current chapter and Chapters 4 and 5 is an updated version of the data extraction used in Chapters 2 and 3. The populations at risk are therefore not identical across all chapters. For the same reason, years defined as having high IMR and those defined as having specific epidemics vary slightly in the different studies. However, these differences were minor and should not affect the results substantially.

The design used in this work may present other limitations. The first relates to the fact that because we have no data on morbidity, it is not possible to precisely determine which individuals were exposed to disease. Moreover, prices and IMR represent yearly averages, and this information was linked to all individuals of the same cohort, regardless of their month of conception or birth. As a result of these two limitations, the impact of these early life exposures may be underestimated. The choice to remove the trend from the price and IMR series rather than considering their effective values, as well as the threshold levels used to define years with high IMR or high prices, could also bias the results. The dependence of the results on these methodological choices is evaluated within a sensitivity analysis in several of the studies conducted.

The data used to identify epidemics were the numbers and causes of death of the five Scanian parishes. The same indicators of IMR and disease were linked to all individuals of the same cohort, irrespective of which of the five parishes they were born in or whether they were migrants. Scania was characterised by very high migration rates (Dribe, 2000; 2003). Slightly more than half of the population considered in this work was not born in the same parish as their current residence. However, the vast majority of migrants were born in a parish located nearby. Of the total population considered in this analysis, 85.6% was born within a 34 km radius of the parishes, 12.7% in the rest of Sweden, and 1.8% in Denmark or other countries. The types of diseases that characterised the studied period were primarily airborne infectious diseases, which spread rapidly across the population. This means that individuals in a specific cohort born in any of the five studied parishes or in the territory surrounding them are likely to have experienced the same disease environment in infancy. In fact, the diseases that were most diffused in the studied parishes coincided, in almost all years, with the most diffused causes of death for Malmöhus County (where these five parishes are located), as reported in

the official statistics[7]. In each of the chapters, nevertheless, as part of the sensitivity analysis, estimations are also made only considering a subset of individuals born in the studied parishes or within a 17 km radius of them (approximately 77% of the total population).

Another aspect to consider is which types of control variables to include in the different models estimated as well as how to treat the trend, particularly when focusing on mortality. These choices are discussed in each of the chapters and are evaluated within a sensitivity analysis. In addition, it is important to assess whether IMR and prices can represent two measures of distinct early life exposures and whether the individuals exposed to high prices or high IMR may have different underlying characteristics than those who were not exposed. Both of these aspects are evaluated in the sub-section that follows.

Finally, it is important to assess possible biases arising from the fact that the individuals born in years with high prices, high IMR, measles, scarlet fever or whooping cough epidemics are compared to those born in all years of low-medium prices or a low-medium disease load, regardless of the proximity of the reference years to the high price or epidemic year. To test this in relation to disease exposures, in a sensitivity analysis (Chapter 3) a single year with epidemics of measles, scarlet fever or whooping cough is selected, and those individuals born in this year are compared to those born some years just before or after. Attempts have also been made to conduct the same type of studies in relation to IMR and prices. However, given the high frequency of years of high prices or high IMR (approximately one every five years), it is difficult to select specific cohorts that were not exposed to either of these conditions during their foetal stage, infancy or in the second year of life. In addition, due to small numbers the models for prices failed to converge. Nevertheless as years with high IMR and high prices are evenly spread across the studied period, the choice to compare all exposed cohorts to all non-exposed cohorts should not bias the results substantially.

7 The only exceptions were 1835 and 1894. The most common cause in 1835 was whooping cough in the Scanian parishes and in Malmöhus County, measles, although many deaths from whooping cough were also observed in the county as a whole. Instead, the main cause in 1894 was whooping cough in the studied parishes and in Malmöhus County, diphtheria, although there the number of deaths from whooping cough was also high. The data from Malmöhus County were obtained from the *Tabellverket*, published by the statistical committee *Tabellkommissionen*, which preceded the National Central Bureau of Statistics.

1.5.1 Grain prices and IMR as indicators of nutrition and disease in early life

This section discusses and evaluates the use of IMR and prices as exogenous and independent indicators of early life exposures and the possible consideration of these exposures as causal to later life health. The setup of studies examining the long-term effects of early life exposures is complex. One of the main criticisms made regarding the use of variables such as birth weight is that it is confounded with SES, as adverse social conditions in early ages might lead individuals into life paths that influence their health negatively (Kramer, 2000). Furthermore, low birth weight could not only result from maternal malnutrition but also from genotypes that limit growth *in-utero* (Carr-Hill et al., 1987) and cause health problems in adulthood (Hattersley & Tooke, 1999). Sources of external variation from natural events such as famines, season of birth, epidemics or economical fluctuations are, however, not related to the life course and are therefore free of sources of confounding, meaning that they could be used to identify causal effects (Doblhammer, 2007; Lindeboom et al., 2010). Bengtsson and Lindström (2000; 2003) claimed that longitudinal individual-level data can be combined with local IMR or grain prices to evaluate the causal impact of exogenous variations in early life conditions. Exogenous variations in early life conditions have also been taken into account through the cyclical component of GDP or GNP (e.g., van den Berg et al., 2009). Alternatively, other scholars have evaluated the effect of malnutrition during the foetal stage by considering exposure to famines (e.g., Lindeboom et al., 2010; Painter et al., 2005).

Contextual variables, however, are not always free of limitations. Brown's (2011) criticism of Almond's (2006) seminal work on the long-term effects of exposure during the foetal stage to the 1918 U.S. influenza pandemic is that the parents of children in the 'treatment' group were less literate, had lower SES, and lower incomes than those in the 'control' group. The reason given by this author for such selection was that the influenza pandemic coincided with World War I, which meant that the healthier groups of males were drafted, and therefore those who fathered children during this period had lower 'parental qualities' due to factors not directly related to the influenza pandemic. Brown showed that when proxies for these characteristics are included in the models, the magnitude and statistical significance of many of the results obtained by Almond are reduced.

Other scholars that have focused on the Finnish famine of 1866-1868 or on the famine created by the Nazi occupation of Leningrad have not found any long-term effects of such exposures (e.g., Kannisto, Christensen, & Vaupel, 1997; Stanner et al., 1997). The lack of significant findings might be because the long-term effects of these famines could be counterbalanced by selective fertility or foetal

mortality. It has been shown, for example, that during the Dutch hunger winter of 1944-1945, fertility was higher in relative terms among couples with higher SES (Stein et al., 1975). Similarly, in a study based on contemporary data, it was shown that babies conceived during periods of high unemployment have a lower incidence of low and very low birth weight, fewer congenital malformations, and are less likely to die in the postneonatal phase (Dehejia & Lleras-Muney, 2004). The authors of this work explained that such differences in health are related to selection (mothers conceiving during recessions have different characteristics) and improvements in health behaviour during recessions. Selection could not only occur through fertility but also in terms of spontaneous abortions. As a result of strong foetal mortality, children born after having experienced malnutrition *in-utero* may be comparatively healthier.

The discussion presented above shows that prior to measuring the long-term effects of early life exposures, it is important to evaluate whether prices of the year of conception and IMR of the year of birth can be used to measure the causal effects of nutrition or disease exposure within the context of Scania. This assessment can be made by studying whether individuals in the group exposed to these adverse conditions differed from the rest of the population.

We begin by evaluating the characteristics of children exposed to a high IMR in infancy. There is no direct data on exposures, but we can test whether the probability of dying in infancy during years defined as having high or low-medium IMR differed by SES. Table 3 presents the results of a Cox proportional-hazard model that introduces an interaction between an indicator variable for the level of IMR in the current year and SES. Children belonging to families of low SES do not present significantly different probabilities of dying at ages 0-1 than those of medium-high SES, neither in years with low-medium IMR nor in those with high IMR.

Table 3: Hazard ratios of death in ages 0-1 introducing an interaction between the IMR level of the current year and SES, Scania 1813-1898

	Means	Hazard ratio	p-value	95% Conf. Interval
IMR current year				
Low-medium	79.96	ref.		
High	20.04	1.816	0.000	1.526 - 2.160
SES at birth				
Medium-high	37.60	ref.		
Low	49.19	1.012	0.865	0.886 - 1.154
Low SES at birth * year with high IMR		0.887	0.313	0.702 - 1.120
Number of individuals	12216			
Number of deaths	1540			

Notes: the models control for year of birth (continuous variable), parish, and an indicator of whether the child was born in one of the studied parishes.

Table 4: Hazard ratios of second and higher order birth introducing an interaction between IMR level of the current year and SES, Scania 1813-1898

	Means	Hazard ratio	p-value	95% Conf. Interval
IMR current year				
Low-medium	78.98	ref.		
High	21.02	0.961	0.275	0.894 - 1.032
Current SES				
Medium-high	49.34	ref.		
Low	45.61	0.834	0.000	0.796 - 0.874
Low current SES * year with high IMR		1.024	0.650	0.925 - 1.132
Number of women	12216			
Number of births	3378			

Notes: the models control for mother´s age (15-19, 20-24, 25-29,30-34,35-39,40-44,45-49), decade, parish of residence and an indicator of the survival status of the previously born child (alive, dead and less than two years had elapsed from the previous birth, dead and more than two years had elapsed from the previous birth).

Next, we consider whether birth rates differ in years when IMR is high. Epidemics occurring during the first months of the year could cause selective fertility (i.e., only certain couples give birth) or selective foetal mortality (i.e., the weakest foetuses die), therefore influencing the characteristics of children born towards the latter part of the year. To evaluate these hypotheses, a Cox-proportional hazard model is estimated to measure the hazard of second and higher order births, including as the primary explanatory variables an indicator for the IMR level in the current year and the current SES of the woman, as well as an interaction between the two. As can be seen from the results obtained (Table 4), the probability of birth does not change during years with high IMR, neither for women of low SES nor for those of medium-high SES.

Finally, we can measure the distribution of SES for children born in years with different IMR levels. The proportions born in families of medium-high SES were 0.42 and 0.43 in years with high or low-medium IMR, respectively. This difference was not statistically significant when conducting a T-test.

Evaluations can also be made to assess whether associations between exposure to high grain prices during the foetal stage and later life health can be claimed to be causal. In Scania and for the period 1766-1864, Bengtsson and Dribe (2006) found evidence for landless groups of deliberate decisions to control births if high prices were foreseen, as well as reductions in fertility due to subfecundity or spontaneous abortions caused by severe malnutrition. These authors reached such conclusions by modelling the hazard of experiencing second and higher order births based on current and lagged rye prices. A similar estimation can be made for the data extraction considered in this work. Table 5 shows the results of Cox proportional hazard models estimating the probability of experiencing second and higher order births for landless women, including current and lagged

Table 5: Hazard ratios of second and higher order birth for landless women according to current and lagged rye prices, Scania 1813-1869

	Means	Hazard ratio	p-value	95% Conf. Interval
Rye price (t)				
Low-medium	74.38	ref.		
High	25.62	0.858	0.000	0.789 - 0.933
Rye price (t-1)				
Low-medium	75.89	ref.		
High	24.11	0.921	0.056	0.847 - 1.002
Number of women	1062			
Number of births	3084			

Notes: the models control for mother´s age (15-19, 20-24, 25-29,30-34,35-39,40-44,45-49), decade, parish of residence and an indicator of the survival status of the previously born child (alive, dead and less than two years had elapsed from the previous birth, dead and more than two years had elapsed from the previous birth).

rye prices as the primary explanatory variables (in both cases thresholds levels). This model is only estimated for women who were currently landless and for the period until 1869.

Reduced hazards of birth are observed in relation to current and lagged grain prices (Table 5). The probability of birth was 10% lower in connection to high lagged rye prices and 16% lower in connection to high current rye prices. The patterns of the results observed therefore confirm those found earlier by Bengtsson and Dribe (2006). These authors claimed that the reduced probability of birth in connection to price changes in previous years was an involuntary response related to malnutrition, likely operating through lower fecundability, temporary sterility and a greater proportion of spontaneous abortions. Instead, they explained that the rapid response to short-term economic stress was a sign that couples could foresee high prices and planned their childbearing accordingly, through coitus interrupts, abstinence or, less likely, induced abortions. Such adjustments were not made to achieve a certain family size but rather to reduce the negative impact of short-term economic stress (Bengtsson & Dribe, 2006). The effects of rapid and voluntary responses that were caused by planning were shown to have stronger effects than lagged involuntary responses related to malnutrition, both in these previous studies and the calculations made here.

Having observed that landless families had lower probabilities of birth in reaction to high prices, it is also important to compare the characteristics of couples that gave birth in periods of high prices to the characteristics of those that gave birth in other years. As we are here only focusing on the landless group, it is not particularly informative to measure SES differences between the two groups. Instead, we calculate the average ages of women who gave birth, which could be a characteristic that also has a long-term impact on the health of these children. The average ages of mothers at the time of births were 33.1 and 33.8 during years with

high or low-medium prices, respectively (if current prices are considered), and the results of a T-test reveal that this difference was statistically significant at the 1% level. Differences in ages were smaller when considering lagged prices.

Based on the considerations and calculations made in this section, it is possible to state that grain prices, at least for the period up to 1870, serve as an exogenous measure of short-term economic stress and the level of nutrition perceived by the population, including pregnant women. If associations are found between exposure to high prices during the foetal stage and later life health, however, these associations cannot be considered completely causal, as part of the impact of exposure to high prices works through reduced fertility levels. As a result of selective fertility or selective foetal mortality, individuals born after periods of high prices may not necessarily share the same characteristics (for example in relation to health and wealth) as those born after periods of low-medium prices. This may counterbalance the possible negative long-term effects of undernutrition during the foetal stage. It is difficult, however, to hypothesise the expected direction of this selection, as it is possible that during periods of high prices, only a subgroup of the healthiest couples conceived and gave birth to a live child or, instead, that those conceiving were a subgroup of individuals unable to control their fertility because of lower abilities. In the models that analyse the long-term effects of prices (Chapter 2), controls can be included for the age of the mother at the individual's birth, at least as a preliminary step to determine whether a characteristic shown to differ between the two groups confounds the results. Instead, the calculations made in this section in relation to IMR show that this variable can be considered an exogenous indicator of the disease load experienced by individuals in infancy, and any association found between this indicator and later life health could be considered causal.

A final aspect to consider is whether IMR and prices can be assumed as two independent types of early life exposures or if instead they are probably both caused by the same underlying factor. Correlations can be calculated and tabulations can be made in order to make this assessment. When taking into account IMR and the logarithm of rye prices of the same year, the correlation between the series of the full values of IMR and prices is -0.28, while the correlation between the series of their deviation components[8] is 0.25. Of those years which were defined as having a high IMR, 35% were also identified as having high prices. When conducting the same calculations for IMR and the logarithm of rye prices of the preceding year, the correlation between the series of full values is -0.44, the correlation between the series of deviation components is -0.06, and for 35% of the years identified as having high IMR, the previous year was identified as having high

8 We consider the deviation component of the logarithm of rye prices and the relative deviations of the IMR.

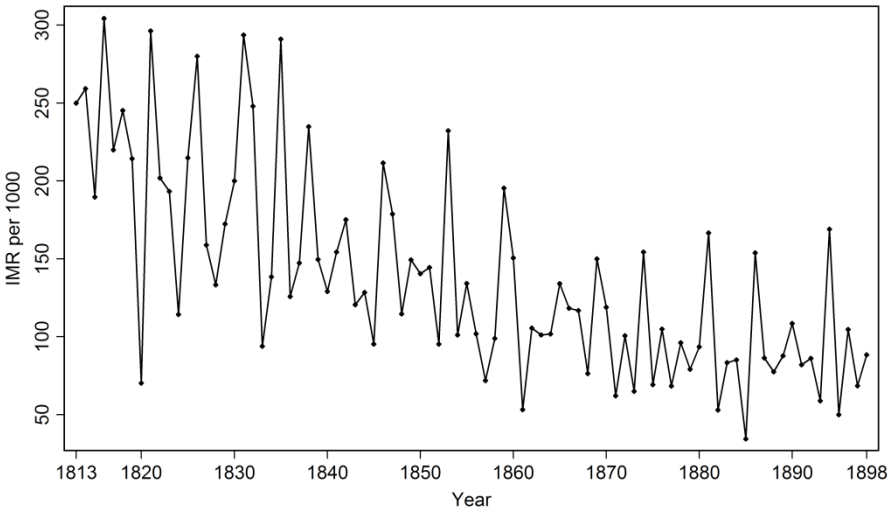
prices. These calculations therefore show that only part of the changes in infant mortality rates are the result of fluctuations in food prices or of the factors that cause such fluctuations. Based on these results, IMR and prices can be considered as independent measures of diet and disease.

1.6 The long-term development of mortality in the five Scanian parishes

Prior to measuring the impact of early life conditions on later life health, an overview of the development of mortality in the five Scanian parishes is presented. This can provide an initial, basic understanding of the context of study. In this section, the rates of infant and old-age mortality for each cohort, as well as period life expectancies and the distribution of deaths by cause, are shown. The life expectancies of the five parishes are compared to those of Sweden as a whole.

The infant mortality rates are depicted in Figure 8. They were calculated for the years 1813-1898, as these were the cohorts selected for this study. A declining trend can be observed; IMR changed from roughly 250 per 1000 at the beginning

Figure 8: Infant mortality rates in Scania, 1813-1898



Source: Elaborations from SEDD

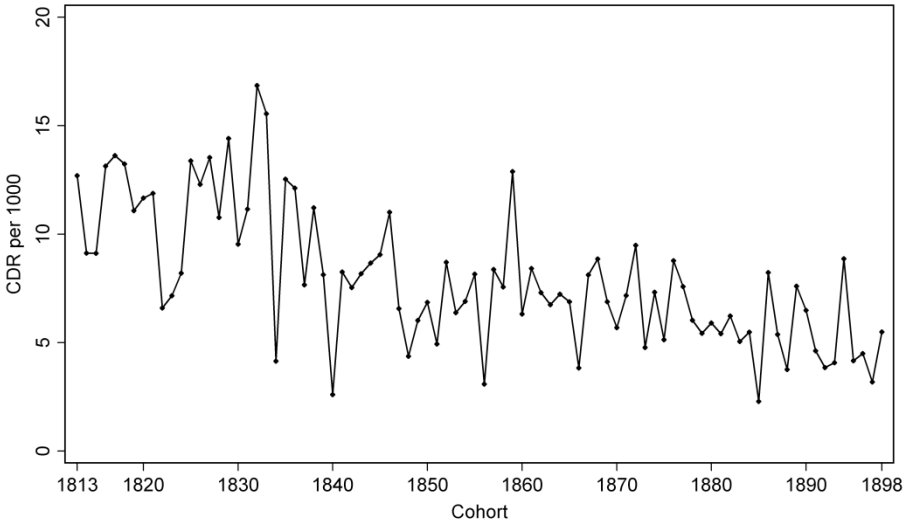
of the studied period to approximately 90 per 1000 in the latter years. The trend could be divided into three sections, with the years 1840 and 1870 as boundaries. In each of these periods, the trend in IMR became less steep and year-to-year fluctuations less pronounced. After 1870, IMR was more stable.

IMR can be compared to old-age mortality. Figure 9 presents crude death rates among ages 50-70, calculated by cohort. A declining trend can also be observed in this chart, and here more pronounced year-to-year fluctuations are seen for the first cohorts than for those born towards the end of the period. Old-age mortality was higher among those born prior to 1840, and the trend became less steep for the succeeding cohorts. If death rates are averaged across the five cohorts, values of 11.5 deaths and 5.2 deaths per 1000 are obtained, respectively, for those born in 1813-1817 and 1894-1898. This means that across nearly 80 cohorts, the rates of old-age mortality were nearly halved.

Life expectancies were also calculated based on the values of average longevity obtained as the integral of the survival functions estimated using Kaplan-Meier estimators. These were calculated for periods (for the years 1813 to 1968) and not for cohorts, as the final cohorts cannot be followed until their death. In Figure 10, the values for the five Scanian parishes are compared to those of Sweden. Year-to-year fluctuations are wider in Scania than in Sweden, which is not unexpected given the much smaller size of the population. The trends in both areas are similar, although a slightly steeper increase is observed in Scania relative to the country as a whole in the latter part of the studied period. If averages are calculated across years, values of 39.0 and 76.8 are obtained, respectively, during the years 1813-1817 and 1964-1968 for Scania. This means that life expectancy doubled in slightly more than 150 years. In the case of Sweden, values of 39.5 and 74.0 are obtained for the same 5-year periods. Life expectancy was therefore slightly lower in Scania in the initial period, but it was almost three years longer in the final part. This difference is likely because the five parishes considered were located in the countryside.

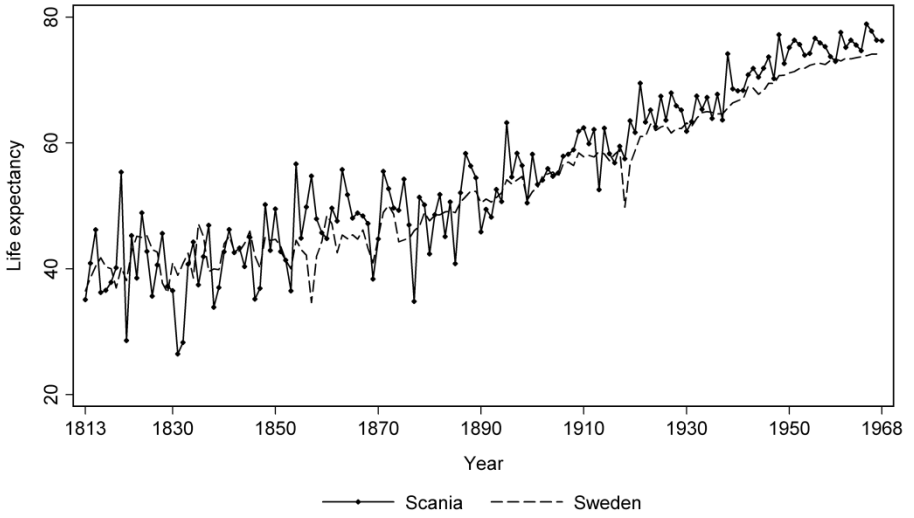
We can also calculate average remaining life expectancies at different ages. Figure 11 depicts values for groups of 5-years at the beginning, middle and end of the studied period, calculated at ages 0, 1, 20 and 50 and by sex. Comparing average remaining years of life at different ages, in 1813-1817, substantial differences can be observed in the values at birth or at age 1, a pattern caused by the high levels of infant mortality in these cohorts (Figure 11). Differences in the values at these two ages became less marked in the periods 1888-1892 and 1964-1968, as IMR had already declined rather substantially. If the estimates are compared across sex, it can be seen that in 1964-1968, females exhibit higher life expectancies at all ages, while in 1813-1817, the values are very similar for males and females. In 1813-1817, life expectancies are higher for females only after age

Figure 9: Crude death rates for ages 50-70 in Scania, cohorts 1813-1898



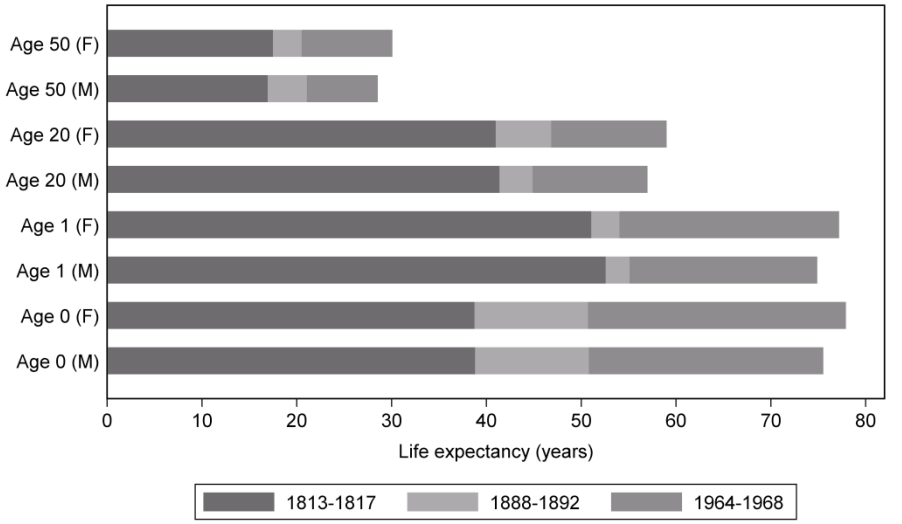
Source: Elaborations from SEDD

Figure 10: Period life expectancies in Scania and Sweden, 1813-1968



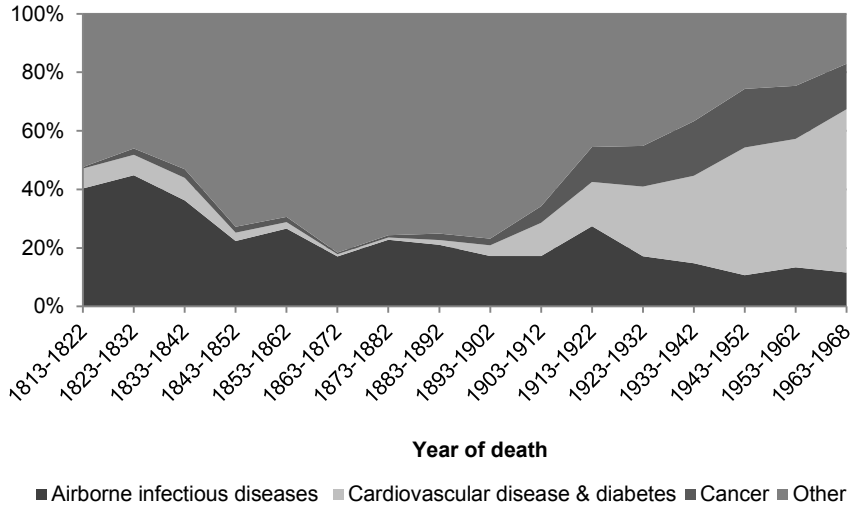
Source: Scania – elaborations from SEDD. Sweden – The Human Mortality Database.

Figure 11: Period remaining life expectancies by age and sex in Scania, 1813-1968



Source: Elaborations from SEDD

Figure 12: Distribution of deaths by cause in Scania, 1813-1968



Source: Elaborations from SEDD

50, although this difference is very small. The change in the patterns observed over these two periods could be a result of declines in maternal mortality.

Another characteristic to evaluate is the development of causes of death over time. Figure 12 depicts the distribution of deaths by cause for 10-year periods, taking into account deaths occurring at all ages. The main aspects that can be noted from this figure are the declining trend in the percentage of deaths from airborne infectious diseases and an increase in the proportion of deaths from cardiovascular diseases, diabetes, and cancers, particularly after the turn of the century. Evidence of changes from infectious diseases to man-made diseases, in other words of the epidemiological transition (Omran, 2005), is therefore found in the five Scanian parishes studied in this work.

To summarise, we have shown in this section that in the period under consideration, important transformations have been observed in the five Scanian parishes studied. From the first to the last cohorts considered, IMR dropped to slightly more than a third, old-age mortality nearly halved, and from the first to the last years of the studied period, life expectancy doubled. It was also demonstrated that the development of mortality in the five studied parishes was very similar to that of Sweden as a whole, except for a greater decline towards the end of the period related to the fact that environmental conditions were better in rural areas.

The results obtained in this section make it possible to emphasise two points. The first is that it is interesting to measure whether early life conditions had an impact on later life health across periods that present changes as substantial as those observed in the figures shown here. The second is that the similarities in the development of life expectancy in these parishes to that of Sweden as a whole imply that the five rural communities can serve as a good example of the conditions experienced over wider territories, and therefore the findings obtained could be generalised to other contexts.

1.7 The impact of early life conditions on mortality in old age

We begin the analysis by making a broad study of the impact of early life conditions on mortality in old age. Before exclusively focusing on the long-term effects of exposure to IMR in infancy and prices during the foetal stage following the methodologies described in earlier sections, we first measure the impact of these and two additional indicators of early life conditions; prices in the year of birth

and the rates of female mortality in reproductive ages (CDR_{20-50})[9]. The impact of these four indicators is modelled by considering their actual values, their trend and deviation components, and threshold levels of deviations from the trend. Here we examine males and females of all SES groups within the same estimations.

Table 6 presents the results of Cox models estimating the risk of dying at ages 50-70, using the full values of IMR of the year of birth, rye prices of the year of conception and of the year of birth, female CDR_{20-50} in the year of conception, and SES at birth as explanatory variables. The IMR of the year of birth has a statistically significant, positive effect on the risk of dying in old age, meaning that the higher the rates of infant mortality in the year of an individual's birth, the greater his/her probability of dying between ages 50-70. No statistically significant effects are observed in connection to the price levels in the year of conception or birth, or to the disease load experienced by mothers during gestation. SES at birth does not have significant effects on the probability of dying in old age.

The impacts of these indicators of early life conditions can also be measured by considering the components of trend and deviation from the trend of these series rather than their actual values. These estimations are presented in Table 7. No statistically significant effects are observed regarding the prices in the year of conception or birth or female CDR_{20-50} in the year of conception. Instead, a positive and statistically significant association is found between the deviation component of the trend in IMR in infancy and mortality in old age.

To conclude, the same model is estimated considering threshold levels of deviations from the trend in the series of prices and mortality rates in early life. As can be seen in Table 8, the results remain unchanged when using this formulation of the indicators of early life conditions. Individuals born in years with a high IMR exhibit a 17% higher risk of dying in old age, statistically significant at the 5% level. Instead, no statistically significant impacts are found in relation to the other indicators of early life conditions.

This section showed that, regardless of whether these indicators are considered using their full values, trend and deviation components, or threshold levels of deviations from the trend, exposure to high IMR in the year of birth is associated with greater probabilities of dying in old age, while there is no significant effect of prices during the foetal stage or infancy or of the disease exposure of mothers during the foetal stage. The results are in line with those obtained by Bengtsson and Lindström (2000; 2003) in earlier works conducted on data from four of the

9 Female adult mortality rates were calculated directly from the data, considering crude death rates at ages 20 to 50. This series was decomposed into a trend and a cycle component using the Hodrick Prescott filter with a filtering factor of 6.25, and years having relative deviations from the trend greater than or equal to 40% were defined as having high adult female mortality. This threshold level corresponded to roughly the eightieth percentile in the distribution of death rates, meaning that essentially one out of every five years had high mortality.

Table 6: Hazard ratios of death between ages 50-70 considering the full values of indicators of early life conditions, Scania cohorts 1813-1898

	Hazard ratio	p-value	95% Conf. Interval		
IMR year of birth	1.001	0.036	1.000	-	1.002
Prices year of conception	1.031	0.914	0.586	-	1.815
Prices year of birth	1.014	0.962	0.577	-	1.783
CDR 20-50	1.005	0.649	0.984	-	1.027
SES at birth					
Medium-high	ref.				
Low	0.970	0.636	0.856	-	1.100
Unknown	0.984	0.827	0.854	-	1.135
Sex					
Male	ref.				
Female	0.982	0.744	0.883	-	1.093
Birthyear	0.992	0.000	0.988	-	0.995
Parish of residence					
Hög	1.001	0.996	0.806	-	1.243
Kävlinge	ref.				
Halmstad	1.096	0.351	0.904	-	1.330
Sireköpinge	1.100	0.224	0.943	-	1.283
Kågeröd	1.003	0.967	0.869	-	1.158
Birth place					
In studied parishes	ref.				
Other	0.934	0.284	0.825	-	1.058
Number of individuals	7108				
Number of deaths	1348				

Notes: the models control for sex, year of birth (considered as a continuous variable), parish of residence and an indicator of whether the individual was born in one of the studied parishes or migrated to them.

parishes considered here for the years 1760 and 1894. It is possible to conclude that the patterns found by these authors are also confirmed when focusing on mortality during the 19th and 20th centuries.

The findings obtained here also raise a series of questions. Having observed that the disease load experienced by individuals during infancy affects their probability of dying in old age, it is also important to attempt to understand what mechanisms could be causing this association. Studying whether exposure to distinct disease environments may have different impacts on mortality later in life is a first step towards understanding such mechanisms. To not condition on survival until old age, another important question is whether early life exposures also have an effect on mortality in younger ages and whether these impacts differ across sex. Moreover, as mortality rates are not particularly high during childbearing and working ages, other measures of health must also be considered,

Table 7: Hazard ratios of death between ages 50-70 considering the trend and deviation components of indicators of early life conditions, Scania cohorts 1813-1898

	Hazard ratio	p-value	95% Conf. Interval		
IMR year of birth					
Trend	1.001	0.584	0.997	-	1.005
Cycle	1.001	0.037	1.000	-	1.003
Prices year of conception					
Trend	0.402	0.382	0.052	-	3.102
Cycle	1.348	0.476	0.593	-	3.066
Prices year of birth					
Trend	2.565	0.363	0.337	-	19.524
Cycle	0.789	0.550	0.363	-	1.715
CDR 20-50					
Trend	1.007	0.768	0.960	-	1.057
Cycle	1.006	0.687	0.977	-	1.036
SES at birth					
Medium-high	ref.				
Low	0.969	0.620	0.855	-	1.098
Unknown	0.985	0.838	0.855	-	1.136
Sex					
Male	ref.				
Female	0.981	0.731	0.882	-	1.092
Birthyear	0.991	0.020	0.984	-	0.999
Parish of residence					
Hög	1.001	0.993	0.806	-	1.243
Kävlinge	ref.				
Halmstad	1.096	0.352	0.903	-	1.330
Sireköpinge	1.097	0.237	0.941	-	1.280
Kågeröd	1.004	0.959	0.870	-	1.159
Birth place					
In studied parishes	ref.				
Other	0.935	0.288	0.825	-	1.059
Number of individuals	7108				
Number of deaths	1348				

Notes: the models control for sex, year of birth (considered as a continuous variable), parish of residence and an indicator of whether the individual was born in one of the studied parishes or migrated to them.

for example SES attainment and reproductive health. These questions establish the aims of the four articles included in this thesis. Although no statistically significant associations were found between prices in the year of conception and mortality in old age when considering the full population, in the next chapters, further analyses are conducted in relation to this indicator, focusing specifically on individuals originating from families who could not meet

Table 8: Hazard ratios of death between ages 50-70 considering threshold levels of deviations from the trends of the indicators of early life conditions, Scania cohorts 1813-1898

	Hazard ratio	p-value	95% Conf. Interval		
IMR year of birth					
Low-medium	ref.			-	
High	1.169	0.018	1.027	-	1.330
Prices year of conception					
Low-medium	ref.				
High	0.951	0.735	0.711	-	1.273
Prices year of birth					
Low-medium	ref.				
High	1.006	0.966	0.755	-	1.342
CDR 20-50					
Low-medium	ref.				
High	1.018	0.791	0.890	-	1.164
SES at birth					
Medium-high	ref.				
Low	0.971	0.648	0.857	-	1.101
Unknown	0.986	0.842	0.855	-	1.136
Sex					
Male	ref.				
Female	0.985	0.782	0.885	-	1.096
Birthyear	0.990	0.000	0.987	-	0.992
Parish of residence					
Hög	0.998	0.986	0.804	-	1.239
Kävlinge	ref.				
Halmstad	1.097	0.347	0.904	-	1.331
Sireköpinge	1.099	0.228	0.943	-	1.282
Kågeröd	1.003	0.967	0.869	-	1.158
Birth place					
In studied parishes	ref.				
Other	0.932	0.268	0.823	-	1.056
Number of individuals	7108				
Number of deaths	1348				

Notes: the models control for sex, year of birth (considered as a continuous variable), parish of residence and an indicator of whether the individual was born in one of the studied parishes or migrated to them.

their subsistence needs using land and estimating distinct models for each sex. The price levels in the year of birth and female CDR_{20-50} in the year of conception are not considered further, as they lacked a significant impact both here and in the results observed by Bengtsson and Lindström (2000; 2003).

1.8 Summary of Chapters

1.8.1 Paper I – Selection and scarring across the life course: the effects of early life conditions on mortality by sex in 19th and 20th century Southern Sweden

This article evaluated the impacts of exposure to high prices in the year of conception or high IMR in the first year of life on mortality later in life, considering these two measures of early life conditions as exogenous indicators of the level of nutrition perceived during the foetal stage and the disease load experienced in infancy, respectively. The impact of exposure to disease was evaluated for the entire population, while that of exposure to high prices was only considered for individuals born into landless families, as grain prices only represent a measure of nutrition for net consumers.

This work considered individuals born between 1813 and 1898, following them from birth until age 70. Separate models were estimated for early childhood, late childhood and adolescence, adulthood, and old age. In addition to using arbitrary fixed age boundaries for these models, flexible age boundaries are considered. The lack of previous research did not allow the construction of well-defined formulations of when the results are expected to fluctuate. For this reason, an iterative procedure was programmed to repeatedly run the same estimations for different age boundaries, therefore allowing us to capture stages where selection dominated scarring and *vice-versa*.

During the initial stages of the life course and for both types of early life exposures, the patterns observed were similar for males and females, with selection dominating in early childhood, followed by scarring until early adolescence. Marked sex differences were observed during the childbearing and working years. In this stage selection prevailed for females in relation to both exposures. Among adult males, scarring dominated from the early 20s for those exposed to a high IMR in infancy, while no strong impacts of exposure to high prices during the foetal stage were observed in this age group. In old age, the foetal origin hypothesis was confirmed for landless males, and the infancy inflammation hypothesis was confirmed for all individuals. Males conceived in years with high prices presented stronger negative repercussions on health in old age than females (this difference was statistically significant), while the opposite was true among those born in years high IMR. However, males exposed to high IMR exhibited an earlier onset of the dominance of net scarring than females. In adulthood and old age, the impacts of exposure to disease in the first year of life were stronger than those of

exposure to low SES at birth. Moreover, the interaction term between IMR and SES at birth was not statistically significant for any of the age groups considered.

The average number of years lived was calculated to measure the size of these effects. Between ages 1 and 70 for individuals originating from landless families, females exposed to high prices during their foetal stage lived for approximately 3 years longer than those conceived in years with low-medium prices, while males lived roughly 1 year less. No large differences in the average number of years lived were observed between ages 1 and 70 for individuals born in a year with high IMR, but exposed males who survived until adulthood presented a loss of 1.8 years, while the females who survived until the end of their reproductive ages presented a loss of 0.9 years.

When comparing the impact of exposure to high IMR in infancy across cohorts, scarring began to dominate from earlier ages among those born after 1850, a pattern that was observed for males and females. Among males, stronger negative effects were also observed in old age for those born after 1850.

1.8.2 Paper II – Early life exposure to measles, scarlet fever or whooping cough and sex differences in mortality across the life course: Southern Sweden, 1813-1968

The second article of this thesis aimed to study the impact of exposure to epidemics of measles, scarlet fever and whooping cough in infancy on mortality throughout the life course, while capturing sex differences in such effects. Also in this case, individuals born between 1813 and 1898 were considered, following them from birth until age 70.

With the purpose of understanding the magnitude of the potential impacts on health, the risk of dying at ages 0-1 was measured during years with these epidemics as a preliminary study. In years when measles dominated, boys presented significantly lower probabilities of dying than girls, while no statistically significant differences by sex were observed in years when scarlet fever or whooping cough prevailed. The strongest effects were observed in years with whooping cough, where the hazard of death in infancy was twice that in years with a low-medium disease load.

The remainder of this work evaluated the impact of exposure in infancy to these disease environments on mortality later in life. To capture changes throughout the life course, estimations were performed while considering fixed and flexible age boundaries, in the latter case adopting the same iterative procedure used in Paper I. The main outcome considered in the analysis was all-cause mortality, but the probabilities of dying from airborne infectious diseases, cardiovascular diseases

and diabetes, or cancer were also measured. When considering all-cause mortality, interactions between disease exposure and SES in early life were also measured. In addition, the impact of exposure to whooping cough was estimated for two different cohorts.

Strong sex differences were observed during the childbearing and working years in relation to exposure to measles and scarlet fever. Females exposed to these diseases in infancy presented a dominance of selection, primarily through lower probabilities of dying from airborne infectious diseases. Males exhibited a dominance of net scarring in relation to these two types of disease exposures. The sex differences observed during these ages were only statistically significant in relation to scarlet fever.

The impact of whooping cough, instead, was constant across sex. Scarring dominated from approximately age 20 for males and age 24 for females. These higher mortality rates were related to deaths from airborne infectious diseases and cancer, and to a lesser extent cardiovascular diseases and diabetes for females. For males, they were related to greater probability of dying from cardiovascular diseases and diabetes, and airborne infectious diseases. Only the last of these results was statistically significant. The average number of years lived was also calculated, and between ages 20 and 70, females exposed to whooping cough in infancy presented averages that were 1.6 years shorter than for those born in a year with low-medium disease load, while the difference for males was 3.1 years. The effect of exposure to whooping cough was stronger in relative terms for individuals born after 1850, and for these cohorts, scarring also dominated from an earlier age than for those born prior to this year. The interaction terms between disease exposure in infancy and SES at birth were not statistically significant for any of the three epidemics considered.

1.8.3 Paper III – The impact of early life conditions on the offspring sex ratio at birth by socioeconomic status in 19th and 20th century Southern Sweden

This paper studied the impact of women's early life exposures on their offspring sex ratio at birth. Early life conditions were measured using indicators that considered whether the woman was conceived in a year with high prices or born in a year with high IMR or whooping cough epidemic. When evaluating the effect of exposure to high prices during the foetal stage, models were estimated for all women and only for those born into landless families. The sample considered included women born between 1813 and 1898 and who gave birth in the period 1828 to 1948. This full sample of women was considered in the initial models, but further

estimations were also made for separate groups according to women's current SES. It was hypothesised that the patterns of fertility or living conditions (for example in relation to nutrition, quality of housing, workload, etc.) of families of high or low SES could have differed and that such differences could have worked as modifiers in the relationship between early life exposures and the offspring sex ratio at birth.

Females exposed to high IMR in infancy presented a lower offspring sex ratio at birth, although these results were not statistically significant. Similar patterns were observed in relation to specific exposure to whooping cough, for which the effects were even stronger. At ages 25 or older, women of low SES gave birth to a lower proportion of males if they had been born in years with whooping cough epidemics. Sex ratios of 112.5 and 90.9 boys per 100 girls were observed for unexposed and exposed women, respectively. However, no relative differences in their offspring sex ratio at birth were seen for mothers of medium-high SES according to their disease exposure in infancy. Cohort changes were also considered, which showed stronger negative effects of whooping cough exposure in infancy for women born after 1850 than for those born before that year. Exposure to high prices during the foetal stage did not impose any significant effects on the sex ratio at birth of a woman's offspring, although for mothers of medium-high SES, weak signs of higher sex ratios were observed among those exposed.

Additional estimations were performed to identify possible mechanisms causing the patterns observed for women who had been exposed to whooping cough in infancy. In particular, the impact of fathers' early life exposure to this epidemic on the offspring sex ratio at birth and the effect of exposure of either parent to this disease on offspring neonatal mortality were also measured. The risk of dying in the first 28 days of life for offspring born to exposed mothers depended on the sex of the child. Relatively higher rates of death were observed for boys born to mothers exposed to a low-medium disease load, while boys born to mothers exposed to whooping cough showed relatively lower mortality. Because the risk of spontaneous abortions is higher for male foetuses, this health selective advantage of newborn boys over girls is likely to indicate that women exposed to whooping cough experienced a higher incidence of spontaneous abortions of male foetuses. Similar differences of offspring mortality in relation to the offspring's sex were observed when considering the father's disease exposure, although the impacts for fathers were of smaller magnitude and statistical significance than those for mothers. Moreover, fathers born in years with whooping cough showed only a small reduction in the sex ratio at birth of their offspring.

1.8.4 Paper IV – The impact of early life conditions on socioeconomic status in adulthood, fertility and offspring neonatal mortality among 19th and 20th century women in Southern Sweden

The last article in this thesis was devoted to studying the impact of exposure to adverse early life conditions on the probability that a woman would attain high SES in adulthood, her likelihood of experiencing a birth, and her offspring neonatal mortality. Early life conditions were measured through three exogenous indicators: exposure to high prices during the foetal stage and to high IMR or specifically to whooping cough epidemics in infancy. The impact of exposure to high prices was evaluated for the full sample of women but also specifically for those whose families of origin were of low SES, as grain prices could only serve as a measure of nutrition for net consumers. The study considered women born between 1813 and 1898, and the models focusing on fertility and offspring neonatal mortality were estimated separately for the periods that preceded or followed the fertility decline.

No significant impacts were found in relation to exposure to high grain prices during a woman's foetal stage for any of the outcomes considered, neither when focusing on the full sample of women nor specifically on those whose families of origin were of low SES. Although neither of these effects was strong nor statistically significant, odds ratios above unity were obtained when measuring the probability of attaining high SES in adulthood, while in 1829-1889, reduced odds of experiencing offspring neonatal mortality were observed for exposed women.

Females who were of low SES at birth had lower probabilities of attaining high SES during the childbearing and working years if they had been exposed in infancy to high IMR or specifically to whooping cough epidemics. Those whose families of origin were of high SES, instead, did not present variations in their likelihood of attaining high SES in adulthood in relation to their early life disease exposures. When focusing on offspring neonatal mortality, in the period preceding the fertility decline, higher mortality was observed among offspring born to mothers who had experienced high IMR or specifically whooping cough epidemics in infancy. In 1890-1948, lower probabilities that the woman's offspring died in their neonatal stage were observed among those with similar early life exposures, although these effects lacked statistical significance.

The study that considered the hazard of experiencing second and higher order births as an outcome failed to obtain statistically significant results in relation to the disease load experienced by these women in infancy. Those exposed to whooping cough epidemics presented somewhat reduced probabilities of birth in 1829-1889. This effect was only statistically significant when excluding age controls from the models. Conversely, higher probabilities of birth were observed

among women whose last-born child died in the first month of life, while lower fertility was observed for low SES females.

1.9 Discussion

The findings of the four analytical chapters can be discussed simultaneously to attempt to provide more thorough interpretations. Important aspects to consider are the differences observed in the long-term impacts of early life exposures by age, sex, and cohort, as well as the observed effects on reproductive health.

Chapters 2 and 3 showed that the impacts of early life exposures changed throughout the life course. Although the ages at which these fluctuations occurred and the magnitude of the effects at each of these stages varied somewhat, the pattern observed in relation to exposures to high prices or a high IMR in early life took the form of selection/scarring/selection/scarring. The lower probabilities of dying observed in early childhood for boys and girls exposed to high prices during their foetal stage or disease in infancy could be explained by the fact that during years with high prices or epidemics, weak foetuses and infants do not live past birth or age one and those surviving are consequently stronger than the average child who had not faced conditions of stress prior to that time. In the case of whooping cough, selection dominated until early adulthood, an effect likely related to the severity of this epidemic and its rapid and efficient spread. In years with epidemics of this disease, the risk of dying from ages 0 to 1 was twice that in years with a low-medium disease load.

The fluctuations observed during later stages of childhood and adolescence could be linked to the demands made on the body from the tempo of growth, which we know changes, particularly during mid-childhood and adolescence. After maturation, the strength and direction of the impacts of early life exposures may be influenced by childbearing and involvement in the labour market. These relationships could cause part of the differences by sex that characterised such ages. In old age, instead, we found support for the foetal origins hypothesis for landless males and the infancy inflammation hypothesis for all individuals (Chapter 2). As explained in previous studies, these are the ages at which chronic diseases that relate to such exposures are likely to be manifested.

Studying the full life course and males and females separately also permitted us to show that the impact of several of the early life exposures considered were sex-specific during adulthood (Chapters 2 and 3). The dominance of selection observed among females exposed to high prices while *in-utero* is rather intriguing. Chapter

2 hypothesised that this pattern could be partly due to differences in childbearing. There are, in fact, short- and long-term relationships between reproduction and health and mortality (e.g., Doblhammer & Oeppen, 2003; Dribe, 2004). According to the theory of life history regulation, fertility and bodily maintenance are in mutual balance, and an increased investment in one can only be achieved at the expense of a reduced investment in the other (Stearns, 1992). If females exposed to high prices during their foetal stage gave birth to a smaller number of children at older ages, they could have experienced relatively lower mortality. This hypothesis was in part tested in Chapters 4 and 5 but was not confirmed. On the contrary, females exposed to high prices during the foetal stage exhibited some small indications of better reproductive health, therefore presenting further evidence of net selection.

In Chapter 2, we also discussed how the relatively lower mortality presented by these women may in part be a consequence of reductions in fertility during years with high prices (i.e., when these females were conceived) and alterations in the sex ratio at birth. It has been previously shown that there were reductions in fertility among the landless in Scania when high prices were anticipated (Bengtsson & Dribe, 2006), and these patterns were confirmed in calculations made in earlier sections of this chapter. Trivers and Willard (1973) relate the sex ratio at birth to natural selection, stating that the highest number of grand-offspring is achieved when parents experiencing above-average conditions produce more sons and parents facing poor conditions produce more daughters. Based on these findings and hypotheses, it is possible that during periods with high prices, only a select group of couples with better health or higher wealth conceived and gave birth to live children, resulting in healthier offspring for both sexes and a higher proportion of male births.

This hypothesis is confirmed among landless families, among which statistically significant differences in the sex ratio at birth are observed for the period before 1870. The ratio was 124 males per 100 females for those conceived in years with high prices and 108 males per 100 females for those conceived in other years. It is likely that in years with low-medium prices, healthier couples also gave birth to a higher proportion of males, while less healthy couples produced a higher proportion of females. Such patterns could explain why, in relative terms, females that had been exposed to high prices while *in-utero* had longer lives on average than those exposed to low-medium prices. The above arguments could also justify why selective mechanisms did not dominate among males. However, these hypotheses can only explain a portion of the differences observed, as the models that included an interaction between prices and sex showed that among those exposed to high prices during the foetal stage, old-age males had significantly higher mortality than old-age females. Even if fertility were selective during years with high prices, for

males conceived in those periods evidence of long-term damaging effects on health was nevertheless observed. There could therefore also be biological mechanisms linking malnutrition *in-utero* to later life health that are sex-specific.

In Chapter 2, sex differences, although of a smaller magnitude, were also observed during adulthood in connection to exposure to high IMR in infancy. Chapter 3 revealed that such differences were related to individuals exposed to measles and scarlet fever, where selection dominated among females and scarring dominated among males. In years with measles epidemics, boys exhibited lower probabilities of dying at ages 0 to 1 than girls (Chapter 3), which could be related to the fact that girls lose maternal antibodies to this disease more rapidly than boys (Martins et al., 2009). Selection during infancy could therefore have been stronger for females, resulting in lower relative rates of mortality in early adulthood.

The lower probabilities of dying during adulthood observed for females exposed to measles or scarlet fever could also be partly connected to childbearing. For these women, some indications of reduced probabilities of dying from airborne infectious diseases were observed (Chapter 3). In historical populations, death from tuberculosis was very common shortly after giving birth. Although direct immunity to this disease cannot be conferred by previous measles or scarlet fever infections, there may be heterologous immunity effects or links between infections and autoimmune responses. Immunity is heterologous when an individual is immunised to one type of pathogen after having been exposed to non-identical pathogens (see e.g., Selin et al., 2002; Welsh et al., 2010). The interpretations for these results and those pertaining to the impacts observed for females in connection to prices provided here are, however, only speculative, and further research is required to better identify the potential causal mechanisms and observe whether these findings are replicated in other populations.

The impact of exposure to whooping cough during the first year of life on mortality was instead similar across all individuals, exhibiting a dominance of scarring from early adulthood, and females also experienced negative impacts on SES attainment and reproductive health. These effects could be explained by different mechanisms, for example related to direct damage to the body's organs, systems and cells or inflammatory processes, which result in impaired function or chronic disease at later ages and for females also result in reduced ability to carry a pregnancy to term or worse foetal health. No previous studies specifically examine the impact of exposure to whooping cough in early life on female reproductive health. However, we know from the existing literature that exposure to this disease in early life can lead to retarded infant weight gain (Barker et al., 1991) and to reduced lung function (Barker et al., 1991; Jedrychowski et al., 2002) and higher risk of contracting diabetes in later life (Montgomery et al., 2002), while other works have found increased risks of experiencing pregnancy complications for

women who faced these types of health problems (e.g., Bánhidy et al., 2008; Bhatia & Bhatia, 2000; Department of Health and Human Services, 2001; Felten et al., 1999; Greenberger & Patterson, 1988; Jonasson et al., 2007). These mechanisms could explain the observed results. When measuring the impact of early life disease exposures on cause-specific mortality in Chapter 3, we found some evidence that individuals born in years with whooping cough epidemics had a greater risk of dying from airborne infectious diseases, cardiovascular diseases and diabetes at older ages, although these models were limited by small sample size.

Despite that exposure to either high IMR in infancy or to whooping cough in particular was demonstrated to have negative consequences on later life health, when focusing on fertility only small reductions on the probabilities of birth were observed (Chapter 5). This indicates that reproduction may be more robust to adverse early life exposures than mortality (Chapters 2 and 3), or that the nature of this relationship may be complex and not necessarily direct. Foetal losses are more common during the first stages of embryological development, and if they occur in this period, birth intervals are not substantially affected. However, even if foetal mortality and eventual difficulties conceiving would have prolonged the space between consecutive births, there could have been other consequences of these adverse early life exposures that affected fertility in the opposite direction. For example, exposed women could have chosen to restrict the breastfeeding period or post-partum abstinence to replace deceased children. Moreover, couples could have made more frequent attempts to conceive and give birth in anticipation of the likelihood that some of their offspring would die. In addition, the premature death of a nursing infant causes the interruption of the biological mechanism that restrains ovulation during lactation. We observed that offspring born to mothers who had been exposed to disease in early life had higher neonatal mortality and that the probability of birth was higher after an early death of the previously born child. These two effects indirectly resulted in greater fertility. However, indirect reductions in the probability of birth mediated through SES were also observed, as women exposed to disease in early life had lower probabilities of attaining high SES in adulthood, and low SES families had lower fertility. These two indirect effects could have counteracted one another, reducing the total effect of early life exposures on the probability of birth.

Parts of this thesis also studied cohort changes in the impacts of adverse early life conditions on later life health. Stronger relative effects of exposure to either generally high IMR or specifically whooping cough epidemics were observed for those born after 1850, when considering either mortality or the sex ratio at birth of the females' offspring as the outcome of interest (Chapters 2, 3 and 4). These results could be related to changes in alternative disease environments. In addition to whooping cough, other epidemics that dominated in high disease

years were measles and smallpox before 1850 and measles and scarlet fever after that year. However, more importantly, the rates of infant mortality were much higher prior to 1850. This means that among the first cohorts, infection during infancy (i.e., scarring) could also have been experienced by those born in years that we considered as having a low disease load. However, in relative terms, the impact of exposure to whooping cough on later life health was substantially more severe during periods when competing disease environments in early life were weaker. These findings also demonstrate that the relative impact of adverse early life exposures may be stronger when morbidity in adulthood and old age is more closely related to degenerative diseases than infectious diseases.

Several of the results obtained in this thesis could be better supported and explained by conducting additional research in the future. The recent inclusion of midwife reports in the SEDD will allow us to focus on other measures of reproductive health such as birth weight or delivery conditions. These variables could also be used as additional indicators of early life exposures, thereby more closely following the works of Barker (see e.g., Barker et al., 1989; 1990; Barker, 1994; 1995) and some of the research conducted using the Uppsala Birth Cohort Multigenerational Studies (see e.g., Koupil et al., 2005; Koupil, 2007; McCormack et al., 2005) for example. The types of early life exposures considered in this thesis could be integrated with indicators of health behaviours and risk factors at later stages in the life course, such as parity and birth timing, to observe the joint effect of these conditions on female health in old age (see e.g., Kuh & Hardy, 2002). The recent inclusion of data on heights (Öberg, 2013) will also allow future researchers to use this variable as another supporting indicator of early life exposures (see e.g., Floud et al., 2011; Fogel, 2004; Steckel, 2005; 2008) and determine whether, at least for males, the patterns observed are confirmed when considering a summary measure of nutrition and disease exposures across different stages of development. In addition, the recently begun process of linking the SEDD to contemporary population records will also enable future studies to consider additional years, thereby observing transformations across wider periods. This will also make it possible to consider other aspects that influence health during more contemporary periods, for example income inequality (see e.g., Steckel, 1983; Steckel & Moehling, 2001).

1.10 Conclusions

In recent centuries, the world has experienced remarkable transformations, with large declines in mortality, increases in life expectancy and improvements in health and wellbeing. There is a long-standing debate over which factors led to the beginning of the mortality decline and continue to influence the length and quality of our lives. Large parts of this debate have focused on the role of improvements in nutrition (McKeown, 1976) or net nutrition (Floud et al., 2011; Fogel, 1994b; Fogel, 2004) and the importance of disease and changes in the virulence of pathogens (Fridlizius, 1984; Perrenoud, 1984; Schofield, 1984). Fogel (1994b; 2004) and Floud et al. (2011) have argued that individuals have primarily become healthier and stronger as a result of advances in diet that increased their productive capacity and the health and wealth that are transferred across generations. One of the aims of this thesis was to contribute to this long-standing debate and the general literature on the long-term effects of early life conditions.

Our knowledge of the factors causing the substantial transformations that have been experienced throughout history is primarily based on works that lack an empirical basis or studies that establish associations using macro-level data. One of the important contributions of this thesis is that empirical tests were performed using micro-level data and a full life course approach to evaluate the importance of diet and disease in early life for later life health and longevity. This was possible thanks to the richness of the Scanian Economic Demographic Database, which allowed us to follow 86 cohorts from birth until old age during the years 1813 to 1968. Individual-level data on this large number of cohorts throughout the life course are rarely available for these periods. We showed that large declines in mortality occurred in the parishes studied and the trend in life expectancy in this territory was very similar to that of Sweden as a whole, making it possible to analyse these processes of transformation and generalise the findings of this thesis to wider contexts.

The majority of previous studies that have examined the long-term impacts of early life conditions have only measured these effects for specific age groups. By following individuals from birth until old age and separately analysing males and females when evaluating the effects of these exposures on mortality, this thesis has shown that there is no net dominance of selection or scarring over the entire life course but that these pathways fluctuate across age and vary by sex. Selection prevails at younger ages, and the length of this dominance depends on the severity of the exposure sustained in early life. At later ages, the effects not only depend on the type of exposure experienced and on its severity but also on conditions that are specific to different age groups and each sex, for example physical growth and

childbearing. These characteristics impose different demands on the body, which can influence the impact that early life exposures have on health during such stages. The results of this thesis have therefore demonstrated that when attempting to understand the long-term effects of early life conditions, it is essential to focus separately on different types of exposures and to evaluate their impacts over the full life course and by sex.

Previous studies have shown that mortality increased and fertility declined in Scania during years with short-term economic stress (Bengtsson & Dribe, 2005; 2006; 2010), patterns that were also observed at the macro-level for Sweden as a whole (Bengtsson & Ohlsson, 1985a). These effects exhibited a social gradient, primarily affecting the landless and semi-landless (Bengtsson & Dribe, 2006; 2010; Bengtsson, 2000; 2004b). From these results, we know that individuals were affected in the short-term by fluctuations in food prices, but only the lower classes of the population, and those individuals who were affected had the capacity to plan ahead. By controlling fertility in anticipation of increases in food prices, the number of pregnant women, and therefore of foetuses who were exposed to malnutrition was reduced, thereby also limiting the average long-term effects of short-term economic stress. In this thesis, exposure to high prices during the foetal stage was not observed to have impacts on mortality in old age when focusing on the entire population, confirming the results obtained previously by Bengtsson and Lindström for the years 1766-1895 (Bengtsson & Lindström, 2000; 2003). When focusing on specific groups, some evidence of reductions in the length of life was observed, but only for males of landless origin. No signs of negative, long-term repercussions were observed among exposed landless females, who instead exhibited relatively lower mortality from adulthood until old age. In addition, no impacts were observed regarding women's capacity to attain high SES in adulthood, confirming previous findings by Bengtsson and Broström (2009), and there were also no effects found regarding their reproductive health, providing no evidence of transfers across generations.

In line with these results, we have not observed any strong evidence of effects of SES at birth on mortality in old age. As shown in previous studies that considered the five parishes in Scania and other rural communities, a socioeconomic gradient in mortality is a phenomenon that only emerged rather recently (Bengtsson & van Poppel, 2011; Bengtsson & Dribe, 2011). This confirms further the assertion that, at least within rural contexts, during periods of substantial transformations and large declines in mortality, longevity was not primarily determined by standards of living and access to food. The results obtained in this work therefore cast doubt on the claims made by Fogel (1994b; 2004) and Floud et al. (2011) of the strong importance of diet.

The long-term effects of exposure to disease in infancy observed in this thesis were instead much stronger, and they were similar across individuals of all socioeconomic origins. By separately considering males and females exposed to measles, scarlet fever and whooping cough, we found that the mechanisms linking exposure to infections in early life to later life health depend on the type of disease experienced and sex. Among those exposed to measles and scarlet fever, at adult ages selection dominated for females and scarring dominated for males. It was also possible to observe that the long-term effects of whooping cough were substantial and affected all individuals equally. Scarring dominated from early adulthood and until old age, shortening the lives of those born in years with these epidemics. Economic transfers in the studied populations were strong, and SES at adult ages was highly correlated with SES at birth. However, this thesis has also shown that women born into low SES families had reduced capacities to attain high SES at adult ages if they were exposed to disease in infancy. Negative impacts were observed in their reproductive health and the health of their offspring. We therefore find empirical evidence of the associations between early life exposures and productive capacity and transfers of health across generations that Fogel (1994b; 2004) and Floud et al. (2011) described, but only in connection to disease.

To summarise, this thesis adds new findings to the debate over which factors caused the historical decline in mortality and improvements in health and wellbeing. In this empirical study, which was conducted based on individual-level data from five rural parishes in southern Sweden for the period 1813 to 1968, disease, and in particular whooping cough, was shown to have influenced the length of people's lives, as well as the health of succeeding generations, more markedly than nutrition. This thesis found evidence that adverse early life conditions affect the longevity of individuals and the capacity of females to obtain wealth in adult ages and produce healthy offspring, as Fogel (1994b; 2004) and Floud et al. (2011) discussed, but it has shown that disease had more of an effect on these long-term outcomes than diet. Economic stress had severe consequences in the short-term, but only the lower classes of the population were affected by these changes. Through planning and reduced fertility, intentionally or unintentionally, those belonging to these groups were capable of limiting the long-term impacts of short-term economic stress and inadequate nutrition faced by future generations. The impact of exposure to disease in early life was instead more intense and affected individuals of all socioeconomic groups and males and females equally. The period considered in this thesis links historical eras to the years following after modernisation, the introduction of sanitation and the spread of penicillin and modern medicine, as well as improvements in the standards of living. In spite of these broad changes, individuals exposed to infection in infancy were scarred for life.

The findings obtained in this work also set scope for further research and suggest policy implications. To observe whether the results obtained in this thesis are confirmed over wider contexts, it is important that other studies employ individual-level data, a full life course approach, and separately consider individuals on the basis of sex and type of early life exposure. This thesis has also shown that exposure to diseases in early life have to considered when assessing the long-term effects of early life conditions on female reproductive health. In addition, it has demonstrated that there is a demand for interventions that limit infections and inflammation processes in infancy and procedures that follow up on the health of individuals who have faced these adverse exposures. The necessity of additional care and control is particularly important for females during their childbearing ages, especially in the early stages of gestation and in the neonatal development of their offspring. The findings of this work not only relate to historical epochs, as the types of disease exposures considered here have not been completely eradicated, and outbreaks of whooping cough, for example, are still found both in developing countries and in Western nations.

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Chapter 2

Selection and scarring across the life course: the effects of early life conditions on mortality by sex in 19th and 20th century Southern Sweden

2.1 Abstract

Using individual level data from Southern Sweden for 1813 to 1968, this work evaluates the impact of early life conditions on mortality at all stages of the life course and distinguishing by sex. Early life conditions are measured using local infant mortality rates, grain prices, and socioeconomic status at birth as indicators to assess the influences of the disease environment experienced in infancy, of access to nutrition during the foetal stage and of the characteristics of the family of origin. Evidence for the foetal origin hypothesis was found for landless males, while the infancy inflammation hypothesis was confirmed for all individuals. Sex differences were observed during the childbearing and working ages: the males conceived in years with high prices or born in years with a high disease load faced higher risks of death than those encountering more favourable early life conditions, while a lower relative mortality was seen among females. In adulthood and old age, the negative impact of exposure in early life to disease was stronger than that of having a low SES at birth.

2.2 Introduction

Literature showing that early life conditions strongly influence later life health has existed for centuries and has rapidly grown in recent years, spreading across disciplines (see e.g., Barker, 1994; Bengtsson & Lindström, 2000; Bengtsson & Mineau, 2009; Bozzoli, Deaton, & Quintana-Domeque, 2009; Case & Paxson, 2010; Elo & Preston, 1992; Finch & Crimmins, 2004; Gluckman et al., 2008;

Steckel, 2005; van den Berg, Doblhammer, & Christensen, 2009). It has been demonstrated that poor health in later life may result from malnutrition during gestation, as is stated by the foetal origins hypothesis (Barker, 1994; 1995; 1997; 2001), or from exposure to disease in the first year of life, as is claimed by the infancy inflammation hypothesis (Bengtsson & Lindström, 2000; 2003; Finch & Crimmins, 2004; Liuba, 2003). Studies focusing on early life conditions have also made important contributions to the general understanding of mortality, showing, among other things, that the declines in the death rates that characterised the 19th century were more influenced by cohort than by period changes (Fridlizius, 1989; Kermack, McKendrick, & McKinlay, 1934) and that these changes were determined by nutrition (Floud et al., 2011; Fogel, 1994; Fogel & Costa, 1997; McKeown & Record, 1962; McKeown, 1976) and/or disease exposures (Fridlizius, 1989; Perrenoud, 1984).

Although many works look at the long-term effects of adverse early life exposures, there are no studies capturing the changes in these impacts across the life course and by sex. This absence is partly due to a lack of longitudinal databases that follow individuals from birth until death. With the exception of the Helsinki Birth Cohort Study and the Uppsala Birth Cohort Multigeneration Study, most databases only permit the observation of events between birth and early adulthood, as in the 1958 and 1970 British cohort studies or the National Longitudinal Survey of Youth 1979, or from early adulthood to old age and death, as in the US Health and Retirement Study and the UK Whitehall II Study[10] (Case & Paxson, 2010). Furthermore, much of the literature linking early life conditions to mortality focuses on the elderly, because adverse exposures in the foetal stage and infancy have primarily been associated with the development of chronic problems such as coronary heart disease (Barker, 1995) and diabetes (Ravelli et al., 1998). These studies, however, must condition on survival until old age, without understanding what occurs in the stages that precede it.

By using individual level data for five rural/semi-industrial parishes from southern Sweden for the 1813 to 1968 period, and by evaluating the effects of nutrition during the foetal stage and of exposure to disease during infancy on mortality from early childhood to old age distinguishing males and females, this work aims to cover some of these gaps. To measure early life conditions, the price of rye for the year prior to birth and the local infant mortality rate (IMR) for the year of birth are employed as exogenous indicators. The likelihood of dying at different stages of the life course for individuals conceived in years with high prices

10 For the Helsinki Birth Cohort Study see, e.g., (Räikkönen et al., 2009); for the Uppsala Birth Cohort Multigeneration Study see, e.g., (Koupil, Leon, & Lithell, 2005; McCormack et al., 2005); for the 1958 and 1970 British cohort studies see, e.g., (Case, Fertig, & Paxson, 2005); for the US Health and Retirement Study see, e.g., (Karp, 2007); and for the Whitehall II Study see, e.g., (Marmot & Brunner, 2005).

or born in years with a high disease load is compared to that of those experiencing more favourable conditions. The impact of exposure to disease is evaluated over the entire population, while the impact of prices is only estimated for individuals born into landless families because grain prices represent a measure of nutrition only for net consumers. We also compare the effect of exposure to high IMR to that of socioeconomic status (SES) at birth.

The design used here is based on methodologies adopted previously by different scholars. Bengtsson and Lindström (2000; 2003) introduced the idea of combining longitudinal individual-level data with the local IMR to evaluate the causal impact of exogenous variations in early life conditions. In four parishes in southern Sweden for 1766-1895, they measured the influence on old age mortality of the transitory components of the price of rye and of the IMR to reflect food accessibility and exposure to disease in early life. These authors found neither an influence from nutrition during the foetal stage and infancy or from maternal disease exposure during pregnancy. Instead, they observed a strong impact from the disease load experienced during the year of birth on mortality later in life and concluded that exposure to airborne infectious diseases throughout infancy increased old-age mortality, particularly in terms of deaths from infectious and chest diseases. They later described that the years with high disease loads were characterised by smallpox and whooping cough epidemics. For the same parishes and period, Bengtsson and Broström (2009) found direct effects from early life conditions on old age mortality and social mobility, but no evidence for an indirect impact through attained socioeconomic status (SES). Also using Swedish data, but adopting a macro-level perspective, Finch and Crimmins (2004) observed that a cohort's mortality in old age is related more closely to its infant than its later childhood mortality. In analyses on French-Canadians from the 17th and 18th centuries, instead, old-age mortality rates were not correlated with the cohorts' IMR, while significant impacts were observed from period changes and family-shared demographic and biological characteristics (Gagnon & Mazan, 2009).

Exogenous variations in early life conditions have also been measured by taking into account the cyclical component of GDP or GNP, showing that individuals born during business cycle booms have a lower mortality after age 35 (van den Berg et al., 2009). Alternatively, other scholars have evaluated the effect of undernutrition *in-utero* by considering exposure to the Chinese, Dutch or Finnish famines, in several cases finding increases in mortality (Lindeboom, Portrait, & van den Berg, 2010). In some of these studies, no significant impacts were found, partly because only the healthiest among those exposed to stress may have been selected to survive until old age (Painter et al., 2005). Other works have emphasised social and indirect pathways, showing that early life conditions also influence cognitive ability and education (Almond, 2006; Case & Paxson,

2010; Palloni et al., 2009), height (Bozzoli et al., 2009; Steckel, 2008) and SES (Almond, 2006; Bengtsson & Broström, 2009).

2.3 The expected impact of early life conditions on mortality

One of the pathways through which adverse early life conditions can affect later life health is 'selection'. Those who are able to resist harsh early life conditions may, in fact, be genetically or congenitally stronger and face a greater probability of survival at older ages (Preston, Hill, & Drevenstedt, 1998). Selection can occur at the time when the adverse exposures are perceived, with only healthier couples having the ability to conceive and bear a live child or only stronger children surviving their first birthdays. When focusing specifically on the impact of maternal malnutrition, selective mechanisms could occur before as well as after conception. Fertility can be reduced during periods of scarcity through deliberate or unintended control. The number of conceptions can decline during famines through increases in the length of postpartum amenorrhea or anovulation, loss of libido or reductions in male sperm production (Bongaarts, 1980; Menken, Trussell, & Watkins, 1981). Insufficient nutrition could also cause a postponement of menarche or an anticipation of menopause, although these changes may not necessarily affect fertility because in Western Europe, the proportion of births occurring at the two extremes of a woman's fertile period were minor. Moreover, the link between nutrition and reproduction could work through indirect social mechanisms, such as reduced coital frequency, deliberate postponement of childbearing, male seasonal or temporal migration, or increased adult mortality (Menken et al., 1981). After conception, selection could also take place through the death of the less fit foetuses. In relation to exposure to malnutrition or to disease in early life, selection can also be manifested through the death of less fit individuals in the transition from childhood/adolescence/adulthood to the subsequent stage.

Through a process that has been referred to as 'scarring', conditions of stress in early life can also permanently damage the body, causing increases in death rates later in life (Preston et al., 1998). The development of organs and cells is fastest during the foetal stage and infancy, and the effects of adverse exposures perceived in these periods are therefore irreversible and last throughout the entire life course (Ben-Shlomo & Kuh, 2002; Kuh & Ben-Shlomo, 2004). For this reason, relative differences in mortality that originate in early childhood persist until old age (Fridlizius, 1989).

Later life health can be largely influenced by the nutrition experienced in early life. According to the foetal origins hypothesis introduced by Barker and his colleagues (2001; 1997; 1995; 1994), a 'disproportionate' retardation in growth caused by the lack of sufficient nutrition during the second and third trimesters of pregnancy leads to low birth weight, increasing systolic blood pressure at the adult ages and the risk of heart disease later in life (for recent reviews of the literature see e.g., Gluckman et al., 2008; Currie & Vogl, 2012; Almond & Currie, 2011). The rate of cell division, which under normal conditions is very rapid during the foetal stage, may be lowered as an adaptive mechanism to insufficient supplies of nutrients or oxygen, primarily affecting the tissues that are undergoing 'critical' development when undernutrition occurs (Barker, 1995). These permanent changes in the body's structure and function 'program' disease in later life. However, although birth weight has a significant effect on blood pressure, some works have shown that it is rather small (Christensen, 2007; Huxley, Neil, & Collins, 2002).

Another type of early life condition that can affect later life health is exposure to disease. This link could be manifested through different mechanisms, although the complete aetiology is not yet fully understood. The first mechanism involves direct damage to the organs and cells of the body. For example, associations have been found between respiratory infections in early life and lung impairments at older ages (Barker et al., 1991; Bengtsson & Lindström, 2003; Shaheen et al., 1994) and between streptococcal infections and rheumatic heart disease (Jones, 1956). Exposure to disease in the first years of life can also reduce an individual's general immunity to disease, as has been claimed by Fridlizius (1984; 1989). Moreover, through inflammatory mechanisms, short-term adaptive responses to infections or injury may become maladaptive in the long run (Finch & Crimmins, 2004), leading to chronic disease in the older ages. Infections in early life may also cause arterial structure dysfunction (Liuba, 2003). As a reaction to inflammation, serum levels of C-reactive protein (CRP, an acute-phase protein) rise, increasing the risk of cardiovascular disease and hypertension (Willerson & Ridker, 2004; Zhu et al., 2000).

The hypotheses of inflammatory infection and nutrition are not necessarily competing or contradictory but can be complementary (Finch & Crimmins, 2004). In fact, the amount of nutrients that can be used for growth is a measure of the quantities consumed net of the energy needed for the maintenance of the body, to resist disease, to work and to play (Floud et al., 2011). Infections influence the nutritional status of an individual by reducing the appetite, worsening the quality of the diet ingested, increasing the metabolic loss of nutrients and the metabolic needs of the body and reducing the absorption of nutrients (Bellagio conference authors, 1983).

In this work, the role of nutrition is evaluated by measuring the price levels during an individual's foetal stage, while that of exposure to disease by measuring its level in infancy. Nutrition during infancy is not analysed because fluctuations in food availability rarely compromise children's health prior to weaning. The health of children during the first year of life was primarily influenced by the conditions and behaviours of their mothers and exposures to epidemic diseases; infants are not vulnerable to short-term economic stress while they were breastfed (Bengtsson, 2004). The impact of maternal exposure to disease during pregnancy is also not accounted for in this work because the primary epidemics in the period studied were measles, scarlet fever and whooping cough, which were principally childhood diseases. In addition, the inflammatory processes and direct damage to organs relate primarily to infection occurring during infancy. Moreover, the work conducted by Bengtsson and Lindström (2000; 2003) in this area for the period 1766-1895 had not found any significant impacts from the disease load experienced by mothers during gestation on old age mortality, and a similar finding was also observed in Chapter 1.

The adoption of a full life course approach allows the distinguishing of stages where individuals are exposed to stress (i.e., critical windows) and those where the impact of these exposures is measured. But most importantly, even if deaths related to conditions that originate during early development are more common in old age, it is important to identify the phases where selection/immunisation dominate over scarring or *vice-versa*. Childhood, adolescence, childbearing/working ages and old age are here analysed separately because each may represent a different stage in development or functioning of the body. The tempo of growth for the different organs, in fact, changes across ages. The velocity of height development, for example, has a rapid decline from birth until age 4 or 5, followed by a slight increase at around ages 6 to 8 (referred to as the mid-growth) and later by further declines (Tanner, 1989). There is a growth spurt in adolescence, where the rate is nearly half of that during infancy, followed by rapid drops in the growth rate until maturity (Steckel, Floud, & Sandberg, 1997). Most skeletal and muscular dimensions of the body as well as internal organs such as the liver, spleen and kidney have similar growth curves to height, with the exception of the brain, skull and some other organs such as the reproductive system or the intestines, which have different tempos of development (Tanner, 1989). As a result of fluctuations in the rates of development, the impact of adverse early life conditions on health may differ in each of these stages. These fluctuations may not only be related to the rates of growth but also to later life activities such as reproduction or intense manual labour, which are both influenced by, but are also influential factors for, health and the functioning of the body. The impact of early life conditions on health can differ in periods where individuals are net consumers or net producers.

Studying males and females separately is also important. The mechanisms linking early life conditions to later life health could differ by sex in connection to factors relating to the time when these exposures occur or when the long-term impacts of these exposures are measured. Only a few studies introduce a gender dimension, showing that in old age, men were affected more negatively than women from exposure during the year of birth to the Dutch or Finnish famines or to business cycle recessions (Doblhammer-Reiter, van den Berg, & Lumey, 2011; Lindeboom et al., 2010; van den Berg et al., 2009).

Differences in mortality by gender result from an interaction between biology, behaviour and the environment (Alter, Manfredini, & Nystedt, 2004). Females may be less vulnerable to stress in early life because X-linked immunoregulatory genes provide a greater resistance to infectious diseases (Waldron, 1983) and also because males are usually born at younger gestational ages (Hall & Carr-Hill, 1982) and, for a given gestational age, with less developed respiratory systems (Torday et al., 1981). Males are more susceptible to respiratory infections and accidents in childbirth, and they therefore experience greater perinatal mortality, a difference that diminishes within the first year of life (Waldron, 1986). Some diseases such as measles, however, cause higher death rates among girls because they lose maternal antibodies more rapidly than boys (Martins et al., 2009).

At older ages, instead, females are more protected against cardiovascular diseases as a result of behavioural and biological factors (Matthews, 1989). Biological protection is likely to be linked to reproductive hormones such as oestrogen. However, females experience higher mortality during the adult ages as a result of childbearing. This excess mortality is not necessarily a result of complications of childbirth, but may be linked to maternal depletion from the greater resource requirements during pregnancy and lactation, which make women more susceptible to certain infectious diseases (Alter et al., 2004). Economic roles, behaviour and the unequal distribution of resources may also lead to differences in mortality between the sexes. In the past, males had greater involvement in the fields and in the care of animals, and they were therefore more prone to accidents. Females, instead, were responsible for household chores and rearing children. As a consequence, they were more exposed to infectious diseases because they spent a vast amount of time in poorly ventilated rooms (Fridlizius, 1988). Females were also more exposed to infectious pathogens because they were often in charge of taking care of the sick (Alter et al., 2004). The excess in female mortality could also be related to the unequal distribution of resources within the household, in particular, nutrition and health care, where males were often favoured because their tasks were believed to be more physically demanding (Alter et al., 2004). There could also be differences in mortality that relate to the culturally induced

engagement in alcohol consumption, cigarette smoking and behaviours leading to death from accidents or violent causes (Waldron, 1983).

These differences in mortality could have influenced the long-term effects of early life exposures. The greater vulnerability in the early life of males could have made them more susceptible to complications during gestation and to infections in infancy. The effect of such exposures, however, could have been counterbalanced by their higher mortality at these stages of the life course, and therefore by stronger selection. At the older ages, behaviour could have interacted with the impact of these exposures. Females, however, could have been less susceptible to adverse early life exposures, but due to childbearing, the unequal distribution of resources or a greater exposure to pathogens at an older age, the negative long-term effect of these conditions could have been amplified.

In the works that use individual level data to summarise population characteristics, only the net of selection and scarring effects can be shown. In particular, if individuals conceived in years with low food availability or born in years with a high disease load experience reduced mortality with respect to those conceived or born during more favourable periods, selection prevails over scarring. Instead, when mortality is higher for this group, scarring is greater than selection. The lack of significant differences in the rate of mortality, however, could indicate the absence of impacts or that selective and scarring effects have similar magnitudes and cancel each other out. Moreover, in this work, no distinction is made between the direct or indirect mechanisms connecting early life conditions to mortality later in life but, rather, the total impact is measured.

Based on the theories and results described above, we expect to find evidence for the foetal origins hypothesis for individuals born in families that could not cover their subsistence from land and of the infancy inflammation hypothesis for the entire population. We also anticipate finding variations across the life course and by sex in the dominance of selection and scarring, with selection being more important in the young ages and scarring among the elderly.

2.4 Data and methods

2.4.1 Source material

The source material used for this work is the Scanian Economic Demographic Database (SEDD)[11], which comprises births, deaths, marriages and migrations

11 The SEDD was created in a collaborative project between the Regional Archives in Lund and the Centre for Economic Demography at Lund University (Bengtsson, Dribe, & Svensson,

occurring in the years 1813 to 1968 in the parishes of Halmstad, Hög, Kävlinge, Kågeröd and Sireköpinge, located in the southernmost area of Sweden in the region of Scania. This data is, in part, the same as used in Bengtsson and Lindström (2000; 2003) and Bengtsson and Broström (2009), although here a fifth parish as well as an extended time period are considered. The complete cohorts are analysed, following them from birth until age 70, and therefore the individuals studied are those born between 1813 and 1898. With the recent extension of the SEDD until the year 1968 and because this database is largely based on population registers, 86 cohorts can be followed from birth until old age and from historical to modern periods, knowing at all times the size of the population at risk as well as their SES. Moreover, the quality of the parish register material is high and the gaps for births, deaths and marriages are limited (Bengtsson & Lindström, 2000)[12]. The five parishes were located near one another, and they present variations that were common in peasant societies with regards to topography, size, and socio-economic conditions. The entire area was open farmland, except for the northern part of Halmstad, which was more wooded. The southern localities became industrialised and urbanised in the last decades of the 19th century.

The SEDD also contains information on occupations, which is obtained from poll-tax (*mantalslängder*) and income (*inkomslängder*) registers. These data are available for the individual and the head of the current household and of the household of birth. To expand the information relating to the SES at birth, when constructing the database, where possible, the ever-married immigrants were traced in the registers of their previous residences. All occupations included in the SEDD were coded into HISCO (van Leeuwen, Maas, & Miles, 2002) and later classified according to SOCPO (van de Putte & Miles, 2005), which is a scheme of classification that comprises five categories based on level of skills, degree of supervision, and whether self-employed or not, as well as on pure status. SOCPO 5 indicates the highest status and 1 the lowest. In this work, we only consider the occupation of the individual's family of origin, and we use the SOCPO scheme to determine SES[13].

Data on rye prices is also employed. This cereal is considered because it was the most common grain in this part of the country (Bengtsson & Dribe, 1997). We use prices of the *födgeri* of Landskrona (Bengtsson & Dribe, 1997). A *födgeri* is a rural level below the county and prices were reported shortly after the harvest

2012), and it has been structured to follow the format suggested by the Intermediate Data Structure (Alter, Mandemakers, & Gutmann, 2009). The data used in this work was extracted on February 20, 2012, and it was converted into spells using the code developed by Quaranta (2012).

12 Calculations show that for all occupational groups, at least 40% of all infant deaths occurred within the first month of the life of babies.

13 The code developed by Dribe (2012) was used to assign the SES.

in the fall. It was not possible to use quarterly or monthly data because it is only available for shorter periods. Nevertheless, the seasonal fluctuations were limited and variations in prices were dominated by year-to-year changes.

The impact of exposure to high prices during the foetal stage is only evaluated for the individuals who could not cover their subsistence from land. In fact, grain prices represent a measure of nutrition only for the individuals who were net consumers, particularly in historical societies, where a large fraction of income was spent on food. Research conducted on 19th century Scania, for example, showed a social gradient in the fertility and mortality response to short-term economic stress; the landless and semi-landless were more vulnerable than individuals pertaining to other social groups (Bengtsson & Dribe, 2006; 2010; Bengtsson, 2000; 2004). We use *mantal* information to distinguish the group of net consumers group[14]. This data was obtained from poll-tax registers, which show where families lived and whether they had access to land. These registers were used annually for the collection of taxes and, among other things, they provide information on the size of the landholding, therefore evidencing the productive potential of the farms (Dribe, 2000).

2.4.2 Measures of early life conditions

The setup of studies that link early life conditions to later life health is complex. Critics of the Barker hypothesis claim that birth weight is confounded with SES because adverse social conditions during early life might lead individuals into life paths that influence their health negatively (Kramer, 2000). Furthermore, low birth weight might not only result from maternal malnutrition but also from genotypes that limit growth *in-utero* (Carr-Hill et al., 1987) and cause health problems in adulthood (Hattersley & Tooke, 1999). Instead, indicators that are not related to the life course and that are free of confounders should be used (Lindeboom et al., 2010). Macro-level variables experienced by a cohort during early life can be employed as indicators for individual conditions (Bengtsson & Lindström, 2000; 2003; van den Berg, Lindeboom, & Portrait, 2006; 2009). The sources of external variation from events such as famines, season of birth,

14 Previous works have shown that in the early decades of the 19th century, a mantal of 1/16 was sufficient for subsistence (Bengtsson & Dribe, 2006; Dribe, 2000). For the latter part of the century, there are no studies measuring farm productivity in this area. While a mantal of at least 1/16 was sufficient for subsistence in all years, due to improvements in farming in later periods, it could have been possible to live off less land. To increase homogeneity, we consider those with a mantal below 1/16 to be landless if they were born between 1813 and 1839, 1/32 if they were born between 1840 and 1869 and 1/64 if they were born between 1870 and 1898. Higher occupations and skilled workers were excluded from the landless group to increase homogeneity. To distinguish land ownership, we consider each individual's family of origin.

epidemics or economic fluctuations are independent of confounders and could reveal causal mechanisms (Lindeboom et al., 2010).

In this work, the impacts of nutrition during the foetal stage and of exposure to disease during infancy on mortality are evaluated, respectively, by using as indicators the rye prices from the year prior to birth and the IMR of the year of birth; the latter is calculated directly from the data. Each individual is linked to the price of the harvest year[15] covering at least half of the last two trimesters of their foetal stage, because previous studies have shown that nutrition during the second and third trimesters of pregnancy is the most influential on later life health. We compare the risks of dying of men and women conceived in years with high prices or born in years with a high disease load with that of those conceived or born in other years. This comparison allows us to evaluate the possible effects of the two types of shocks, epidemics or food shortages, and to distinguish fluctuations in these impacts across the life course, evidencing stages where selection prevails over scarring and *vice-versa*.

These indicators have the advantage of being exogenous. However, a limitation in their use is that it is not possible to determine which individuals were exposed to high prices or a high disease load, which restrains the explanatory power of these measures. Another limitation is that these indicators are constructed from yearly averages of mortality rates or prices and they are linked to all individuals of the same cohort, regardless of their month of birth or conception. The impact of these early life exposures may therefore be underestimated. Moreover, as was shown in Chapter 1, due to selective fertility or foetal mortality, the individuals conceived in years with high prices may not necessarily have the same characteristics (for example, in relation to health and wealth) as those conceived in years with low-medium prices. This effect could counterbalance possible negative long-term consequences of undernutrition during the foetal stage. We evaluate this possibility by including further controls in the models in the sensitivity analysis. Nevertheless, even if prices can measure the exogenous short-term variations in nutrition, the long-term impact of prices on health cannot be claimed as causal, because it is a summary measure of some effects that are working through selection prior to conception and during the foetal stage, and others that are affecting health.

The series of local IMRs and of the logarithms of rye prices were decomposed into a trend and a cycle component using the Hodrick-Prescott filter with a filtering factor of 6.25, the value usually selected for yearly series. The trend components of early life conditions are highly correlated with current macro-conditions, preventing these effects from being separated (Lindeboom et al., 2010). The

15 A harvest year relates to the period between October 1st and September 30th of the successive year.

trends in IMRs and prices are, in fact, likely to reflect long-term changes in the development of healthcare and the economy. Instead, we are interested in measuring the effects of short-term variations in the disease environment and the level of nutrition, particularly years of epidemics or severe malnutrition, which are better captured by cyclical fluctuations. A very high correlation (0.7) was observed between the IMR and its cyclical component, implying that short-term deviations were high primarily in years when the actual value of IMR was also high. Relative rather than absolute deviations were therefore used to select the years with a high disease load, calculated by dividing the short-term component of the IMR by its long-term trend. For prices, the actual deviations from the trend were used because logarithms represent relative values. The years with a positive relative deviation from the IMR trend of at least 0.20 were considered to be years with a high disease load and the years with a positive deviation from the trend of the logarithm of rye prices of at least 0.12 were considered to be years with low food availability[16]. Within a sensitivity analysis we evaluate whether the results obtained depend on the decision to remove the trend from the price and IMR series rather than considering their effective values, as well as the threshold levels used to define years with high IMR or high prices.

2.4.3 Statistical models

To follow the aims of this work, separate analyses are conducted for males and females and for different age groups. We first estimate models considering the following fixed age boundaries: 1-4 for early childhood, where vulnerabilities from airborne and waterborne infectious diseases is very high; 5-19 for late childhood and adolescence; 20-49 for childbearing and working ages, where mortality is largely influenced by reproduction and involvement in the labour market; and 50-70 for old age, where chronic disease is more likely to occur. A model that considers all individuals is also estimated, including an interaction between the indicator of early life conditions and sex, to identify whether statistically significant differences in these effects are present for the two groups.

Due to the lack of previous research, it is not possible to make an *a priori* assumption on the exact stages when the patterns of the results are expected to fluctuate, and the age boundaries presented above are merely arbitrary. We therefore

16 These threshold levels correspond to roughly the eightieth percentile in the distribution of relative deviations from the trend in IMR and of deviations from the trend of the logarithm of rye prices, meaning that roughly one every five years had high prices or a high IMR. Years with a high IMR are 1816, 1821, 1826, 1831, 1832, 1835, 1838, 1846, 1853, 1859, 1860, 1869, 1874, 1881, 1886 and 1894, while those with high prices are 1818, 1819, 1826, 1831, 1837, 1841, 1842, 1846, 1847, 1853, 1855, 1861, 1867, 1868, 1873, 1880, 1881 and 1891.

also consider flexible age boundaries, determined from empirical evidence and through an exploratory and iterative procedure that was programmed to run the same estimations multiple times using different parameters. Starting with childhood, the same estimation is repeated between age one and different upper age boundaries, increased by half a year at each iteration. The results obtained together with graphical evidence are used to define the points at which the direction of the effects fluctuates, and this age is set as the lower boundary in the models of the next age group. Due to space limitations, only the final outcome of these steps is shown. This same procedure is used to study each age group and the impact of prices. Because the effects are not expected to fluctuate at the same ages, the two indicators of early life conditions are modelled separately. For each indicator, we present the results of the statistical models as well as figures showing the cumulative hazard curves for ages 1-70 and for the different life course stages using the age boundaries determined through these steps.

All estimations are made using Cox proportional hazard models (Therneau & Grambsch, 2000) and using STATA 12. Each model controls for year of birth (included as a continuous variable) to account for changes in mortality across time, parish of residence and an indicator of whether the individual was born in one of the five studied parishes or migrated to them. The models measuring the impact of exposure to a high IMR in infancy also include an indicator for the SES of the individual's family of origin to compare the effect of this early life condition with those of disease exposure. We consider three SES categories, low (SOCPO 1-2) and medium-high (SOCPO 3-5) and unknown, although the latter is not reported in the tables due to a lack of homogeneity within the group. The models do not take into account current SES because it is highly correlated with early life conditions and also because it has been shown that in pre-industrial agricultural societies, social differences in mortality were limited (Bengtsson & van Poppel, 2011).

The hazard of death for an individual j could therefore be summarised as

$$h_j(t) = h_0(t)exp\left(\gamma_0 + \gamma_1 early\ life\ exposures_i + \beta X_j\right)$$

where $h_0(t)$ represents the baseline hazard and X_j is the vector of control variables.

Table 1 shows the distribution of individual exposure time for the age groups 1-4, 5-19, 20-49 and 50-70 for each of the categories of explanatory or control variables included in the models. The upper part relates to all individuals and the lower part to those who were landless at birth. As can be observed from this table, when considering all individuals, between 17 and 20% of exposure time corresponds to those born in years with high prices. The SES at birth is known for 60 to 75% of the studied population and between 31 and 40% were from a low SES.

Table 1: Descriptive statistics

	Females				Males			
	1-4	5-19	20-49	50-70	1-4	5-19	20-49	50-70
All individuals								
IMR in year of birth [a] (%)								
Low-medium	82.4	82.2	82.2	82.7	80.8	80.8	80.0	79.5
High [b]	17.6	17.8	17.9	17.3	19.2	19.2	20.0	20.5
Birth SES (%)								
Low	39.7	31.4	32.6	36.2	40.3	31.3	32.3	37.1
Medium-high	34.2	28.9	30.6	32.2	34.1	27.8	31.4	33.7
Unknown	26.1	39.8	36.9	31.7	25.6	40.9	36.4	29.2
Parish of residence (%)								
Hög	9.1	9.6	9.6	8.2	9.2	10.1	9.3	8.0
Kävlinge	14.3	16.6	28.0	35.4	14.3	17.0	28.0	34.8
Halmstad	18.2	17.5	13.4	9.4	17.3	16.6	12.4	8.5
Sireköpinge	23.0	22.0	21.2	19.6	24.2	22.1	21.2	18.9
Kågeröd	35.4	34.4	27.8	27.5	35.0	34.3	29.1	29.8
Birth place (%)								
Studied parishes	79.1	60.9	25.8	19.3	80.3	61.7	29.9	22.2
Other	20.9	39.1	74.2	80.7	19.7	38.3	70.1	77.9
Birth Year (n years)	1861.8	1859.8	1858.2	1859.8	1861.8	1859.8	1858.7	1860.9
Landless at birth								
Prices in year of conception [c] (%)								
Low-medium	79.4	79.5	79.0	74.6	78.9	79.0	81.0	81.8
High [d]	20.6	20.5	21.0	25.4	21.1	21.1	19.0	18.2
Parish of residence (%)								
Hög	7.3	6.5	5.8	4.8	7.5	7.5	5.2	2.6
Kävlinge	12.6	12.1	12.4	14.4	12.5	12.7	14.3	15.0
Halmstad	19.5	18.7	17.1	14.5	19.0	18.3	14.4	12.0
Sireköpinge	22.8	21.2	19.1	20.8	23.6	20.2	15.7	16.2
Kågeröd	37.7	41.5	45.5	45.6	37.4	41.4	50.5	54.3
Birth place (%)								
Studied parishes	75.4	75.8	80.6	80.8	76.6	76.3	82.7	84.1
Other	24.6	24.2	19.4	19.2	23.4	23.7	17.3	15.9
Birth Year (n years)	1862.3	1857.5	1850.8	1851.7	1862.1	1858.1	1855.8	1859.8

Notes: % represents the percentage of individual exposure time (person years) in each category. a – determined from relative deviations from the trend in IMR, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25. b – years with relative deviations from the trend in IMR greater than or equal to 0.2. c – determined from deviations from the trend in the logarithm of rye prices, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25. d – years with deviations from the trend in logarithm of rye prices greater than or equal to 0.12.

In the age groups 20 to 49 and 50 to 70, the percentage of individuals born outside of the studied parishes are rather large (70-81%), even if the majority of these were born within a 17 km radius of them and it is therefore likely that they experienced

the same early life exposures as natives (see Chapter 1 for further discussions). Nevertheless, this assumption is evaluated within the sensitivity analysis. Among men and women born into landless families, between 18 and 25% of the individual exposure time corresponds to those conceived in years with high prices. The total population studied in this work was 42,030 when considering all individuals and 12,073 when focusing on those who were landless at birth.

Tests based on the Shoenfeld residuals are conducted after each model to assess the proportionality of the hazards. When estimating the models considering fixed age boundaries, in the 1-4 age group, violations of the proportional hazard assumptions were observed in relation to the indicators of the IMR and prices. Instead, when utilising flexible boundaries, no statistically significant violations are obtained in relation to these variables for the different age groups considered.

To measure the size of the impacts of early life conditions, the average number of years lived were calculated based on the values of average longevity obtained as the integral of the survival functions estimated using Kaplan-Meier estimators. These estimations are adjusted for year of birth, centred in 1855. Because we are not able to follow all cohorts until their death, all person-times were censored at age 70. These estimations, therefore, do not show full measures of life expectancy but, rather, the average number of years lived until age 70.

Cohort changes in the impacts of exposure to a high IMR in early life are also evaluated. For the age groups 1-4, 5-19, 20-49 and 50-70 and for males and females separately, models are estimated for individuals born before or after 1850. This breakpoint divides the cohorts roughly in half and also, because infant mortality was much higher for the first cohorts than for the second, it allows for a comparison of the effects over years when competing disease environments were rather different. Moreover, the individuals from these two cohorts reached age 15 before or after 1865; 15 was the common age to commence working as well as the age of the onset of female fecundity. The year 1865 represents an important dividing point in the history of this region. In fact, the period until 1864 includes the agricultural transformation, the early stages of industrialisation and the first phase of the demographic transition, with declining infant and child mortality (Bengtsson & Dribe, 2011). The second period was, instead, characterised by the breakthrough of industrialisation as well as by declines in adult mortality and, later, by a continued industrial expansion and the waning of the rural sector.

When studying the impact on later life mortality of exposure to high prices during the foetal stage for men and women born into landless families, the sample size and number of deaths becomes very small when dividing the study into two cohorts. Instead of reporting these results, we therefore show models for individuals born from 1813 to 1869. During this period in southern Sweden, real wages for workers present short-term fluctuations very similar to those of food

prices, the reason being that while nominal wages change very little annually, food prices change significantly. Thus, if food prices increase by, say, 30%, real wages typically decline by the same amount. However, in the latter parts of the 19th century, nominal wages began to increase faster than food prices and also to show more annual variation. In addition, new commodities, such as the potato, appeared (Bengtsson, 2000). Apparently, grain prices serve as a better representation of short-term changes in the level of nutrition received during the foetal stage for workers before 1870 than afterwards.

A sensitivity analysis is also conducted to assess whether the results obtained in this work are limited by the methodological choices adopted. The first part of the analysis considers different formulations for the indicators of early life conditions. More specifically, the same models are estimated including the actual values of the IMR and the logarithm of rye prices, their trend and cycle components as well as different threshold levels to define the years with high prices or high IMR. The second part of the sensitivity analysis includes different control variables in the models. Estimations are made using different formulations of the trend component, more specifically, including both the year of birth and its squared term and replacing the year of birth with the decade of birth, as well as by excluding all control variables. In the models measuring the impact of prices during the foetal stage, additional control variables are also included to assess possible biases in the results from any differences in the characteristics of the two groups that are not necessarily related to price exposures. Because it was shown in Chapter 1 that the average age of the mothers who gave birth in periods with high prices was lower than the average age of mothers who gave birth in other years, we make two additional estimations that include controls for the mother's age at the individual's birth (considering it first as a continuous and later as a categorical variable). Finally, estimates are also made only for the subgroup of individuals born in the studied parishes or within a 17 km radius of them. All models of the sensitivity analysis are estimated considering flexible age boundaries.

2.5 Results

2.5.1 Impact of exposure to high prices during the foetal stage

Measuring mortality across the life course for landless individuals exposed to high prices during their gestation provides evidence in support of the foetal origins hypothesis for men but not for women. Gender differences, in fact, appear

during adulthood and old age. When conducting the analysis considering fixed age boundaries, between ages 20-50 and 50-70, females show a dominance of net selection, while males present a hazard ratio close to unity in the first model, followed by a prevalence of scarring (Table 2). Statistical significance is obtained only in relation to the last of these results. The bottom section of Table 2 presents the results of estimations that consider all individuals and include an interaction between the indicator of the level of prices in the year of conception and sex. Males exposed to high prices during their foetal stage have higher mortality than females between ages 20-49 and 50-70, but this difference is statistically significant only in the latter case.

Table 2: Hazard ratios in relation to the impact of exposure to high prices during the foetal stage for individuals born into landless families, considering fixed age boundaries, Scania cohorts 1813-1898

	Females			
	1-4	5-19	20-49	50-70
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.99	1.01	0.73	0.69
	[0.73,1.34]	[0.69,1.46]	[0.39,1.36]	[0.39,1.23]
Number of individuals	3335	2369	1050	267
Number of deaths	250	173	75	74
	Males			
	1-4	5-19	20-49	50-70
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.86	1.20	0.95	1.61*
	[0.65,1.16]	[0.84,1.73]	[0.56,1.63]	[0.94,2.76]
Number of individuals	3512	2429	1070	279
Number of deaths	294	161	85	74
	All individuals			
	1-4	5-19	20-49	50-70
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.99	0.99	0.73	0.72
	[0.73,1.34]	[0.68,1.43]	[0.39,1.35]	[0.41,1.28]
Females	ref.	ref.	ref.	ref.
Males	1.15	0.84	1.00	0.93
	[0.95,1.39]	[0.66,1.08]	[0.71,1.42]	[0.64,1.36]
High-prices & males	0.87	1.25	1.42	2.28**
	[0.57,1.32]	[0.75,2.09]	[0.63,3.19]	[1.05,4.94]
Number of individuals	6847	4798	2120	546
Number of deaths	544	334	160	148

Notes: see Table 1 for explanations on how prices in the year of conception were determined. The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

Figure 1: Raw impact of exposure to high prices during the foetal stage on mortality across the life course for individuals born into landless families, Scania cohorts 1813-1898

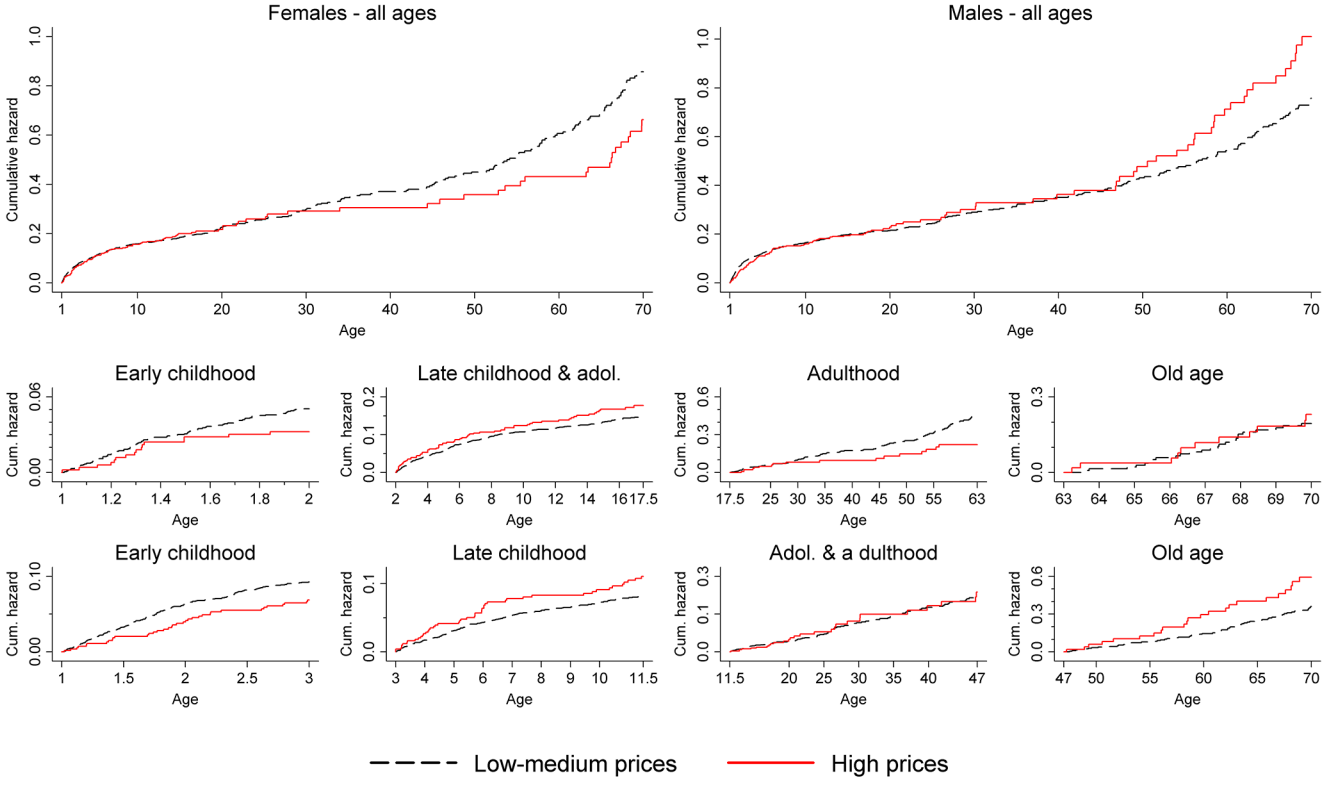

Table 3: Hazard ratios and average number of years lived in relation to the impact of exposure to high prices during the foetal stage for individuals born into landless families, considering flexible age boundaries, Scania cohorts 1813-1898

FEMALES	1-2	2-17.5	17.5-63	63-70
	Hazard ratios [95% C.I.]			
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.62*	1.22	0.53**	1.13
	[0.36,1.05]	[0.93,1.60]	[0.32,0.88]	[0.55,2.31]
	Average number of years lived until age 70			
Low-medium prices (a)	48.69	50.24	42.25	6.47
High prices - a	2.99	2.01	3.79	-0.04
Number of individuals	2691	3024	1298	200
Number of deaths	111	294	131	36
MALES	1-3	3-11.5	11.5-47	47-70
	Hazard ratios [95% C.I.]			
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.72*	1.35*	0.94	1.61*
	[0.50,1.03]	[0.97,1.89]	[0.61,1.44]	[0.97,2.67]
	Average number of years lived until age 70			
Low-medium prices (a)	49.17	52.04	47.83	19.88
High prices - a	-1.08	-2.62	-1.13	-1.16
Number of individuals	3100	2830	1879	308
Number of deaths	217	182	131	84

Notes: see Table 1 for explanations on how prices in the year of conception were determined. The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. The average number of years lived were calculated from the values of average longevity obtained as the integral of the survival functions estimated using Kaplan-Meier estimators. Estimators are adjusted for year of birth, centred in 1855. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

The cumulative hazard curves presented in Figure 1 allow us to observe distinct patterns of fluctuations across the life course within the studied population, showing a dominance of selection in early childhood, followed by scarring, selection and scarring. The dominance of selection is, in fact observed until ages 2 for females and 3 for males, in both cases being statistically significant at the 10% level (Table 3). This effect is followed by the higher probability of dying among the exposed individuals (statistically significant for males at the 10% level), an effect that remains until prior to adolescence for males and past adolescence for females. During the childbearing and working years, females show a significantly lower relative mortality if they were born in years with high prices (47% lower risks between ages 17.5-63), whereas no distinct impacts are seen for males. In old age for men, the risk of dying for those exposed is 61% higher between ages 47-70 (statistically significant at the 10% level), while among females, scarring does not start to prevail after age 63, and this impact is neither strong nor statistically significant.

Table 4: Hazard ratios in relation to the impact of exposure to high prices during the foetal stage for individuals born into landless families, considering fixed age boundaries, Scania cohorts 1813-1869

	Females			
	1-4	5-19	20-49	50-70
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.90	1.40	0.67	0.67
	[0.61,1.32]	[0.92,2.11]	[0.32,1.38]	[0.33,1.32]
Number of individuals	1735	1346	675	169
Number of deaths	158	110	54	54
	Males			
	1-4	5-19	20-49	50-70
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.86	1.23	0.88	1.63
	[0.60,1.23]	[0.81,1.86]	[0.49,1.57]	[0.89,2.99]
Number of individuals	1859	1438	689	161
Number of deaths	176	111	67	53

Notes: see Table 1 for explanations on how prices in the year of conception were determined. The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

The average number of years lived between ages 1-70 for individuals exposed to high grain prices during the foetal stage, as can be seen in Table 3, was 3 years longer for females and 1.1 years shorter for males with respect to those conceived in years with low-medium prices. The women surviving past adolescence lived, on average, 3.8 years longer if they were conceived in years with high prices, while there were almost no differences after age 63. Instead, the men showed a smaller average number of years lived at all ages considered, with a difference of 2.6 years, 1.1 years and 1.2 years, respectively, for those surviving until age 3, 11.5 or 47.

The estimations that study the impact of exposure to high prices during the foetal stage for individuals born before 1870 are limited by small numbers. Nevertheless, as can be observed in Table 4, the patterns of the results observed earlier are still found for this group. In fact, during adulthood and old age, females present a dominance of selection, while in old age, a dominance of scarring is seen for males. However, all of these results lack statistical significance, primarily due to small numbers.

2.5.2 Impact of exposure to high IMR in infancy

Support of the infancy inflammation hypothesis is found for all individuals. In fact, when considering fixed age boundaries, statistically significant dominance of

scarring is observed between ages 50-70 for females and between ages 20-49 for males who were born in a year with high IMR (Table 5). Higher probabilities of dying are also seen for exposed males between ages 50-70, but this effect is weaker and slightly below the threshold of statistical significance. The bottom rows of Table 5 present the results of the estimations that consider all individuals and include an interaction between the indicator for the level of the IMR in the year of birth and sex. The males exposed to a high IMR in their infancy have a higher mortality than the females between ages 20-49, with an interaction term that is statistically significant. No large or statistically significant differences across sex are seen in old age, although the effect for males is very slightly smaller.

Cumulative hazard curves confirm the above patterns, showing that with the exception of the childbearing and working ages, where marked sex differences are observed, the impacts across the life course of exposure to a high IMR in infancy is similar for the two sexes (Figure 2). The ages in which the patterns of these results fluctuate, however, differ to some extent. In early childhood, a dominance of selection is observed, followed by a prevalence of scarring until early adolescence and again by the greater impact of selection, apparent in males until the beginning of adulthood and in females until nearly the end of the childbearing and working ages. From early adulthood for males and the post childbearing period for females, a strong dominance of scarring is seen. The negative impact of exposure to disease in early life is stronger for females during old age, although men exhibit a dominance of scarring from an earlier stage than women.

As can be seen in Table 6, girls born in a year with a high IMR have a 20% lower risk of dying between ages 1-4.5 than those born in more favourable years (not statistically significant), and boys have a 30% lower mortality between ages 1-6.5 (statistically significant at the 1% level). The direction of the results changes in late childhood, where girls have a 28% higher but not significant risk of dying from ages 4.5-12 and boys have a 36% higher risk between ages 6.5-13 (significant at the 10% level). In adolescence, a greater impact from selection is observed, with no stable patterns for males. After adolescence, gender differences become more prominent. In fact, between ages 12-44, women show a 16% lower but not statistically significant risk of dying, meaning that selection extends until the latter parts of the reproductive period. Men, instead, present a 21% higher mortality between ages 23.5 and 70 (significant at the 5% level). Scarring becomes dominant in women at the end of the reproductive period, and between ages 44-70, those born in a year with a high IMR experience a 25% greater risk of mortality (significant at the 5% level) relative to those who experienced more favourable early life conditions.

Table 5: Hazard ratios in relation to the impact of exposure to a high IMR in infancy and to SES at birth for all individuals, considering fixed age boundaries, Scania cohorts 1813-1898

	Females			
	1-4	5-19	20-49	50-70
IMR year of birth				
Low-medium	ref.	ref.	ref.	ref.
High	0.89	1.00	0.94	1.24**
	[0.69,1.15]	[0.76,1.30]	[0.74,1.20]	[1.02,1.50]
SES at birth				
Medium-high	ref.	ref.	ref.	ref.
Low	1.20	1.16	1.10	0.94
	[0.96,1.50]	[0.89,1.52]	[0.87,1.39]	[0.78,1.13]
Number of individuals	5678	9062	12420	3351
Number of deaths	427	377	457	648
	Males			
	1-4	5-19	20-49	50-70
IMR year of birth				
Low-medium	ref.	ref.	ref.	ref.
High	0.75**	0.91	1.29**	1.14
	[0.58,0.95]	[0.69,1.19]	[1.04,1.61]	[0.95,1.38]
SES at birth				
Medium-high	ref.	ref.	ref.	ref.
Low	1.27**	1.16	1.10	1.03
	[1.03,1.56]	[0.88,1.53]	[0.85,1.41]	[0.85,1.25]
Number of individuals	5964	8962	11637	3285
Number of deaths	497	355	431	612
	All individuals			
	1-4	5-19	20-49	50-70
IMR year of birth				
Low-medium	ref.	ref.	ref.	ref.
High	0.89	0.99	0.93	1.22**
	[0.69,1.16]	[0.76,1.30]	[0.73,1.19]	[1.01,1.48]
SES at birth				
Medium-high	ref.	ref.	ref.	ref.
Low	1.24***	1.16	1.10	0.98
	[1.06,1.44]	[0.96,1.41]	[0.93,1.30]	[0.86,1.12]
Sex				
Females	ref.	ref.	ref.	ref.
Males	1.15*	0.93	0.93	1.05
	[1.00,1.32]	[0.79,1.09]	[0.80,1.08]	[0.92,1.19]
IMR year of birth & sex				
High & males	0.83	0.92	1.40**	0.94
	[0.58,1.18]	[0.63,1.34]	[1.02,1.94]	[0.72,1.23]
Number of individuals	11642	18024	24057	6636
Number of deaths	924	732	888	1260

Notes: see Table 1 for explanations on how IMR in the year of birth was determined. The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

Figure 2: Raw impact of exposure to a high IMR in infancy on mortality across the life course for all individuals, Scania cohorts 1813-1898

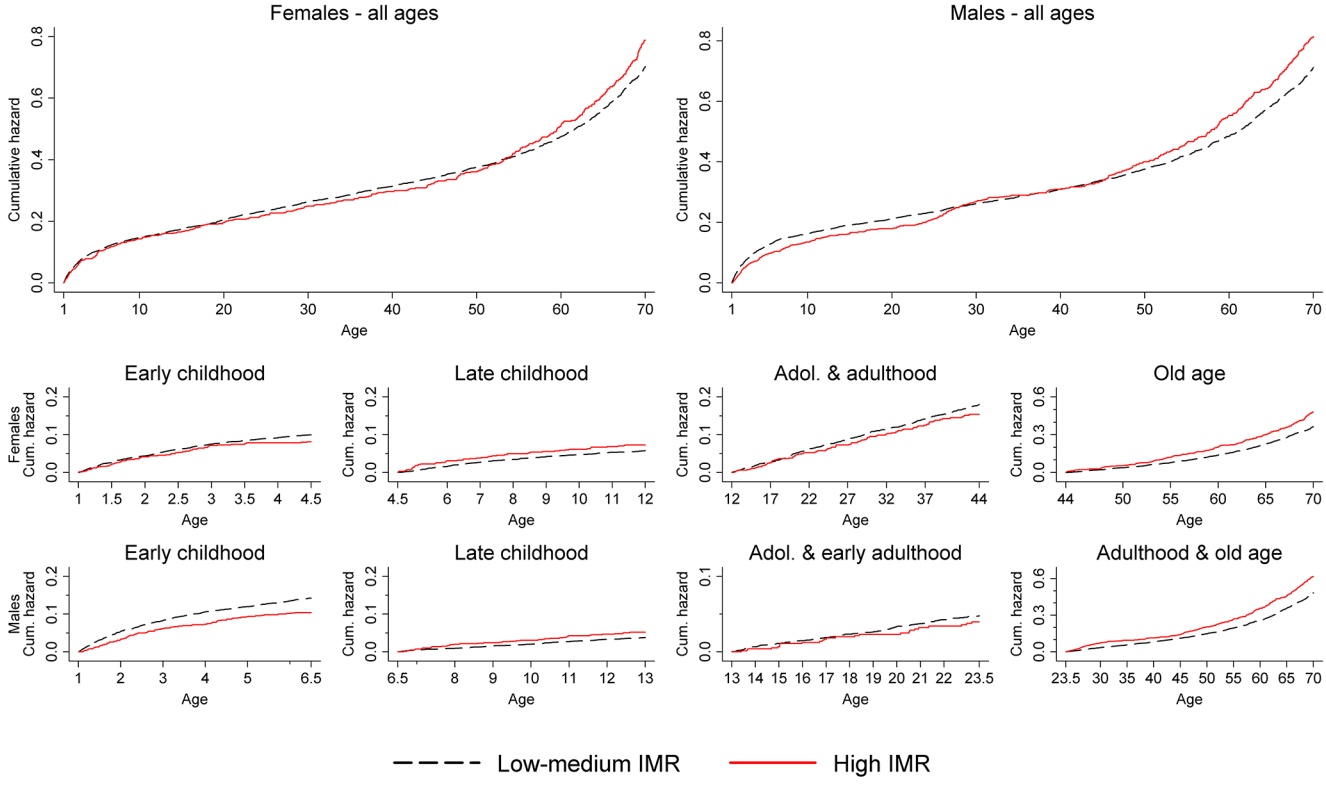

Table 6: Hazard ratios and average number of years lived in relation to the impact of exposure to a high IMR in infancy and to SES at birth for all individuals, considering flexible age boundaries, Scania cohorts 1813-1898

FEMALES	1-4.5	4.5-12	12-44	44-70
	Hazard ratios [95% C.I.]			
IMR year of birth				
Low-medium	ref.	ref.	ref.	ref.
High	0.80	1.28	0.84	1.25**
	[0.61,1.05]	[0.93,1.75]	[0.66,1.06]	[1.05,1.49]
SES at birth				
Medium-high	ref.	ref.	ref.	ref.
Low	1.20	1.30	1.02	0.98
	[0.95,1.50]	[0.93,1.80]	[0.81,1.28]	[0.82,1.16]
	Average number of years lived until age 70			
Low-medium IMR (a)	50.84	52.76	48.27	22.93
High IMR - a	0.56	-0.59	0.16	-0.89
Medium-high SES (b)	52.35	53.61	48.75	22.69
Low SES - b	-1.65	-0.92	-0.29	-0.10
Number of individuals	5518	5791	15145	4193
Number of deaths	403	235	526	745

MALES	1-6.5	6.5-13	13-23.5	23.5-70
	Hazard ratios [95% C.I.]			
IMR year of birth				
Low-medium	ref.	ref.	ref.	ref.
High	0.70***	1.36*	0.80	1.21**
	[0.56,0.89]	[0.94,1.94]	[0.52,1.23]	[1.05,1.39]
SES at birth				
Medium-high	ref.	ref.	ref.	ref.
Low	1.20*	1.38	1.39	1.04
	[0.99,1.45]	[0.92,2.08]	[0.86,2.26]	[0.90,1.22]
	Average number of years lived until age 70			
Low-medium IMR (a)	50.45	52.67	48.15	39.80
High IMR - a	0.58	-1.81	-1.29	-1.78
Medium-high SES (b)	52.40	53.69	48.98	40.01
Low SES - b	-2.14	-1.19	-0.76	-0.35
Number of individuals	6368	5494	8630	10712
Number of deaths	579	162	152	1002

Notes: Notes: see Table 1 for explanations on how IMR in the year of birth was determined. The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. The average number of years lived were calculated from the values of average longevity obtained as the integral of the survival functions estimated using Kaplan-Meier estimators (adjusted for year of birth, centred in 1855). * p <0.10, ** p < 0.05, *** p < 0.01.

Table 6 also evaluates the impact of the SES at birth. At younger ages, the individuals born into families with a low SES show higher probabilities of dying. These effects are statistically significant for boys between ages 1-4 (Table 5) or 1-6.5 (Table 6), but are not significant for girls in childhood. For the older ages, hazard rates closer to unity are obtained. If interactions are included in the models between the SES of the individual's family of origin and the IMR in infancy, the interaction terms do not show statistical significance for any of the models estimated when considering either fixed or flexible age boundaries (results not shown). This result means that the long-term impact of exposure to a high IMR in infancy is similar across individuals who originated from families with different characteristics.

When comparing the average number of years lived for the individuals born in years with high versus low-medium IMR, between the ages of 1 and 70, an excess of 0.6 years is obtained for the exposed men or women (Table 6). For females, fluctuations are observed across the life course, as had been shown above. The exposed women who survived until age 44 lived, on average, 0.9 years less. Among the exposed men, the reduced average numbers of years lived is observed already from a young age. In fact, those surviving until age 6.5, 13 or 23.5, lived between 1.3 and 1.8 years less if they were exposed to a high IMR in infancy. When conducting similar estimations in relation to the SES, those born into low SES families present a shorter average number of years lived between ages 1 and 70. In fact, on average, females and males lived, respectively, 1.7 and 2.1 years less if they were low SES at birth. The differences between the two groups decline across age, becoming rather small among the elderly.

When comparing the effects of exposure to a high IMR in infancy for the different cohorts, the primary differences concern the adult age and old age (Table 7). Among females, even if neither of these effects is statistically significant, selection prevails between ages 20-49 for those born before 1850, while the second cohort shows a hazard ratio that is close to unity but above it. Between ages 50-70, the patterns for women are rather constant for the two cohorts and display a prevalence of scarring. Both of these results lack statistical significance, although they are not far from it. Among men, hazard ratios that are close to unity (although above it) are seen for those born before 1850. Instead, for the second cohort, a very strong dominance of scarring, both in terms of magnitude and statistical significance, is observed between ages 20-49, and scarring also prevails between ages 50-70, even if the magnitude of this effect is smaller and slightly below the threshold for statistical significance. Scarring becomes dominant from the younger ages for the second cohort among males as well as females.

Table 7: Hazard ratios in relation to the impact of exposure to a high IMR in infancy and to SES at birth for all individuals, considering fixed age boundaries, Scania cohorts 1813-1849 and 1850-1898

	Females				Males			
	1-4	5-19	20-49	50-70	1-4	5-19	20-49	50-70
BORN 1813-1849								
IMR year of birth								
Low-medium	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
High	0.86	1.06	0.84	1.24	0.73*	0.85	1.04	1.09
	[0.59,1.25]	[0.71,1.60]	[0.58,1.20]	[0.95,1.63]	[0.50,1.05]	[0.57,1.27]	[0.76,1.43]	[0.83,1.43]
SES at birth								
Medium-high	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Low	1.30	0.82	1.00	0.93	1.16	1.28	1.07	1.19
	[0.91,1.84]	[0.52,1.28]	[0.69,1.45]	[0.71,1.22]	[0.83,1.62]	[0.82,2.00]	[0.73,1.56]	[0.89,1.58]
Number of individuals	1764	2885	3871	1038	1786	2937	3904	990
Number of deaths	173	134	188	284	181	137	187	245
BORN 1850-1898								
IMR year of birth								
Low-medium	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
High	0.93	0.96	1.05	1.21	0.76	0.95	1.56***	1.22
	[0.65,1.32]	[0.68,1.37]	[0.76,1.45]	[0.92,1.59]	[0.55,1.06]	[0.66,1.37]	[1.16,2.10]	[0.94,1.57]
SES at birth								
Medium-high	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Low	1.13	1.46**	1.17	0.96	1.35**	1.10	1.10	0.95
	[0.84,1.52]	[1.03,2.05]	[0.86,1.59]	[0.75,1.24]	[1.03,1.75]	[0.77,1.57]	[0.79,1.53]	[0.74,1.22]
Number of individuals	3914	6177	8549	2313	4178	6025	7733	2295
Number of deaths	254	243	269	364	316	218	244	367

Notes: see Table 1 for explanations on how IMR in the year of birth was determined. The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

Table 8: Sensitivity analysis 1 – hazard ratios of death when considering the actual values of IMR and rye prices, their trend and deviation components and different threshold levels of deviation from the trend, Scania cohorts 1813-1898

HIGH PRICES	Landless females				Landless males			
	1-2	2-17.5	17.5-63	63-70	1-3	3-11.5	11.5-47	47-70
Ln rye prices	0.76	1.68 **	0.77	4.78 **	0.68	1.74 *	1.05	1.42
Ln rye deviation and trend								
Trend	2.32	1.94 *	1.21	8.07 **	1.14	1.65	1.03	0.89
Deviation	0.20 **	1.41	0.38	2.57	0.34 **	1.84	1.06	2.73
Ln rye prices deviation								
0.03	0.75	1.04	0.70 *	1.51	0.77 *	1.26	1.08	1.59 **
0.06	0.71	1.06	0.61 **	0.97	0.72 **	1.26	1.07	1.72 **
0.09	0.75	1.25 *	0.51 **	1.13	0.75 *	1.38 *	1.01	1.56 *
0.12	0.62 *	1.22	0.53 **	1.13	0.72 *	1.35 *	0.94	1.61 *
0.15	0.74	1.15	0.49 **	1.31	0.74	1.28	0.93	1.56
0.18	0.68	1.30 *	0.53 *	1.51	0.73	1.31	0.96	1.42
0.21	0.72	1.25	0.50 **	1.55	0.79	1.19	0.90	1.23
HIGH IMR	All females				All males			
	1-4.5	4.5-12	12-44	44-70	1-6.5	6.5-13	13-23.5	23.5-70
IMR	1.00	1.00	1.00	1.00 **	1.00 **	1.00	1.00	1.00 **
IMR deviation and trend								
Trend	1.00	0.99 **	0.99 **	1.00	0.99 **	1.00	1.01	1.00
Deviation	1.00 *	1.00	1.00	1.00 **	1.00	1.00	1.00 *	1.00 **
Disease load deviation								
0.05	0.76 **	1.11	1.03	1.18 **	0.85 *	1.24	0.85	1.20 ***
0.10	0.75 **	1.08	0.97	1.18 **	0.84 *	1.22	0.82	1.22 ***
0.15	0.75 **	1.14	0.93	1.17 *	0.75 ***	1.23	0.92	1.23 ***
0.20	0.79 *	1.28	0.85	1.25 **	0.70 ***	1.34	0.81	1.21 ***
0.25	0.76 *	1.27	0.80 *	1.29 ***	0.72 ***	1.35	0.86	1.22 **
0.30	0.81	1.24	0.86	1.41 ***	0.69 ***	1.28	0.96	1.24 ***
0.40	0.85	1.08	0.90	1.43 ***	0.76 **	1.35	0.73	1.25 ***

Notes: Each result shown in the tables relates to a separate estimation model, except for trend and deviation, which are included in the same model. Each model controls for year of birth (continuous variable), parish, and an indicator of parish of birth. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Some differences across cohorts are also observed in the impact of being of low SES at birth, although the fluctuations are limited to the younger age groups. Between ages 1-4, higher probabilities of dying are seen for girls and boys of both cohorts born into low SES families, with statistical significance for boys born after 1850. Between ages 5-19, hazard ratios below 1 are obtained for the females born before 1850, while those born after this year have a 46% higher risk of dying if they were born into low SES families. Males, instead, present relatively higher probabilities of dying for these ages if they were born into low SES families, although these effects lack statistical significance for both cohorts.

2.5.3 Sensitivity analysis

Except for small variations in the magnitude and statistical significance, the results remain rather constant in the estimations conducted in the sensitivity analysis. When changing how the indicators of early life conditions are considered and modelled, support in favour of the foetal origins hypothesis for landless males and of the infancy inflammation hypothesis for all individuals is still found. The sex differences observed during the childbearing and working years are also confirmed. Table 8, in fact, shows that although the coefficients obtained are not equivalent to those above, the direction of the results and, in many cases, their statistical significance remains constant when conducting estimations that include the full value of the IMR and the logarithm of rye prices, the trend and deviation components, and the different thresholds of deviation from the trend. The results also remain rather constant when changing the control variables that are introduced into the models (Table 9) or when conducting the estimations for the subsample of individuals born in the studied parishes or within a 17 km radius of them (Table 10)[17]. The results of this study are therefore not biased by the methodological choices adopted.

17 In relation to the impact of exposure to high prices during the foetal stage, in this sensitivity analysis, a dominance of selection is still found during the childbearing and working ages for females, while scarring prevails in old age among males. The females whose families of origin were landless display a lower risk of death between ages 17.5-63 if they were conceived in years with high prices, and these results were statistically significant in Table 8 for all threshold levels of relative deviation from the trend, but not for the actual values of the logarithm of rye prices or deviation from the trend. In Table 9, statistical significance is observed when adding the year of birth squared as a control in the model, when replacing birth year by birth decade or when including controls for the mother's age but not when removing all control variables. Men born into landless families have a higher mortality between ages 47-70 if they were born in years with high prices, with statistically significant results for the threshold levels 3%-12% but not for the actual value of prices and of the deviation from the trend (Table 8). Statistical significance is also observed when changing the controls for the trend or when removing all control variables (Models 1-3 in Table 9). The magnitude of the effect remains strong when including controls for

2.6 Discussion

This work was aimed at studying the impact of adverse early life exposures on mortality later in life. Early life conditions were measured by considering the grain prices of the year of conception and the IMR of the year of birth as exogenous indicators of nutrition during the foetal stage and disease exposure in infancy. In both cases, the threshold levels of deviation from the trends were considered to define the years with high prices or a high IMR. The effects of exposure to a high IMR were compared to those of being of a low SES at birth. The full life course was considered, distinguishing different stages by considering both fixed as well as flexible age boundaries. When measuring the impact of exposure to disease, the entire population was taken into account, while the impact of prices was only estimated for individuals born into landless families because grain prices represent a measure of nutrition only for net consumers.

In relation to both types of early life conditions and for all individuals, selection dominated in early childhood, followed by scarring until early adolescence. Sex differences were observed during the childbearing and working years. Selection prevailed among females who were exposed to high prices or to a high IMR, with statistical significance only for the first of these effects. For males, no impacts were seen for these ages in relation to exposure to high prices during the foetal stage, while those born in a year with a high disease load already presented a greater probability of dying from their early 20s. In old age, the foetal origins hypothesis was strongly supported for landless males, while the infancy inflammation hypothesis was confirmed for all individuals. Stronger negative impacts were found in old age for males than for females in relation to exposure to high prices during the foetal stage but not in connection to exposure to a high IMR during infancy, although the men exposed to disease showed an excess in mortality from a much younger age than the females. The effect of exposure to a high IMR in

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the mother's age at birth, but such a result is no longer statistically significant, although it is not far from the 10% threshold level (Models 4-5). A reduction in statistical significance could be related to the smaller size of the sample because data on mother's age was not available for all individuals. When only selecting individuals born in the studied parishes or within a 17 km radius of them, the patterns of the results also remains constant (Table 10). Selection still dominates during the childbearing and working ages for females and scarring still dominates in old age for males. This latter result is not statistically significant, although it is not very far from it.

In relation to the impact of exposure to a high IMR in infancy, a dominance of scarring is observed between ages 44-70 for women and 23.5-70 for men, with the actual values of the IMR, deviations from the trend and all thresholds of deviation presenting statistical significance (Table 8). Effects of strong magnitude and statistical significance are also observed in the three models that consider the different types of control variables (Table 9). The results also remain constant when estimating the models for individuals born within the studied parishes or within a 17 km radius of them (Table 10).

Table 9: Sensitivity analysis 2 – hazard ratios of death when including different control variables in the models, Scania cohorts 1813-1898

HIGH PRICES	Landless females				Landless males			
	1-2	2-17.5	17.5-63	63-70	1-3	3-11.5	11.5-47	47-70
Model 1	N.A.	N.A.	0.51**	1.08	0.72*	N.A.	0.92	1.58*
Model 2	0.60*	1.25	0.51**	1.3	0.71*	1.36*	0.87	1.64*
Model 3	0.8	1.28	0.84	1.25**	0.70***	1.36*	0.8	1.21**
Model 4	0.68	1.34*	0.49**	1.20	0.79	1.25	0.97	1.66
Model 5	0.68	1.34*	0.48**	1.22	0.79	1.24	0.96	1.72

HIGH IMR	All females				All males			
	1-4.5	4.5-12	12-44	44-70	1-6.5	6.5-13	13-23.5	23.5-70
Model 1	0.80	N.A.	0.83	1.25**	N.A.	1.35	0.80	1.20**
Model 2	0.81	1.26	0.85	1.25**	0.72***	1.31	0.76	1.21**
Model 3	0.82	1.28	0.87	1.33***	0.73***	1.38*	0.84	1.31***

Notes: see Table 1 for explanations on how IMR in the year of birth and prices in the year of conception were determined. Model 1 controls for year of birth (continuous variable), year of birth squared, parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. Model 2 controls for decade of birth, parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. Model 3 does not include any control variables. Model 4 controls for year of birth, parish, an indicator of whether the individual was born in one of the studied parishes or migrated to them, and mother's age at the individual's birth (continuous variable). Model 5 controls for year of birth, parish, an indicator of whether the individual was born in one of the studied parishes or migrated to them, and mother's age at the individual's birth (categorical variable 15-24, 25-34, 35-50). The sample size is smaller when controlling for mother's age, since this information was not available for all individuals. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 10: Sensitivity analysis 3 – hazard ratios of death for individuals born in the five studied parishes or within a 17 km radius of them, Scania cohorts 1813-1898

HIGH PRICES	Landless females				Landless males			
	1-2	2-17.5	17.5-63	63-70	1-3	3-11.5	11.5-47	47-70
Prices year of conception								
Low-medium	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
High	0.58*	1.21	0.61*	0.79	0.72*	1.37*	1.00	1.52
	[0.33,1.03]	[0.92,1.59]	[0.37,1.03]	[0.34,1.87]	[0.50,1.05]	[0.97,1.93]	[0.65,1.54]	[0.91,2.53]
Number of individuals	2505	2654	1210	180	2858	2527	1774	293
Number of deaths	103	277	121	30	200	167	124	84

HIGH IMR	All females				All males			
	1-4.5	4.5-12	12-44	44-70	1-6.5	6.5-13	13-23.5	23.5-70
IMR year of birth								
Low-medium	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
High	0.78*	1.37*	0.81	1.33**	0.74**	1.36	0.62*	1.19*
	[0.59,1.04]	[0.99,1.89]	[0.61,1.07]	[1.07,1.65]	[0.58,0.93]	[0.92,1.99]	[0.37,1.04]	[0.99,1.43]
SES at birth								
Medium-high	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Low	1.19	1.29	1.06	0.92	1.20*	1.38	1.40	1.08
	[0.95,1.50]	[0.92,1.79]	[0.82,1.38]	[0.74,1.13]	[0.99,1.46]	[0.92,2.08]	[0.86,2.27]	[0.90,1.29]
Number of individuals	4984	4727	9052	2105	5633	4517	6515	5609
Number of deaths	379	212	378	470	530	143	127	624

Notes: see Table 1 for explanations on how IMR in the year of birth and prices in the year of conception were determined. The models control for year of birth (continuous variable) and parish. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

infancy was constant across socioeconomic groups. The individuals born into families with a low SES presented a higher probability of dying during the young ages than those whose family of origin was of a medium-high SES, but these relative differences declined strongly across age and were very small among the elderly. When comparing the effects of exposure to a high IMR in infancy across cohorts, scarring became dominant from younger ages for the individuals born after 1850, and among men in old age, the negative impact was also stronger for those born after this year.

The calculations of the average number of years lived measured the size of the effects of adverse early life exposure. Between ages 1 and 70, the females born into landless families who were conceived in years with high prices lived roughly 3 years more than those conceived in other years, showing the greatest gain during adulthood. Instead, the males lived roughly 1 year less, with the greatest loss observed in old age. No large differences in the average number of years lived were seen between ages 1 and 70 for the individuals born in a year with a high IMR, but exposed males who survived until adulthood presented a loss of 1.8 years, while the females who survived until the end of their reproductive ages showed a loss of 0.9 years.

The results obtained in this work for the 1813-1869 period in relation to the impact of exposure to disease in early life confirm the patterns found by Bengtsson and Lindström (2000; 2003) for the period 1760-1894 for four of the five parishes considered here. In fact, a higher mortality in old age for the individuals exposed to a high IMR is observed both here and in their study. The work of Bengtsson and Lindström also measured the impact of nutrition during the foetal stage, considering the logarithm of rye prices or the deviation component from its trend and including all individuals in the same model, regardless of their sex or of the SES of the family of origin. They found no significant impacts. Instead, when studying males and females separately, focusing only on the individuals who were landless at birth and utilising a threshold approach, some of the results of this work were statistically significant. The results obtained here differed by sex and also by age, showing a dominance of scarring in old age for landless males and a dominance of selection from adulthood until old age for females.

The findings of this work could be discussed further. In relation to both types of early life condition indicators and for both sexes, although the ages when these fluctuations occurred as well as the magnitude of these effects varied, a pattern of selection/scarring/selection/scarring was always obtained. These changes may be related to the demands made on the body by the characteristics that are specific to each life course stage. Until maturation, these demands could be particularly concerned with the tempo of growth, and afterwards they could be linked to reproduction and involvement in the labour market. In young ages, net selection

dominates because during years with high prices or epidemics, the weak foetuses and infants do not live past birth or age one, and those surviving are consequently stronger than the average children who had not faced stressful conditions up to that time. Instead, as has been previously shown in the literature, during late adulthood and old age, the prevalence of scarring is most likely related to adverse early life exposures leading to the development of chronic disease through inflammatory mechanisms or direct damage to the organs.

Concerning the impacts seen during childbearing and working ages in relation to both types of early life conditions, there may be specific biological mechanisms that explain why gender mattered. For example, these effects could result from inherent differences in childbearing. There are, in fact, short as well as long-term relationships between reproduction and health and mortality (e.g., Doblhammer & Oeppen, 2003; Dribe, 2004). If females exposed to high prices during their foetal stage had lower fertility later in their lives, they could have experienced relatively lower mortality. Alternatively, the relatively longer average number of years lived by females exposed to high prices while *in-utero* could also have, in part, originated from reductions in fertility during the years with high prices. However, because these results have never been shown before in the literature, further research is required, and at this stage interpretations can only be speculative. Partly having the aim of explaining some of the results observed in this work, Chapter 3 analyses, by age and sex, the impact of exposure to specific epidemics during the first year of life, while Chapters 4 and 5 evaluate the effect of exposure to high prices or high IMR in early life on female SES attainment in adulthood and reproductive health, the latter being measured by considering fertility and offspring sex ratio at birth and neonatal mortality.

2.7 Conclusions

Whereas previous works evaluating the impact of adverse early life conditions have focused on the individuals selected to survive until old age, the richness of the Scanian Economic Demographic Database has allowed a full life course approach to be adopted to measure the effects of exposure to high prices during the foetal stage and to a high IMR during infancy. Covering a time period that links historical to contemporary epochs, for the first time individuals are followed from early childhood until old age. Net selection and scarring at all stages of the life course are measured and these effects are evaluated distinguishing by sex.

Using an exogenous indicator of exposure to disease in infancy, we observed sex-specific impacts during the childbearing and working ages. Moreover, we demonstrate that for males, exposure to epidemics in the first year of life not only induces the development of chronic diseases in old age, but may also lead to higher rates of death in the younger ages. Using an exogenous indicator for short-term variations in nutrition during the foetal stage, we also found sex-specific effects in the adult ages. We hypothesise that this pattern could be explained by a mixture of impacts working through selective fertility during periods of high prices, effects on the ability of these women to reproduce, and direct effects on morbidity and mortality. We found the effect of disease to be a more important determinant of longevity than the impact of diet or the impact of SES at birth. Although exploratory in its nature, this works presents results that, to a large extent, are new to the literature and elucidate the importance of focusing on all stages of the life course and on sex differences when studying the impact of early life conditions on later life health.

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Chapter 3

Early life exposure to measles, scarlet fever or whooping cough and sex differences in mortality across the life course: Southern Sweden, 1813-1968

3.1 Abstract

Using data from Southern Sweden for the 1813 to 1968 period, this work evaluates, distinguishing by sex, the impact of exposure in infancy to epidemics of measles, scarlet fever and whooping cough on mortality across the life course. Sex differences in the results were observed during early adulthood for the individuals born in years with measles or scarlet fever. Males, in fact, presented a higher risk of dying, while lower relative mortality was observed among females. These differences were statistically significant only in the case of scarlet fever. Instead, both males and females exposed to whooping cough epidemics showed higher probabilities of dying from early adulthood to old age. The effect of exposure to whooping cough was stronger in relative terms for the individuals born in or after 1850, and the impact of the three disease environments on mortality across the life course did not vary by socioeconomic status at birth.

3.2 Introduction

The foetal stage and first years of life are critical periods characterised by the rapid development of organs and cells. The exposure to adverse conditions during one of these stages may result in the survival of only genetically or congenitally stronger individuals or in permanent and irreversible damage to the body, two processes that have been referred to as 'selection' and 'scarring' (Ben-Shlomo & Kuh, 2002; Kuh & Ben-Shlomo, 2004; Preston, Hill, & Drevenstedt, 1998). Associations between general infection in infancy and the development of chronic diseases in

old age have been found in several historical studies (Barker et al., 1991; Bengtsson & Lindström, 2000; Bengtsson & Mineau, 2009; Bengtsson & Broström, 2009; Bengtsson & Lindström, 2003; Elo & Preston, 1992; Fridlizius, 1989).

To try to identify the causal mechanisms linking early life exposure to disease to later life health, it is important to focus specifically on the long-term effects of specific epidemics. Although some scholars have retrospectively described which disease environment characterised the years where strong correlations were found between the cohorts' infant and old-age mortality (Bengtsson & Lindström, 2003), there is not much research that compares, by age and sex, the impacts on health of experiencing specific epidemics in early life. Some exceptions are the studies that have focused on the effects of exposure *in-utero* to the Spanish flu (e.g., Almond, 2006). There are also few works measuring the effects of exposure to disease in early life on mortality over the entire life course, which is partly due to a lack of longitudinal databases that follow individuals from birth until death. In fact, except for the Helsinki Birth Cohort Study and the Uppsala Birth Cohort Multigeneration Study[18], most databases only permit the observation of events between birth and early adulthood or from early adulthood to old age and death (Case & Paxson, 2010). Furthermore, much of the literature linking early life conditions to mortality later in life focuses on the elderly, therefore conditioning on survival until old age without understanding what may occur in the stages that precede it.

Using data from Southern Sweden for individuals born between 1813 and 1898 and followed from birth until age 70, this work tries to cover some of these gaps. In Chapter 2, which was based on the same sources and methodology employed here, an association was found between general exposure to disease in infancy and increased mortality in old age for all individuals. During early adulthood, sex differences were observed, showing the dominance of selection for females and of scarring for males. The first aim of the current work is to measure, distinguishing by sex, the risk of dying at different ages for the individuals born in years with measles, scarlet fever or whooping cough epidemics. These three diseases were selected for the focus because they were the most diffused causes of death in childhood in the parishes during the period considered. The second aim is to compare the effect of exposure to these epidemics for the individuals born in families with a different socioeconomic status (SES) and to evaluate changes across cohorts on the impacts of exposure to whooping cough. The last aim is to determine whether exposure to these diseases in infancy influences the probability of dying at older ages from airborne infectious disease, cardiovascular diseases and diabetes, or cancers.

18 For the Helsinki Birth Cohort Study see, e.g., (Räikkönen et al., 2009); for the Uppsala Birth Cohort Multigeneration Study see, e.g., (Koupil, Leon, & Lithell, 2005; McCormack et al., 2005); for the 1958 and 1970 British cohort studies see, e.g., (Case, Fertig, & Paxson, 2005); for the US Health and Retirement Study see, e.g., (Karp, 2007); and for the Whitehall II Study see, e.g., (Marmot & Brunner, 2005).

3.3 Background

The literature focusing on the long-term effects of early life conditions has evidenced the importance of the levels of nutrition received during gestation. This link forms the basis of the 'foetal origins hypothesis' developed by Barker and his colleagues (Barker, 1994; 1995b; 1997; 2001; for a review of recent literature see e.g., Almond & Currie, 2011; and Gluckman et al., 2008). In the current work, we do not look specifically on the impact of nutritional intake, but exposure to disease can also have an effect on net nutrition. In fact, the 'nutritional status' of an individual is the net measure of the energy that can be used for growth after consumption for body maintenance, disease resistance and work (Floud et al., 2011). Infections can influence the nutritional status by reducing the appetite, worsening the quality of the ingested diet, increasing the metabolic loss of nutrients and the metabolic needs of the body and decreasing the absorption of nutrients (Bellagio conference authors, 1983). If the supply of nutrients or oxygen is inadequate, the rate of cell division can be lowered as an adaptive mechanism, negatively affecting the tissues that are experiencing critical development (Barker, 1995a). Any changes in the distribution and number of cells and in organ structure and the resetting of hormonal feedback and metabolic activity permanently affect the body's structure, physiology and metabolism (McCance & Widdowson, 1974).

The aetiology of other long-term effects of exposure in early life to disease is still not completely understood, although different scholars have emphasised the importance of various possible mechanisms. Individuals exposed to adverse early life conditions may have a lower relative mortality in later life, and in this case, net selection would dominate (Preston et al., 1998). Selection can occur at the time that the adverse exposures are perceived, with only healthier couples being able to conceive and bear a live child or only stronger children surviving until their first birthdays, but they can also be observed during the transition from childhood/adolescence/adulthood to the subsequent stage. Exposure to disease in early life can also affect health negatively. The infections sustained during the most rapid and critical stages of development can cause direct damage to the organs and cells of the body. For example, associations have been found between streptococcal infections and rheumatic heart disease (Jones, 1956) and between respiratory infections in early life and lung impairments at older ages (Barker et al., 1991; Bengtsson & Lindström, 2003; Shaheen et al., 1994). The exposure to disease in the first years of life can also reduce an individual's general immunity to disease, as has been claimed by Fridlizius (Fridlizius, 1984; 1989). In addition, short-term adaptive responses to infections or injury may become maladaptive in the long

run through inflammatory mechanisms, leading to chronic diseases such as cancer, diabetes, cardiovascular diseases or respiratory diseases in older ages (Finch & Crimmins, 2004). For example, serum levels of C-reactive protein (CRP, an acute-phase protein) increase as a reaction to inflammation, which increases the risk of experiencing cardiovascular disease and hypertension (Willerson & Ridker, 2004; Zhu et al., 2000). Associations have also been found between C-reactive protein and type 2 diabetes (Dehghan et al., March 2007; Keavney, 2008; Pradhan et al., 2001). Other markers of inflammation are elevations of interleukin-6, tumour necrosis factor-α and fibrinogen (Finch & Crimmins, 2004).

Only a few studies focusing on the long-term effects of early life conditions have considered a gender dimension, and none of these looked at the impact of exposure to disease. Some works have shown that in old age, men were affected more negatively than women from exposure to the Dutch or Finnish famines or to business cycle recessions in early life (Doblhammer-Reiter, van den Berg, & Lumey, 2011; Lindeboom, Portrait, & van den Berg, 2010; van den Berg, Doblhammer, & Christensen, 2009). It is important to study males and females separately when trying to understand the possible impacts of exposure to disease in infancy on later life health. The two groups can, in fact, present differences that relate to the conditions at the time of exposure to disease or when the effects of these exposures are measured.

The differences in mortality by gender result from an interaction between biology, behaviour and environment (Alter, Manfredini, & Nystedt, 2004). Females may be less vulnerable to stress in early life because X-linked immunoregulatory genes provide greater resistance to infectious diseases (Waldron, 1983) and also because males are usually born at younger gestational ages (Hall & Carr-Hill, 1982) and for a given gestational age with less developed respiratory systems (Torday et al., 1981). Males are more susceptible to respiratory infections and accidents in childbirth, and they therefore experience greater perinatal mortality, a difference that diminishes within the first year of life (Waldron, 1986). Some diseases such as measles, however, cause higher death rates among girls because they lose their maternal antibodies more rapidly than boys (Martins et al., 2009).

At older ages, instead, females are better protected against cardiovascular diseases as a result of behavioural and biological factors (Matthews, 1989). The biological protection is likely to be linked to female reproductive hormones such as oestrogen. However, higher rates of death are observed among females during adulthood as a result of childbearing. Mortality is higher not necessarily because of complications experienced during childbirth, but often due to maternal depletion and a greater susceptibility to infectious diseases, which is caused by the greater demand of resources during pregnancy and lactation (Alter et al., 2004). Mortality across sex can also differ due to economic roles, behaviour

and unequal distribution of resources. Males were, in the past, more involved in the fields and care of animals, and they were therefore more prone to accidents. Females, instead, were responsible for household chores and rearing children. They were consequently more exposed to infectious diseases because they spent a vast amount of time in poorly ventilated rooms (Fridlizius, 1988); in addition, because they were in charge of taking care of the sick, they were more exposed to infectious pathogens (Alter et al., 2004). The excess in female mortality could also be related to the unequal distribution of resources within the household, particularly in nutrition and health care, where males were often favoured because their tasks were believed to be more physically demanding (Alter et al., 2004). There could also be differences in mortality that relate to the culturally induced engagement in alcohol consumption, cigarette smoking and behaviours leading to death from accidents or violent causes (Waldron, 1983).

The long-term effects of early life exposures could have differed across sex due to an interaction with the patterns described above. As a result of their greater vulnerability in early life, males could have been more susceptible to complications during gestation and to infections in infancy. The effect of these exposures, however, may have been counterbalanced by an excess in mortality during these stages and therefore by stronger selection. The impact of these exposures could have been affected by behaviour later in life. Females, on the other hand, could have been less susceptible to adverse early life exposures, but due to childbearing, the unequal distribution of resources or greater exposure to pathogens at older ages, the negative long-term effect of these conditions could have been amplified.

When studying the long-term impacts of early life exposures, it is also important to adopt a full-life course approach because it allows the distinguishing of stages where individuals are exposed to stress, or critical windows, and those where the impact of these exposures is measured. However, most importantly, even if deaths related to conditions that originate during early development are more common in old age, it is important to identify the phases where selection/immunisation dominate over scarring or *vice-versa*. In this work, we follow individuals from birth until age 70, separately studying childhood, adolescence, childbearing/working ages and old age because each of these stages of life is different in terms of the development or functioning of the body.

The long-term effects of early life exposures could differ at various life course stages as a result of changes in the tempo in the growth of organs. For example, the growth in height declines from birth until age 4 or 5, it increases slightly at approximately ages 6 to 8 (referred to as the mid-growth), and it then declines again (Tanner, 1989). Adolescence is characterised by another spurt in growth, where the rate is nearly half of that during infancy and which is followed by periods of slower growth until maturity (Steckel, Floud, & Sandberg, 1997).

Most skeletal and muscular dimensions of the body as well as internal organs such as the liver, spleen and kidney have growth curves similar to that of height, with the exception of the brain, skull and some other organs such as the reproductive system or the intestines, which have a different tempo of development (Tanner, 1989). The differences in the long-term impacts of early life conditions are not necessarily only related to the velocity of growth, but could also be linked to the characteristics of each age group. For example, childbearing or intense manual labour could be affected by early life conditions, but they also influence the health and the functioning of the body, possibly interacting with the long-term effects of early life exposures.

3.3.1 Possible impacts on later life health of exposure to measles, scarlet fever and whooping cough

When searching for the long-term consequences of exposure in early life to infection, studying the impact of different epidemics separately can help to define disease-specific mechanisms. This work focuses on exposure to measles, scarlet fever and whooping cough because they were the most diffused causes of death in the region and period studied. These are highly contagious diseases and transmission generally occurs through direct contact with the nose or throat secretions of the infected individuals or from the airborne droplets of these secretions.

Measles is caused by a virus in the genus Morbillivirus of the family Paramyoxoviridae, and its greatest incidence in areas with little or no vaccination coverage is in children under the age of 2 (Kim-Farley, 1993). Infection results in life-long immunity and there is also transplacental immunity (Mortimer, 1994). It has been shown that girls lose the maternal measles antibodies more rapidly than boys (Martins et al., 2009). The levels of vitamin A are reduced during infections, and this depression is also associated with higher morbidity and mortality (Mortimer, 1994). Other possible complications include ear infection, pneumonia, hepatitis, meningitis and encephalitis. Pneumonia is the most common cause of death among individuals infected with measles (Mortimer, 1994).

Scarlet fever is an infectious disease caused by certain types of the bacteria group A haemolytic streptococci (Hardy, 1993a). Infection by this disease does not confer lifelong immunity. Possible complications include rheumatic fever, which is an inflammation of the heart and joints, and glomerulonephritis, which is an inflammation of the urine-producing structures of the kidney (Encyclopædia Britannica, 2012).

Whooping cough is caused by the bacteria *bordetella pertussis*, which affects the respiratory track (Hardy, 1993b). Infection almost always occurred during

childhood and, particularly, in infancy because there is no effective transplacental immunity (Mortimer, 1994). In a family where one child gets this disease, his or her siblings are also very likely to get it if they have not been previously infected or vaccinated. Today, whooping cough is resurging in many industrialised countries, even when they have high rates of vaccination (Warfel, Beren, & Merkel, 2012). Outbreaks occur every 2-5 years (Cherry, 2005), most likely because immunity wanes after approximately 4-20 years from an infection and 4-12 years from vaccination (Wendelboe et al., 2005). The complications of whooping cough include bronchopneumonia and atelectasis, which are the primary causes of mortality related to this disease, as well as encephalopathy[19], which is less frequent, and in the past also exhaustion and malnutrition due to repeated vomiting (Mortimer, 1994). *Bordetella pertussis* attacks the mucus membrane of the respiratory tract, sometimes destroying this membrane (Swansea Research Unit of the Royal College of General Practitioners, 1985). When the infection from these bacteria is prolonged, the lymphoid tissue of the adenoids can become hypertrophied, leading to a permanent source of infection in the respiratory tract and middle ear (Swansea Research Unit of the Royal College of General Practitioners, 1985). Exposure to whooping cough can also lead to retarded infant weight gain (Barker et al., 1991).

Vaccination against measles became widespread in the 1960s. For scarlet fever, a vaccine was developed in the 1920s, and it ceased to be used in the 1940s after the introduction of penicillin. The mass-vaccination against whooping cough was introduced in Sweden in the late 1940s (Claesson, 2009), and it was stopped in 1979 (Krantz et al., 1990). Vaccinations were therefore not available during the years in which the studied population was born. Because these diseases spread very rapidly, most individuals are likely to have been infected.

Several works have shown that lower respiratory tract infections in early childhood, particularly during infancy, lead to airflow obstruction in later life, possibly through the failure to attain the maximal potential lung function. Individuals with airflow obstruction have been shown to be at greater risk of dying from chronic obstructive airways diseases (Peto et al., 1983) as well as from lung cancer, coronary heart disease and other causes (Wiles & Hnizdo, 1991). The studies that attempt to find associations between early life disease exposure and lung function later in life face difficulty in distinguishing between impacts related to an infectious process and those linked to a pre-existing obstructive airway disease that could increase the susceptibility to respiratory infections in young ages and could also lead to respiratory problems in adult life (von Mutius, 2001), often leading to biased results.

19 Atelectasis is the partial or total collapse of a lung caused by a blockage of the air passages or by external pressure on the lung (A.D.A.M. Medical Encyclopedia, 2012). Encephalopathy is the disease, damage or malfunction of the brain (MedicineNet, 2012).

The long-term effects of exposure in early life to whooping cough have been studied previously, often with a focus on respiratory function. In some of these studies, no associations were found between exposure and lung function reductions in later childhood and in adulthood, although in others, the exposed individuals showed some evidence of a greater incidence of respiratory symptoms (Britten & Wadsworth, 1986; Johnston et al., 1986; 1983; Krantz et al., 1990; Shaheen et al., 1994; 1998; Tennant, John Gibson, & Pearce, 2008). Other works have found long-term consequences for children infected with whooping cough, including impaired lung function, increased respiratory symptoms, higher rates of hospital admittance, lower median intelligence quotient and lower educational attainments (Jedrychowski et al., 2002; Swansea Research Unit of the Royal College of General Practitioners, 1985; 1987). A study conducted using data from men born in Hertfordshire between 1911 and 1930 showed that the reductions in lung function later in life were greater if infection from whooping cough had occurred in infancy rather than during ages 1 to 5, and these effects were independent of birth weight, smoking and social class (Barker et al., 1991). In another study conducted by Bengtsson and Linström (2003) based on data from four of the parishes considered in this work for the 1766-1894 time period, the children who were exposed to high infant mortality rates (IMR) in their year of birth had a higher risk of dying from airborne infectious diseases in old age. The authors of this work retrospectively showed that, in the studied area and period, the years with high IMR were dominated by smallpox and whooping cough epidemics.

Exposure in early life to whooping cough has also been associated with later life impairments that are not related to the respiratory system. One work has shown associations between whooping cough infections in infancy and type 1 diabetes mellitus, and these patterns were constant across socioeconomic groups (Montgomery et al., 2002). A delay between infection and the onset of diabetes was observed, from which the authors concluded that infection in early life could cause the start of an autoimmune process or raise the hazard of delayed autoimmunity. Infections have, in fact, been associated with the development of autoimmune diseases (Rose & Mackay, 2000). Many works have shown that type 1 diabetes can lead to many complications, and it can even become fatal unless treated with insulin.

The literature focusing on the long-term effects of exposure in early life to measles is more limited. Within the study based on data from Hertfordshire, where associations had been found between exposure in early life to whooping cough and reduced lung function later in life, no long-term effects from measles were observed (Barker et al., 1991). The authors of this work concluded that the absence of a relationship could be because measles infections generally occur later in infancy than whooping cough, at a stage when the lungs are growing less rapidly. However, another work based on aggregative data from England and

Wales had found a correlation between infant mortality from measles and other infectious diseases and the rates of death from lung disease 70 years later for the same cohorts (Barker & Osmond, 1986).

There are also few studies that examine the long-term effects of exposure in early life to scarlet fever. Streptococcal infections have been associated with two types of sequelae, acute rheumatic fever and acute glomerulonephritis (Bisno, 1991). Rheumatic fever is an inflammatory disease that is mediated by humoral and cellular autoimmune responses that occur some time after a streptococcus infection (Guilherme & Kalil, 2004). Approximately 30-45% of patients with rheumatic fever suffer from carditis, leading to lesions of the mitral and aortic valves and causing rheumatic heart disease (Guilherme & Kalil, 2004).

Based on the existing but scant literature, we expect that the individuals exposed in infancy to epidemics of measles, scarlet fever or whooping cough will experience greater mortality later in life than those born in years with more favourable environments. We anticipate finding higher mortality from cardiovascular diseases for those exposed to scarlet fever, and from airborne infectious diseases or diabetes for those exposed to whooping cough. Based on the literature presented above, we also anticipate observing stronger negative effects from whooping cough than from measles or scarlet fever. Moreover, because in Chapter 2 sex differences were observed for the impact of exposure to high IMR in infancy on mortality during the childbearing and working years, we presume that we will also observe sex differences in the long-term effects of the exposures considered here, although, due to the lack of previous research, we cannot formulate expectations on the disease-specific sex differences.

3.4 Data and methods

3.4.1 Source material

This work uses data from the Scanian Economic Demographic Database (SEDD)[20], which contains information on births, deaths, marriages and migrations occurring between 1813 and 1968 in the parishes of Halmstad, Hög, Kävlinge, Kågeröd and Sireköpinge, located in the southernmost part of Sweden. The five parishes

20 The SEDD was created in a collaborative project between the Regional Archives in Lund and the Centre for Economic Demography at Lund University (Bengtsson, Dribe, & Svensson, 2012), and it has been structured to follow the format suggested by the Intermediate Data Structure (Alter, Mandemakers, & Gutmann, 2009). The data used in this work was extracted on February 20, 2012, and it was converted into spells using the code developed by Quaranta (2012).

were situated near one another, and they present variations that were common in peasant societies with regard to topography, size and socioeconomic conditions. The entire area was open farmland, except for the northern part of Halmstad, which was more wooded. The southern localities became industrialised and urbanised in the last decades of the 19th century. The parish register material is of high quality, and the gaps for births, deaths and marriages are minimal (Bengtsson & Lindström, 2000)[21]. The study is limited to individuals born between 1813 and 1898, who are followed from birth until age 70.

The SEDD contains information on occupation, which is obtained from poll tax and income registers. All occupations in the database were coded into HISCO (van Leeuwen, Maas, & Miles, 2002) and later classified according to SOCPO (van de Putte & Miles, 2005), which is a scheme of classification that consists of five categories based on level of skill, degree of supervision, and whether self-employed or not, as well as on pure status. SOCPO 5 indicates the highest status and 1 the lowest. When constructing the SEDD, where possible, the immigrants were traced in the registers of their previous residences to determine the occupation of the head of each individual's family of origin. We use this information to determine the SES at birth of each individual.

Moreover, the SEDD also includes data on the causes of death, which were registered by the clergymen. The death records of these parishes were of high quality, and the data on causes of death in Sweden are very valid and reliable (for a thorough discussion on the validity and reliability of these sources see Bengtsson & Lindström, 2000; 2003). When estimating models on cause-specific mortality, three categories are considered: deaths from airborne infectious diseases, cardiovascular diseases and diabetes, and cancers. The same categorisation presented by Bengtsson and Lindström (2000) is utilised here[22].

Table 1 shows descriptive statistics. As observed from this table, between 4 and 5% of the observed person-years relate to those exposed in infancy to measles, another 4-5% to scarlet fever, and between 8 and 9% to whooping cough. The SES at birth is known for approximately 60 to 75% of the studied population. In the age groups 20 to 49 and 50 to 70, the percentages of individuals born outside of the studied parishes are rather large (70-81%), even if the majority of these were born within a 17 km radius of them and are likely to have faced the same disease environment in infancy as the locals. Due to this conspicuous

21 Calculations showed that for all occupational groups, at least 40% of all infant deaths occurred within the first month of the babies' life.

22 'Airborne infectious diseases' include deaths from smallpox, measles, whooping cough, diphtheria, tonsillitis, inflammation and diseases of the throat, pneumonia, stich and sting, chest disease, coughing, and other infectious diseases; 'cardiovascular diseases and diabetes' include sudden death, coronary heart disease, stroke and diabetes; 'cancers' include tumours, degenerative diseases and cancers (Bengtsson & Lindström, 2000).

Table 1: Descriptive statistics

	Females				Males			
	1-4	5-9	20-49	50-70	1-4	5-9	20-49	50-70
Disease exposure [a] (%)								
Low-medium disease load	83.4	83.6	83.2	83.0	81.7	82.6	81.6	81.6
Measles	4.8	4.4	4.7	5.2	5.0	4.6	5.1	5.2
Scarlet fever	4.1	3.9	4.1	4.2	4.6	3.8	4.0	4.4
Whooping cough	7.7	8.1	8.0	7.7	8.7	9.0	9.3	8.8
Birth SES [b] (%)								
Low	39.8	31.6	32.9	36.2	40.3	31.3	32.2	36.9
Medium-high	34.1	28.7	30.5	32.5	34.1	27.8	31.7	33.9
Unknown	26.2	39.7	36.6	31.3	25.5	40.9	36.1	29.2
Parish of residence (%)								
Hög	8.9	9.6	9.5	7.9	9.2	10.1	9.3	8.0
Kävlinge	14.5	16.6	28.0	35.3	14.3	16.9	27.9	34.7
Halmstad	18.2	17.4	13.2	9.2	17.5	16.8	12.5	8.7
Sireköpinge	23.3	22.0	21.4	19.8	24.2	22.1	21.3	18.8
Kågeröd	35.2	34.4	28.0	27.8	34.8	34.2	29.1	29.8
Birth parish (%)								
Studied parishes	79.2	61.0	25.6	19.2	80.5	61.8	30.2	22.2
Other	20.8	39.0	74.4	80.8	19.5	38.2	69.8	77.8
Birth Year (n years)	1861.7	1859.8	1858.2	1859.8	1861.6	1859.6	1858.5	1860.6

Notes: The values shown in the table are calculated as the average for birth year and for all other variables as the percentage of person years in each category. a – low-medium disease load are years with a relative deviation from the trend in IMR, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25, lower than 0.2, while years with measles, scarlet fever or whooping cough are those with relative deviations from the trend in IMR higher than or equal to 0.2 and where these diseases were the main causes of death among children. b – low SES are SOCPO 1-2 and medium-high SES are SOCPO 3-5.

proportion, however, in the sensitivity analysis, estimations are also made only for the subgroup of individuals born within this 17 km radius.

3.4.2 Early life disease environment

The disease environment that predominated each year was determined to allow the study of the long-term effects of exposure in infancy to specific epidemics. Local IMR were first calculated from the data, and they were decomposed into trend and cycle components using the Hodrick-Prescott filter with a filtering factor of 6.25, the value usually selected for yearly series. Separating the trend and cycle allowed us to identify the years with a high disease load, defined as those having a relative deviation from the trend in IMR that exceeded 20%[23], and to

23 This threshold level corresponds to roughly the eightieth percentile in the distribution of relative deviations from the trend in IMR, meaning that one of every five years had a high disease load, more or less.

later specify which cause was the main determinant of these deaths. Due to small numbers, the causes of death for all children deceased in ages 0-10, rather than only infants, were considered. As a result of these steps, 1821, 1846, 1862 and 1874 were identified as years with epidemics of measles; 1838 of smallpox; 1860, 1869 and 1877 of scarlet fever; and 1816, 1826, 1831, 1835, 1853, 1859 and 1894 of whooping cough, while the years with a low relative deviation from the trend in IMR were considered to have a low-medium disease load. Although the threshold level to indicate a high IMR was not exceeded in 1862 and 1877, these years were defined as epidemic years because over 50% of all deaths of children resulted, respectively, from measles and scarlet fever. Conversely, even though the IMR was high in 1832, 1881 and 1886, the primary causes of death could not be determined due to indications of symptomatic conditions (dropsy, pain, etc.) rather than specific pathologies or due to missing data. The individuals born in these years were therefore excluded from the study. Those born in the single year of the smallpox epidemic were also excluded because of small numbers. The sample considered includes 40,140 individuals.

Indicators such as IMR and the type of epidemic that was most diffused in a population are exogenous measures of early life conditions. The advantage of using contextual variables is that they are not related to the life course and are therefore free of sources of confounding (Doblhammer, 2007; Lindeboom et al., 2010). However, the indicators considered have several limitations. These indicators are, in fact, constructed from yearly averages, and the same value is linked to all individuals of the same cohort regardless of their month of birth. The effects of exposure to epidemics could therefore be underestimated. The lack of nominative data on infections represents a second shortcoming, although the types of diseases considered here spread rather rapidly across the population, in particular among children. The choice to define years where the relative deviation from the trend in IMR was high as being those with a high disease load could also have biased the results. However, in a previous work that adopted this same identification strategy (Chapter 2), the impact of general exposure to disease remained constant when the estimations instead considered the actual values of IMR, trend and deviation or different threshold levels of deviation from the trend. Finally, comparing individuals born in years with epidemics to a control group born in years that are not strictly contiguous can also bias the results. This potential bias is evaluated within the sensitivity analysis.

3.4.3 Statistical models

The analysis is structured in different sections. First, we conduct a preliminary study to measure mortality during ages 0-1 during years with epidemics of measles, scarlet fever and whooping cough; next, we focus on the long-term effects of exposure in infancy to these epidemics by age and sex; then, we evaluate the SES and cohort variations on these impacts; and to conclude, we measure the impact of exposure in early life to these epidemics on cause-specific mortality.

As a preliminary study, the risk of dying during ages 0-1 is measured during the years with measles, scarlet fever and whooping cough to understand the actual magnitude of the exposure to these epidemics and to capture possible sex differences in mortality during those years. Cox proportional hazard models are used. Epidemics are considered to be a period effect, and their impact on the probability of dying is estimated by introducing a time varying covariate that changes value each year. This variable is also interacted with the infant's sex. The models control for year (continuous variable) and parish. All estimations in this work are made using STATA 12.

The second part of this study evaluates the impact of exposure in infancy to one of these epidemics on mortality at all stages of the life course. The estimations are made using Cox proportional hazard models that consider the type of disease environment experienced by the individual in their first year of life, measured through a categorical variable with four levels: epidemics of measles, scarlet fever or whooping cough or a low-medium disease load. The models introduce controls for the year of birth (continuous variable) to account for changes in mortality across time, as well as for parish of residence and for whether the individual was born in the parishes or migrated to them. The same controls are included in all other models estimated in this work.

The hazard of death for an individual j could therefore be summarised as

$$h_j(t) = h_0(t)exp\left(\gamma_0 + \gamma_1 disease_i + \beta X_j\right)$$

where $h_0(t)$ represents the baseline hazard and X_j is the vector of control variables.

The results obtained on the long-term effects of these early life exposures capture the net effect between selection and scarring effects. Scarring prevails when individuals exposed to epidemics experience higher mortality than their peers who faced low-medium disease loads, while selection dominates if the death rates are lower. However, the lack of marked differences could result from the actual absence of influential impacts or because these mechanisms are of almost identical magnitude.

To capture the possible variations in the impact of the disease environment experienced in infancy, separate models are constructed for males and females and for different life course stages. Because there are no previous studies that

allow us to formulate expectations of which ages may reveal distinct patterns, the estimations first consider fixed ages and later flexible age boundaries through an exploratory study.

When considering fixed ages, we estimate the impact of exposure to the three epidemics within the same model. The age groups considered are 1-4 for early childhood, where vulnerability to airborne and waterborne infectious diseases is very high; 5-19 for late childhood and adolescence; 20-49 for the childbearing and working ages, where mortality is largely influenced by reproduction and involvement in the labour market; and 50-70 for old age, where chronic disease is more likely to occur. Separate estimations are made for males and females, and also within a common model an interaction between sex and disease environment is introduced to determine whether the differences between the two groups are statistically significant. The size of the impacts of exposure to disease in infancy on later life health is also quantified by showing the average number of years lived, calculated using the values of average longevity obtained as the integral of the survival functions, which were estimated using Kaplan-Meier estimators. The estimators are adjusted for the year of birth, centred in 1855. Because we are not able to follow all cohorts until their death, all person-times were censored at age 70. These estimations therefore do not show full measures of life expectancy but, rather, the average number of years lived until age 70.

The change across the life course in the impact of exposure in early life to epidemics is further investigated through an exploratory study based on empirical evidence. Cumulative hazard curves are used, as well as a looping procedure that was programmed to run the same estimation considering different upper and lower age boundaries, separately studying each epidemic. Every analysis begins in childhood, and the same estimation is repeatedly run between age one and a changing upper age boundary, which is increased by half a year at each iteration. The results obtained together with the graphical evidence are used to define the point at which the direction of the effects fluctuates, and this age is set as the lower boundary in the models of the next age group. Due to space limitations, only the final outcome of these steps is shown. These same procedures are used to study each age group and the impact of the three epidemics.

The third part of this work measures the possible variations by SES and cohort on the impact of disease exposure in infancy. With separate models for the fixed age groups 1-4, 5-19, 20-49 and 50-70 and for males and females, we introduce an interaction between disease exposure and SES at birth. This interaction allows us to observe whether the impact of these epidemics was dependent on the characteristics of the individual's family of origin. SES is included in the analysis as a dichotomous variable, considering the low (SOCPO 1-2) and medium-high

(SOCPO 3-5) categories. The individuals with an unknown SES at birth were excluded from these estimations.

The cohort changes in the impacts of exposure to disease are only evaluated for whooping cough because the number of years with measles or scarlet fever epidemics is more limited. For the fixed age groups 1-4, 5-19, 20-49 and 50-70 and for males and females separately, estimations are made for individuals born before or after 1850. This breakpoint divides the cohorts roughly in half, and also because infant mortality was much higher for the first cohorts than for the second, it can be used to compare the effects over the years when competing disease environments were rather different. Moreover, with this division, the individuals reaching the age of 15 (the common age to commence working and the age of the onset of female fecundity) before or after 1865 can be studied separately. This year represents an important dividing point in the history of this region. In fact, the period until 1864 includes the agricultural transformation, the early stages of industrialisation as well as the first phase of the demographic transition, with declining infant and child mortality (Bengtsson & Dribe, 2011). The second period was, instead, characterised by the breakthrough of industrialisation as well as by declines in adult mortality and, later, by a continued industrial expansion and the waning of the rural sector.

The last section of this work evaluates the impact of exposure in infancy to measles, scarlet fever and whooping cough on cause-specific mortality. A competing risk framework is utilised, where the death from one specific cause prevents a death from other causes from occurring. Three different types of mortality events are studied: death from airborne infectious diseases, cardiovascular diseases and diabetes, and cancers. Each failure was attributed to one of these types of mortality or to other causes (no study was conducted in relation to the latter). In cases where more than one cause of death was reported in the register, the primary cause was considered. For example, if both cancer and heart attack were indicated, then cancer was taken into account. The *stcrreg* package in STATA is used for this part of the study; it performs a competing risk regression analysis according to the model introduced by Fine and Gray (1999). Separate estimations are run for each combination of outcome variable (death cause) and explanatory variable (disease environment experienced in infancy). In every model, death due to any other cause is considered as a competing risk, and the impact of the disease load experienced in infancy is evaluated using an indicator variable comparing the specific epidemic to the reference group consisting of those born in a year with a low-medium disease load. Males and females are studied separately and, due to small numbers, this part of the work focuses only on the adult ages. The same flexible age boundaries defined through the iterative procedure described above are considered here, but the estimations are only made for those age groups

where statistically significant impacts from early life conditions on mortality are found in the other estimations conducted.

To conclude this study, a sensitivity analysis is conducted with the aim of evaluating whether the results obtained are dependent on the methodological choices adopted. The first part consists of testing possible biases arising from the fact that the individuals born in years with measles, scarlet fever and whooping cough epidemics are compared to those born in all years of low-medium disease load, regardless of the proximity of the reference years to the epidemic year. A single year with epidemics of measles, scarlet fever or whooping cough is selected, and those individuals born in this year are compared to those born some years just before or after. The reference categories in these models are individuals born after the epidemic because they should not have been exposed to it. Because the epidemics of whooping cough are more numerous, two different years are selected, one at the beginning and one at the end of the studied period. These estimations are limited by very small numbers, but nevertheless, they can show patterns that asses the validity of the previous findings. We only look at the adult ages (20-49 and 50-70).

We also evaluate whether the choice to consider the individual as having been exposed to the type of disease environment most diffused during in their year of birth within the five studied parishes even for those who were not born in these localities influences the results. For this purpose, models are estimated for only the subset of individuals born in the studied parishes or within a 17 km radius of them. The final part of the sensitivity analysis considers different control variables. For the full sample of individuals, the models are re-estimated including the decade of birth instead of the year and also excluding all control variables.

3.5 Results

3.5.1 The impact of current disease exposure on mortality in infancy

The risk of dying in the first year of life is significantly higher during epidemic years (Table 2). Relative to years with a low-medium disease load, differences of 72% for years with measles, 36% for scarlet fever, and 100% for whooping cough are observed. Boys experience significantly higher mortality than girls in the years with a low-medium disease load, but this pattern is not confirmed in connection with the three epidemics. In the years with measles epidemics, the males present relatively lower mortality than the females (1.23 x 0.68 = 0.84), while there are

Table 2: Hazard ratios of death for ages 0-1 in relation to current exposure to measles, scarlet fever or whooping cough epidemics, Scania 1813-1898

	Hazard ratio	p-value	95% C.I.
Disease environment			
Low-medium disease load (ref.)	1.00	ref.	[ref.]
Measles epidemic	1.72	0.000	[1.32,2.25]
Scarlet fever epidemic	1.36	0.102	[0.94,1.97]
Whooping cough epidemic	2.00	0.000	[1.64,2.44]
Sex			
Female (ref.)	1.00	ref.	[ref.]
Male	1.23	0.000	[1.10,1.37]
Disease environment & Sex interaction			
Measles & Male	0.68	0.045	[0.47,0.99]
Scarlet fever & Male	0.81	0.388	[0.49,1.32]
Whooping cough & Male	0.77	0.069	[0.59,1.02]

Notes: The models control for year (continuous variable) and parish.

no significant sex-differences in the years with scarlet fever (1.23 x 0.81 = 1.00) or whooping cough (1.23 x 0.77 = 0.95).

3.5.2 The impact of disease exposure in infancy on all-cause mortality by age and sex

When evaluating whether exposure to disease in infancy influences the probability of dying across stages of the life course using fixed age boundaries, different impacts are observed for each type of epidemic experienced and also for the two sexes (Table 3). Among females, between ages 1-4 a dominance of selection is seen for those born in years with scarlet fever, while the hazards are close to 1 for those exposed to measles or whooping cough. Between ages 5-19, again, notable impacts are only seen for those born in years with scarlet fever, who display a dominance of scarring. In ages 20-49, selection prevails for those born in years with epidemics of measles or scarlet fever and scarring dominates among those exposed to whooping cough, while between ages 50-70, net scarring is observed in relation to the three types of disease environments. All of these results, however, lacked statistical significance except for the impact of exposure to measles in infancy on the risk of dying in ages 50-70.

Table 3: Hazard ratios of death by age and average remaining years of life until age 70 in relation to the type of disease environment experienced in infancy – females and males, Scania cohorts 1813-1898

	Females			
	1 to 4	5 to 19	20 to 49	50 to 70
	Hazard ratios [95% C.I.]			
Low medium disease load (ref.)	ref	ref	ref	ref.
Measles	0.95	1.00	0.88	1.32*
	[0.60,1.49]	[0.60,1.65]	[0.55,1.40]	[0.96,1.81]
Scarlet fever	0.85	1.27	0.70	1.18
	[0.49,1.49]	[0.78,2.07]	[0.39,1.25]	[0.79,1.75]
Whooping cough	0.95	0.95	1.12	1.25
	[0.66,1.36]	[0.64,1.41]	[0.81,1.55]	[0.95,1.63]
	Average number of years lived until age 70			
Low-medium disease load (a)	50.88	52.55	42.53	17.72
Measles - a	0.16	0.18	-0.22	-0.75
Scarlet fever - a	6.25	2.73	3.75	1.27
Whooping cough - a	-1.18	-1.38	-1.55	-0.93
Number of individuals	5441	8667	11853	3208
Number of deaths	414	360	435	616

	Males			
	1 to 4	5 to 19	20 to 49	50 to 70
	Hazard ratios [95% C.I.]			
Low medium disease load (ref.)	ref.	ref	ref	ref.
Measles	0.88	1.01	1.22	1.08
	[0.59,1.34]	[0.62,1.66]	[0.82,1.82]	[0.76,1.52]
Scarlet fever	0.77	1.09	1.48*	0.94
	[0.48,1.26]	[0.64,1.87]	[0.95,2.31]	[0.61,1.46]
Whooping cough	0.71*	0.92	1.43**	1.38**
	[0.50,1.02]	[0.63,1.35]	[1.08,1.91]	[1.08,1.76]
	Average number of years lived until age 70			
Low-medium disease load (a)	50.46	52.97	42.7	17.53
Measles - a	-0.45	-0.99	-1.18	-0.1
Scarlet fever - a	-3.79	-3.94	-4.04	-0.49
Whooping cough - a	-0.11	-2.42	-3.07	-1.03
Number of individuals	5743	8541	11100	3148
Number of deaths	485	344	416	583

Notes: The models control for the year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or immigrated there. The average number of years lived until age 70 (for individuals surviving until ages 1, 5, 20, 50) were calculated from the values of average longevity obtained as the integral of the survival functions estimated using Kaplan-Meier estimators. Estimators are adjusted for year of birth, centred in 1855. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

For males, selection dominates between ages 1-4 for those exposed to all three different types of disease environments, and these effects are statistically significant for those born in years with whooping cough. The magnitudes of the impacts

are, instead, always close to unity between ages 5-19. Between ages 20-49, the statistically significant dominance of scarring is observed for those exposed in infancy to scarlet fever and between ages 20-49 and 50-70 for those exposed to whooping cough. Higher but not statistically significant rates of mortality are also seen between ages 20-49 for those born in a year with measles.

Comparing the results by sex, the primary differences appear during adulthood. In fact, between ages 20-49, the females exposed to measles or scarlet fever show a dominance of net selection, while the males show a prevalence of scarring. Table 4 shows that the interactions between sex and disease exposure were statistically significant only for scarlet fever. In relation to exposure to whooping cough, a dominance of scarring is observed for both gender groups in these ages, with stronger impacts for males.

When evaluating the impact of exposure to disease in infancy in terms of the differences in the average number of years lived, between ages 1 and 70 for females, the greatest loss in years of life is observed for those who were exposed in infancy to whooping cough, while for males, the greatest loss is seen for those born in years with scarlet fever (Table 3). Whooping cough shortens the lives of females by 1.2 years between ages 1-70, for those surviving to age 20 by 1.6 years and by 0.9 years for those surviving to age 50. For males, the difference is rather meagre at age 1, but it is 3.1 years for those surviving to age 20 and 1 year for those surviving to age 50. The average remaining years of life until age 70 among males exposed to measles is 1.2 years shorter after age 20, but the difference is very small for those surviving to age 50. Instead, females do not present large differences at age 20, but for those surviving to age 50, a penalty of 0.8 years is observed. The impacts on life expectancy are rather large and gender specific in connection to scarlet fever. Between ages 1-70, females show an average of 6.3 more years of life than those who were not exposed, while males live 3.8 years less. A reduction of approximately 4 years is also observed for men surviving until age 20.

The estimations conducted using flexible age boundaries for each life course stage follow similar patterns as those described above, although here it is possible to better distinguish the specific ages where the patterns of the effects fluctuated. During the childbearing and working ages, selection dominated for females and scarring for males who were born in a year with measles or scarlet fever epidemics (Figure 1). More specifically, women exposed to measles experience a 46% lower risk of dying between ages 27-47.5 and a 34% higher risk from ages 47.5-70, both statistically significant. In relation to the same disease, men present higher but not statistically significant risks, with differences of 30% between ages 24-50 and 7% between ages 50-70.

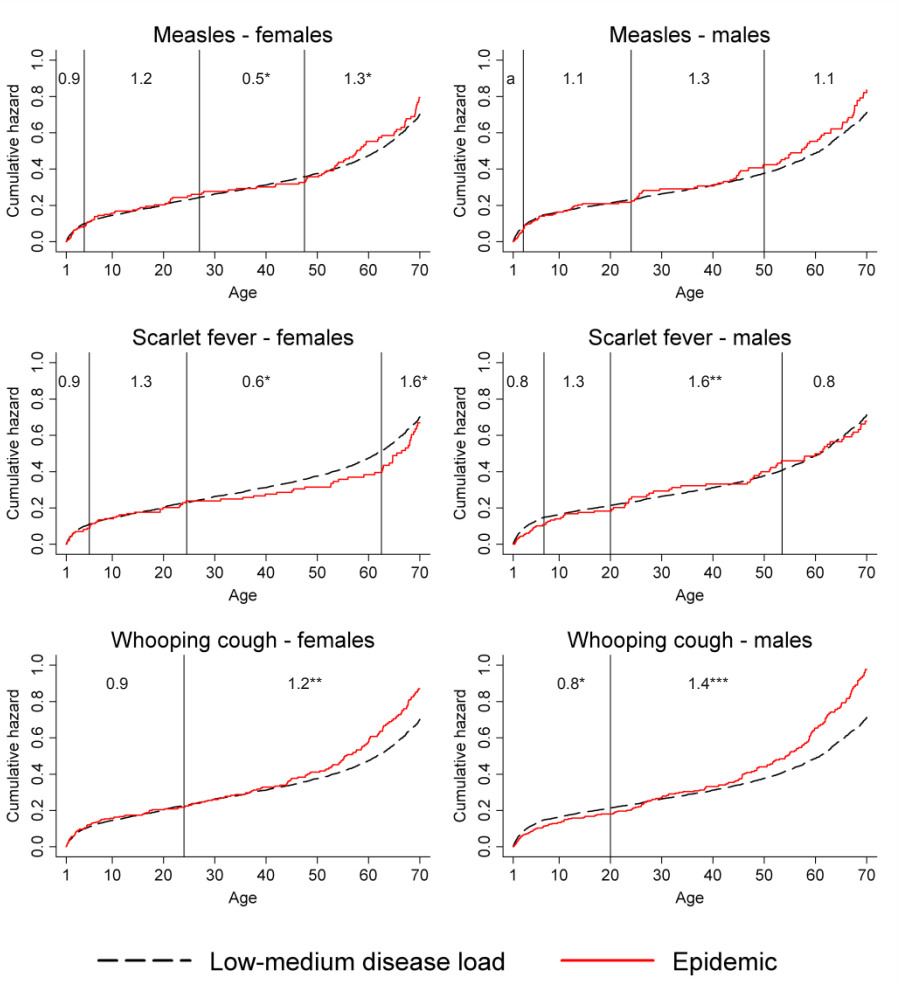
Table 4: Hazard ratios of death by age and average remaining years of life until age 70 in relation to the type of disease environment experienced in infancy – sex interactions, Scania cohorts 1813-1898

	All individuals			
	1 to 4	5 to 19	20 to 49	50 to 70
	Hazard ratios [95% C.I.]			
Low medium disease load (ref.)	ref.	ref	ref	ref
Measles	0.96	0.96	0.86	1.31*
	[0.61,1.51]	[0.58,1.59]	[0.54,1.37]	[0.95,1.80]
Scarlet fever	0.85	1.24	0.71	1.19
	[0.49,1.48]	[0.76,2.03]	[0.40,1.27]	[0.80,1.77]
Whooping cough	0.97	0.93	1.09	1.23
	[0.68,1.40]	[0.63,1.37]	[0.79,1.51]	[0.94,1.59]
Females	1.00	1.00	1.00	1.00
Males	1.18**	0.92	0.95	1.06
	[1.02,1.36]	[0.79,1.09]	[0.82,1.10]	[0.93,1.20]
Measles & males	0.92	1.04	1.41	0.82
	[0.50,1.69]	[0.52,2.10]	[0.76,2.59]	[0.51,1.31]
Scarlet fever & males	0.91	0.88	2.01*	0.77
	[0.44,1.91]	[0.43,1.82]	[0.97,4.16]	[0.43,1.39]
Whooping cough & males	0.72	0.98	1.31	1.11
	[0.43,1.19]	[0.57,1.68]	[0.86,2.01]	[0.78,1.58]
	Average number of years lived until age 70			
Low-medium disease load (a)	50.66	52.76	42.61	17.63
Measles - a	-0.06	-0.32	-0.62	-0.43
Scarlet fever - a	1.81	-0.17	0.61	0.65
Whooping cough - a	-0.70	-1.95	-2.36	-1.00
Number of individuals	11184	17208	22953	6356
Number of deaths	899	704	851	1199

Notes: The models control for the year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or immigrated there. The average number of years lived until age 70 (for individuals surviving until ages 1, 5, 20, 50) were calculated from the values of average longevity obtained as the integral of the survival functions estimated using Kaplan-Meier estimators. Estimators are adjusted for year of birth, centred in 1855. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Among those born in a year with a scarlet fever epidemic, for females, the probabilities of dying are 39% lower between ages 24.5-62.5 and 64% higher between ages 62.5-70, both statistically significant. Among exposed men, the probabilities of dying are 61% (statistically significant) between ages 20-53.5, followed by a non-significant dominance of selection. The patterns related to exposure to whooping cough are more homogenous across the two sexes. Being born in a year with this epidemic resulted in a dominance of selection until early adulthood (statistically significant only for males, who show 20% lower probability of dying), followed by statistically significant dominance of scarring, with differences of 24% between ages 24-70 for females and 39% between ages 20-70 for males.

Figure 1: Cumulative hazard of death by disease environment experienced in infancy, Scania cohorts 1813-1898



Notes: The figures are raw estimates of the cumulative hazards. The results of Cox proportional hazard models which evaluate the risk of dying for individuals born in a year with epidemic relative to those born in a year with low-medium disease load (controlling for year of birth, parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them) are also shown by indicating the coefficient obtained as well as the statistical significance (* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$). a = 0.7. Separate models were constructed for distinct age groups, and these divisions are shown in the graph through vertical lines.

Table 5: Hazard ratios of death by age and sex, introducing an interaction between exposure to epidemics in infancy and SES at birth, Scania cohorts 1813-1898

	Females				Males			
	1 to 4	5 to 19	20 to 49	50 to 70	1 to 4	5 to 19	20 to 49	50 to 70
Low medium disease load	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Measles	0.85	1.29	0.93	1.21	1.15	1.40	1.76*	1.39
	[0.42,1.73]	[0.60,2.78]	[0.43,2.00]	[0.70,2.09]	[0.68,1.95]	[0.71,2.78]	[0.96,3.21]	[0.81,2.36]
Scarlet fever	1.43	1.26	1.26	1.29	1.16	0.72	1.25	1.04
	[0.73,2.81]	[0.51,3.12]	[0.59,2.71]	[0.63,2.63]	[0.61,2.19]	[0.23,2.27]	[0.55,2.86]	[0.51,2.12]
Whooping cough	0.99	1.51	1.05	1.45*	0.77	0.86	0.80	1.05
	[0.58,1.69]	[0.84,2.70]	[0.60,1.83]	[0.96,2.18]	[0.47,1.27]	[0.45,1.66]	[0.42,1.49]	[0.69,1.60]
Low birth SES	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Medium-high birth SES	0.87	0.91	0.91	1.08	0.85	0.85	0.92	0.96
	[0.68,1.12]	[0.67,1.23]	[0.70,1.18]	[0.87,1.33]	[0.67,1.06]	[0.63,1.16]	[0.69,1.23]	[0.77,1.19]
Medium-high SES & measles	1.30	0.81	0.98	1.21	0.65	0.52	0.38	0.63
	[0.45,3.69]	[0.23,2.88]	[0.30,3.18]	[0.56,2.62]	[0.25,1.73]	[0.14,1.99]	[0.12,1.22]	[0.28,1.41]
Medium-high SES & scarlet fever	0.40	0.78	0.34	0.86	0.62	0.73	0.79	0.94
	[0.11,1.51]	[0.20,3.00]	[0.07,1.67]	[0.32,2.36]	[0.21,1.87]	[0.12,4.47]	[0.22,2.89]	[0.34,2.57]
Medium-high SES & whooping cough	0.70	0.64	1.26	0.80	1.08	0.74	1.78	1.22
	[0.29,1.72]	[0.24,1.68]	[0.56,2.85]	[0.43,1.50]	[0.50,2.35]	[0.24,2.26]	[0.79,4.00]	[0.68,2.20]
Number of individuals	3481	3201	5504	2096	3716	3152	5287	2095
Number of deaths	306	211	278	436	374	201	249	429

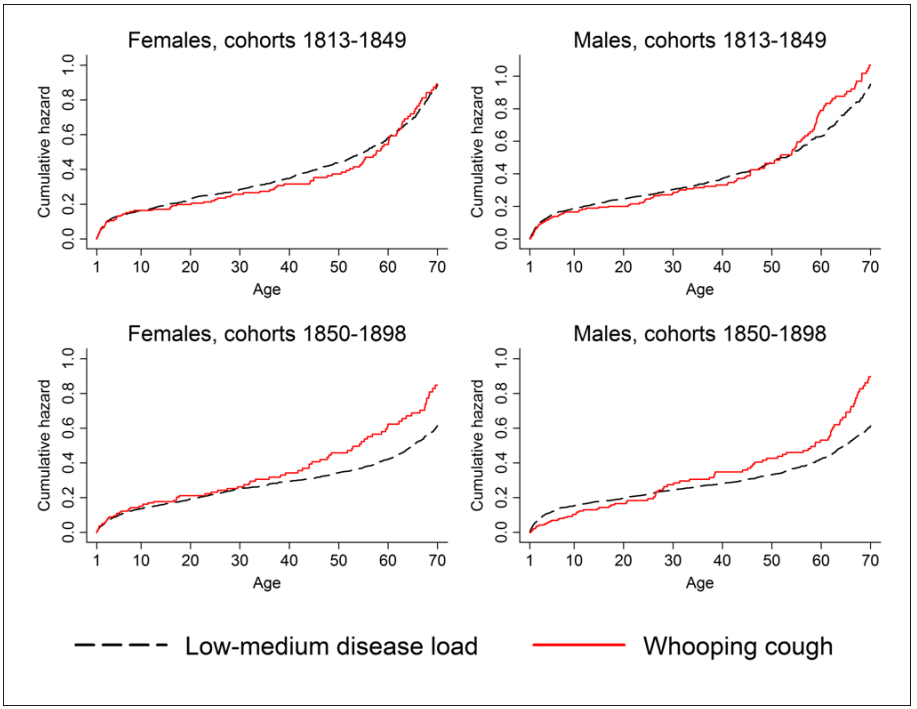
Notes: The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. Individuals with unknown SES at birth were excluded from the models. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals in brackets

3.5.3 SES and cohort changes in the impact of disease exposure in infancy on all-cause mortality over the life course

Table 5 shows the results of estimations that include, for fixed age groups, an interaction between the indicator of disease exposure in infancy and the SES of the family of origin of each individual. Although some of the coefficients differ from 1, none of the interaction terms are statistically significant, indicating that there were no large differences in the impact of exposure to disease according to the characteristics of the families in which individuals were born.

Instead, variations by cohorts are observed in relation to the impact of whooping cough epidemics. As seen when comparing the cumulative hazard curves (Figure 2), for those born before 1850, the scarring effects become dominant at later ages than they do for the men and women born before this year, especially for females, where selection prevailed until after age 50. When conducting estimations for fixed age groups (Table 6), among females born in 1813-1849, hazard ratios below 1 are observed until age 49, while a prevalence of scarring is seen in ages 50 to 70.

Figure 2: Cumulative hazard of death for individuals exposed in infancy to whooping cough or to a low-medium disease load, Scania cohorts 1813-1849 and 1850-1898



Notes: the figures are raw estimates of the cumulative hazards.

Table 6: Hazard ratios of death by age and sex for individuals born in 1813-1849 and 1850-1898 exposed in infancy to whooping cough

BORN 1813-1849	Females				Males			
	1 to 4	5 to 19	20 to 49	50 to 70	1 to 4	5 to 19	20 to 49	50 to 70
Exposure to whooping cough	0.85	0.79	0.90	1.16	0.95	0.69	1.15	1.30
	[0.52,1.39]	[0.43,1.44]	[0.57,1.43]	[0.82,1.65]	[0.60,1.49]	[0.39,1.24]	[0.78,1.69]	[0.93,1.81]
Number of individuals	1586	2593	3474	930	1606	2609	3483	887
Number of deaths	162	115	168	246	170	120	169	217

BORN 1850-1898	Females				Males			
	1 to 4	5 to 19	20 to 49	50 to 70	1 to 4	5 to 19	20 to 49	50-70
Exposure to whooping cough	1.04	1.11	1.53*	1.43*	0.50**	1.20	1.88***	1.47**
	[0.61,1.75]	[0.67,1.85]	[0.97,2.39]	[0.95,2.16]	[0.27,0.91]	[0.73,1.99]	[1.23,2.87]	[1.02,2.13]
Number of individuals	3388	5355	7318	1974	3612	5217	6574	1956
Number of deaths	219	212	236	303	274	193	200	310

Notes: The models control for year of birth (continuous variable), parish, and an indicator of whether the individual was born in one of the studied parishes or migrated to them. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals in brackets

For men born in the same years, the impact of scarring is larger for ages 20 to 49 and 50 to 70. The results for these cohorts lack statistical significance. For females born in 1850-1898, instead, the prevalence of scarring is seen for all age groups considered, and such effects were statistically significant between the ages 20-49 and 50-70. For men, instead, a significant dominance of selection is seen for ages 1 to 4, followed by greater impacts of scarring, with effects of strong magnitude and statistical significance for the age groups 20-49 and 50-70. If the estimations are made considering all individuals within the same model and introducing an interaction between the indicators of whooping cough exposure and the cohort (1813-1849 or 1850-1898), the interaction term was higher than one in all of the models except for males between ages 1-4 (results not shown). Statistical significance was observed for the interaction term in the age group 20-49 for both males and females. These patterns therefore support the change across cohorts that was identified in Figure 2 and Table 6.

3.5.4 The impact of disease exposure in infancy on cause-specific mortality in adulthood

Competing risk regressions are estimated here to study the probability of dying from airborne infectious diseases, cardiovascular diseases and diabetes, and cancer. These estimations are performed separately for each disease exposure but only for the age groups where statistically significant impacts were observed in Figure 1. The results of this study are shown in Table 7. In some cases, the estimations could not be computed due to a small number of deaths. Additionally, because of the small numbers, many of the results lack statistical significance. Regardless of their p-values, the direction of the coefficients is helpful for describing general patterns.

Females born in the years with measles epidemics had a reduced risk of dying from airborne infectious diseases between ages 27.5-47.5 and an increased risk of death from all three causes between ages 47.5-70. Between ages 24.5-63.5, those exposed to scarlet fever had a reduced likelihood of dying from airborne infectious diseases but increased probabilities of death from cardiovascular diseases and diabetes and cancer. Between ages 63.5-70, females presented higher risks of dying from airborne infectious diseases and cardiovascular diseases and diabetes. Between ages 24-70, women born in the years with whooping cough epidemics show a higher likelihood of death from airborne infectious diseases or cancer and, to a lesser extent, also from cardiovascular disease and diabetes. However, none of the results for females are statistically significant.

Table 7: Subhazard ratios of death from airborne infectious diseases, cardiovascular diseases and diabetes or cancer according to the type of disease environment experienced in infancy, Scania cohorts 1813-1898

	Airborne infectious diseases	Cardiovascular diseases & diabetes	Cancer
Measles			
Females ages 27.5-47.5	0.25	N/A	N/A
Females ages 47.5-70	1.49	1.41	1.29
Scarlet fever			
Females ages 24.5-63.5	0.56	1.30	1.56
Females ages 63.5-70	1.20	1.48	0.90
Males ages 20-53.5	1.12	4.52***	2.43
Whooping cough			
Females ages 24-70	1.29	1.12	1.44
Males ages 20-70	1.62**	1.56	0.92

Notes: Each result shown was obtained through a different estimation model. N/A = not estimated due to small numbers. The age and gender groups considered here are those used in Figure 1. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Between ages 20 to 53.5, males exposed in infancy to scarlet fever present increased probabilities of dying from all three diseases, particularly for cancer and cardiovascular diseases and diabetes, where statistical significance is also observed. Those born in years with whooping cough epidemics show higher mortality from airborne infectious diseases and cardiovascular diseases and diabetes; only the first of these results is statistically significant.

3.5.5 Sensitivity analysis

All of the results obtained in the sensitivity analysis show that the earlier findings are not limited by the methodological choices adopted. When estimating models that evaluate the hazard of dying for individuals born in one of the specific epidemic years relative to those born after it (Table 8), the patterns for the results are very similar to those presented in the previous section (Figure 1 and Table 3). The sex differences seen earlier in the impact of measles and scarlet fever during adulthood are still found here because females present a dominance of net selection while males present a prevalence of net scarring. More homogenous patterns by gender are seen in relation to whooping cough both here and earlier, and the impact is strong, particularly for later born cohorts. The effects of the whooping cough epidemic of 1816 are similar to those observed when conducting estimations for individuals born in 1813-1849 (selection in early adulthood followed by scarring in old age), while those of the whooping cough epidemic of

Table 8: Hazard ratios of death by age and sex for individuals born in single epidemic years or surrounding years

	Females		Males	
	20-49	50-70	20-49	50-70
	MEASLES EPIDEMIC OF 1821			
After epidemic (1823 & 1824)	ref.	ref.	ref.	ref.
Epidemic (1821)	0.55	1.53	2.45*	0.86
	[0.16,1.94]	[0.71,3.26]	[0.89,6.75]	[0.37,2.00]
Before epidemic (1818 & 1819)	0.82	0.86	1.85	0.98
	[0.35,1.91]	[0.44,1.65]	[0.69,4.93]	[0.47,2.07]
N individuals	532	140	518	126
N deaths	25	46	28	37
	SCARLET FEVER EPIDEMIC OF 1869			
After epidemic (1871 & 1872)	ref.	ref.	ref.	ref.
Epidemic (1869)	0.70	1.43	3.95***	0.51
	[0.22,2.16]	[0.61,3.37]	[1.46,10.69]	[0.19,1.35]
Before epidemic (1866 & 1867)	0.70	1.52	1.86	0.70
	[0.28,1.78]	[0.76,3.05]	[0.68,5.14]	[0.36,1.35]
N individuals	851	222	738	214
N deaths	23	40	27	41
	WHOOPING COUGH EPIDEMIC OF 1816			
After epidemic (1818 & 1819)	ref.	ref.	ref.	ref.
Epidemic (1816)	0.63	1.18	0.75	1.48
	[0.17,2.34]	[0.55,2.55]	[0.26,2.12]	[0.69,3.17]
Before epidemic (1814 & 1815)	1.57	0.98	1.04	1.29
	[0.69,3.59]	[0.49,1.99]	[0.45,2.40]	[0.64,2.61]
N individuals	487	142	496	122
N deaths	27	42	27	43
	WHOOPING COUGH EPIDEMIC OF 1894			
After epidemic (1897 & 1898)	ref.	ref.	ref.	ref.
Epidemic (1894)	1.83	2.23**	14.79**	1.61
	[0.74,4.50]	[1.06,4.69]	[1.82,120.31]	[0.72,3.60]
Before epidemic (1890 & 1891)	1.29	1.18	5.74	1.04
	[0.56,2.98]	[0.57,2.46]	[0.67,49.14]	[0.49,2.23]
N individuals	966	272	827	251
N deaths	31	42	13	37

Notes: The models do not control for any variables. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals in brackets.

1894 are similar to the effects found for individuals born in 1850-1898 (scarring from early adulthood).

If the models are estimated only selecting individuals born in the studied parishes or within a 17 km radius of them, even if the magnitude as well as the statistical significance of some of the coefficients change (usually presenting stronger effects), the patterns of the results remain unchanged (Table 9). When conducting

Table 9: Hazard ratios of death by age and sex according to the type of disease environment experienced in infancy for individuals born in the studied parishes or within a 17 km radius of them, Scania cohorts 1813-1898

FEMALES	1 to 4	5 to 19	20 to 49	50 to 70
Low medium disease load	ref.	ref.	ref.	ref.
Measles	0.89	1.07	0.89	1.77***
	[0.55,1.43]	[0.64,1.81]	[0.51,1.56]	[1.23,2.55]
Scarlet fever	0.85	1.30	0.74	1.26
	[0.47,1.51]	[0.78,2.15]	[0.36,1.50]	[0.75,2.13]
Whooping cough	0.87	1.17	1.19	1.15
	[0.59,1.28]	[0.79,1.73]	[0.80,1.77]	[0.81,1.64]
Number of individuals	4873	6567	6531	1688
Number of deaths	387	325	280	385
MALES	1 to 4	5 to 19	20 to 49	50 to 70
Low medium disease load	ref.	ref.	ref.	ref.
Measles	0.89	1.06	1.09	0.90
	[0.58,1.36]	[0.64,1.76]	[0.65,1.82]	[0.57,1.42]
Scarlet fever	0.84	1.04	1.63	0.79
	[0.52,1.37]	[0.58,1.86]	[0.90,2.93]	[0.40,1.53]
Whooping cough	0.73*	0.87	1.44**	1.50***
	[0.50,1.06]	[0.57,1.33]	[1.01,2.03]	[1.11,2.04]
Number of individuals	5191	6640	6317	1649
Number of deaths	451	296	269	361

Notes: The models control for year of birth (continuous variable) and parish. 95% confidence intervals in brackets; * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

estimations for the full sample of individuals but considering different controls in the models (Table 10), the results also remain constant. If all controls are removed from the models, the effect of exposure to whooping cough in infancy becomes stronger for females between ages 50-70 and for males between ages 20-50 and 50 to 70.

3.6 Discussion

Using data from southern Sweden for the 1813 to 1968 period, this work analysed, distinguishing by gender and age, the impact on mortality of exposure in early life to measles, scarlet fever and whooping cough. These epidemics were defined by identifying the years that had high infant mortality rates and by specifying for these years the most common cause of death among children. Exposure to these epidemics was therefore exogenous.

Table 10: Hazard ratios of death by age and sex according to the type of disease environment experienced in infancy when changing control variables, Scania cohorts 1813-1898

	Females				Males			
	1 to 4	5 to 19	20 to 49	50 to 70	1 to 4	5 to 19	20 to 49	50 to 70
	Considering birth decade instead of birth year							
Low medium disease load	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Measles	0.95	1.00	0.89	1.34*	0.89	1.02	1.24	1.10
	[0.61,1.50]	[0.60,1.65]	[0.56,1.41]	[0.97,1.84]	[0.59,1.35]	[0.62,1.67]	[0.83,1.85]	[0.78,1.55]
Scarlet fever	0.86	1.27	0.69	1.18	0.77	1.08	1.48*	0.94
	[0.49,1.49]	[0.78,2.07]	[0.39,1.24]	[0.79,1.75]	[0.47,1.25]	[0.63,1.86]	[0.95,2.30]	[0.60,1.46]
Whooping cough	0.95	0.95	1.13	1.24	0.72*	0.93	1.43**	1.38**
	[0.66,1.36]	[0.64,1.41]	[0.82,1.56]	[0.95,1.62]	[0.50,1.02]	[0.63,1.36]	[1.07,1.90]	[1.08,1.77]
	Excluding all control variables							
Low medium disease load	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Measles	0.98	1.01	0.92	1.36*	0.94	1.06	1.33	1.23
	[0.62,1.53]	[0.61,1.67]	[0.58,1.46]	[0.99,1.88]	[0.62,1.42]	[0.65,1.74]	[0.89,1.99]	[0.88,1.74]
Scarlet fever	0.78	1.21	0.67	1.07	0.73	1.06	1.35	0.85
	[0.45,1.36]	[0.74,1.97]	[0.38,1.19]	[0.72,1.58]	[0.45,1.19]	[0.62,1.80]	[0.87,2.10]	[0.55,1.31]
Whooping cough	1.03	0.97	1.21	1.45***	0.77	0.97	1.64***	1.64***
	[0.72,1.47]	[0.66,1.44]	[0.88,1.67]	[1.11,1.88]	[0.54,1.09]	[0.67,1.42]	[1.24,2.17]	[1.29,2.09]
Number of individuals	5441	8667	11853	3208	5743	8541	11100	3148
Number of deaths	414	360	435	616	485	344	416	583

Notes: 95% confidence intervals in brackets; * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

When conducting a preliminary study measuring the probability of dying for ages 0-1, during years of measles, the boys had lower mortality than the girls. This result could be related to the fact that girls lose maternal measles antibodies more rapidly than boys (Martins et al., 2009). These types of different selective mechanisms could possibly explain why in early adulthood, females had a lower probability of dying if they were exposed in infancy to this disease, while males showed a somewhat increased risk. Statistical significance, however, was not obtained for these impacts for males nor for the interaction term between gender and measles exposure. Some indication of lower risks of dying from airborne infectious diseases was observed for the females exposed in infancy to this disease. In historical populations, the deaths from tuberculosis that were linked to pregnancy were very common. Tuberculosis is caused by the bacteria *mycobacterium tuberculosis*, and although direct immunity cannot be conferred from previous measles infections, there may be effects of heterologous immunity or links between infections and autoimmune responses (for heterologous immunity see e.g., Selin et al., 2002; Welsh et al., 2010). In old age, instead, significant impacts were only found for females, who showed a dominance of scarring. No variations according to the SES of the family of origin were found for males and females exposed to this disease in infancy.

Boys and girls did not present statistically significant differences in their risk of dying in infancy during years with scarlet fever. Nevertheless, strong and statistically significant sex differences were found in the probabilities of dying during childbearing and working ages for the individuals born in years with these epidemics. Males, in fact, presented a higher risk of death relative to their peers born in years with a low-medium disease load, while females showed relatively lower probabilities. Exposure to scarlet fever could therefore lead to some sex-specific biological mechanisms that affect later life health. During early adulthood, some indications of reduced mortality from airborne infectious diseases were observed for women, which could have also been related to fewer deaths from tuberculosis in connection with pregnancy, as described above. In old age, significant impacts were only found among females, who showed a prevalence of scarring, but only at rather advanced ages. No variations according to the SES of the family of origin were found for males and females exposed to this disease in infancy.

In years with whooping cough, the risk of death for infants was double that of years with a low-medium disease load, and no large differences in these effects were seen between boys and girls. The strong selection that took place in the first year of life explains why the mortality rates were lower until early adulthood for the individuals exposed to this disease in infancy, particularly for males. From early adulthood, instead, a strong dominance of scarring was observed for both sex groups. Moreover, no significant differences were seen on the impact of this disease

according to the SES at birth, indicating that the impacts of whooping cough on mortality were purely biological and are not related to specific characteristics of the individual's family of origin. From early adulthood, the males exposed to this disease in infancy presented some indications of higher mortality from airborne infectious diseases and cardiovascular diseases and diabetes, and the females from airborne infectious diseases, cancer, and to a lesser extent cardiovascular diseases and diabetes. Although partly due to small numbers, only the result relating to the deaths from airborne infectious diseases for males was statistically significant, these calculations show that the mechanisms linking early life exposure to whooping cough to later life mortality may be related to direct damage to the respiratory system, to the development of autoimmune diseases or perhaps also to inflammatory processes. The results obtained are also consistent with the previous work conducted by other authors that showed a greater prevalence of lung impairments and diabetes among individuals exposed in early life to whooping cough (e.g., Barker et al., 1991; Jedrychowski et al., 2002; Montgomery et al., 2002; Swansea Research Unit of the Royal College of General Practitioners, 1985; Swansea Research Unit of the Royal College of General Practitioners, 1987).

When confronting the impact of exposure to whooping cough for individuals born before or after 1850, stronger effects were observed for the second cohort, where scarring dominated from a much earlier age than for the first cohort. These patterns could be explained by the fact that before 1850, infant mortality rates were higher than they were after this year, and consequently, the first cohorts could have perceived damage to their body even if they were born in years defined as having a low-medium disease load, resulting in compromised later life health. Instead, the relative impact of whooping cough was more severe during epochs when competing disease environments were weaker. Moreover, these different effects may be related to the change observed across history from the prevalence of infectious diseases to that of chronic diseases as determinants of morbidity and mortality in old age (see e.g., Omran, 2005).

3.7 Conclusions

Although limited by the fact that the yearly averages of infant mortality and of causes of death among children were considered to define each type of disease environment rather than nominative data on infections, this work contributes to the literature by examining the distinct impact of exposure to specific epidemics in infancy, utilising a sex as well as a life course perspective. The strong associations

that were identified between exposure to different disease environments and mortality over certain stages of the life course provide a better understanding of which epidemics leave damage to the body and at which ages the consequences of these effects are more important. Because epidemics were defined by considering exogenous shocks, this work also makes a contribution by trying to establish causal mechanisms.

The impacts of exposure in infancy to measles or scarlet fever were less defined and presented sex-specific patterns during the childbearing and working ages, which were statistically significant in the case of scarlet fever. Although the reduced mortality of females could perhaps be explained by fewer deaths from airborne infectious diseases related to pregnancies, further research is required to try to observe whether similar patterns are replicated in other populations that may have more extensive data availability for these disease exposures and to also determine the possible underlying mechanisms causing these effects. The impact of exposure to whooping cough in infancy was, instead, more universal and showed a prevalence of scarring for all sex and SES groups from early adulthood, particularly in relation to greater mortality from airborne infectious diseases, cardiovascular diseases and diabetes. The relative effect of exposure to whooping cough was stronger for the cohorts born after 1850 than for those born before this year, possibly due to weaker competing disease environments in infancy or to changes in the patterns of morbidity in later life.

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Chapter 4

The impact of early life conditions on offspring sex ratio at birth by socioeconomic status in 19th and 20th century Southern Sweden

4.1 Abstract

The importance of early life conditions for later life health and wellbeing has been known for many years. However, there are not many studies that examine the effect of early life conditions during the childbearing and working years and, in particular, the literature focusing on female reproductive health is scant and often inconclusive. Using data from the Scanian Economic Demographic Database for women born between 1813 and 1898, this work evaluates whether exposure to high grain prices during a woman's foetal stage or to high infant mortality rates or whooping cough epidemics in her first year of life affect her offspring sex ratios at birth. We find that women of low socioeconomic status who were exposed in infancy to whooping cough gave birth to a lower proportion of boys, probably as a result of a higher incidence of the spontaneous abortions of male foetuses. Due to this selection *in-utero*, the male offspring of mothers exposed to this disease experience relatively lower neonatal mortality, while the female offspring show greater risks of dying during this stage. No significant effects on the sex ratio at birth are observed in relation to early life disease exposures for women of high socioeconomic status or for all women in connection to high prices.

4.2 Introduction

Broad attention has been given in the recent literature to the understanding of how early life conditions influence later life outcomes. It has been shown that

the level of nutrition and the disease load experienced during the foetal stage and infancy are associated with the development of chronic diseases later in life (for nutrition see for example: Almond & Currie, 2011; Barker, 1994; 1995a; 1995b; 1997; 2001; for inflammation see for example: Bengtsson & Lindström, 2000; 2003; Finch & Crimmins, 2004; Liuba, 2003), as well as with attainments in education (Almond, 2006; Case & Paxson, 2010; Palloni et al., 2009), height (Bozzoli, Deaton, & Quintana-Domeque, 2009; Chen & Zhou, 2007; Steckel, 2008) and socioeconomic status (Almond, 2006; Bengtsson & Broström, 2009).

Early life conditions can affect the health and wellbeing of individuals over their entire life course. Much of the existing literature, however, focuses on establishing linkages with the development of chronic diseases in old age, and aside from education, socioeconomic status (SES) and height, not much is known about the possible effects during the childbearing and working ages. Mortality in early adulthood is low, and therefore to better evaluate the impacts of early life conditions during these stages and to be able to make policy recommendations, other indicators of health need to be considered. Female reproductive health serves as a good measure, particularly characteristics such as offspring birth weight, neonatal mortality and sex ratio at birth. Fecundity is, instead, difficult to study, because it is determined by a mixture of biological as well as behavioural factors, and consequently the pure effect of early life conditions cannot always be identified. Maternal mortality can also be considered, but this rate is usually very low.

The literature evaluating possible influences from early life conditions on reproductive health is scant and inconclusive. Many of the existing studies concentrate on measuring the effects of nutrition during gestation on fecundity, and there are no works evaluating whether exposure to disease in infancy affects female reproductive health. Among other things, previous studies show that low birth weight results in a higher age at first birth (Ekholm et al., 2005) and reduced fecundity (Ekholm et al., 2005; Nohr et al., 2009), that prenatal exposure to famine is associated with a lower offspring birth weight and higher perinatal mortality (Lumey & Stein, 1997) and that for individuals born into landless families, but not into landed ones, the crop yield during the year of birth influences marriage probabilities, fecundity and offspring viability and survival to adulthood (Rickard et al., 2010).

The average sex ratio at birth for humans is around 105 males per 100 females, although variations occur both between and within populations (Sieff et al., 1990). The sex ratio at birth depends on the sex ratio at conception – or the primary sex ratio – and on the sex-specific foetal mortality (Tremblay et al., 2003), therefore making it an important measure of the reproductive health of populations (Allan et al., 1997). Different scholars have concentrated on establishing which characteristics around the time of successful insemination and during gestation can affect the

sex ratio at conception and the sex-specific foetal mortality, thus influencing the sex ratio at birth. The main frame of research includes the hormonal hypothesis developed by James (1971; 1980; 1987a; 2010; 1982), which focuses on the role of parental hormonal levels around the time of conception, and the works of Catalano (Catalano, Bruckner, Anderson et al., 2005; 2005; 2005; 2006; 2008; Catalano, 2003; Catalano & Bruckner, 2005), which describe how exposure to a variety of stressors during gestation could result in sex-selective foetal wastage. These ideas are consistent with the concepts introduced by evolutionary theorists, who state that alterations in the sex ratio take place as a process of evolution, where organisms adapt to environmental changes to increase reproductive success (Williams & Gloster, 1992). The hypothesis introduced by Trivers and Willard (1973), in fact, relates the sex ratio at birth to natural selection, stating that the highest number of grand-offspring is achieved when more sons are produced by parents experiencing above-average conditions and more daughters by those facing poor conditions. The sons of mothers in good conditions can, in fact, produce more offspring than their sisters, while the opposite is true for the sons of mothers in poor conditions (Trivers & Willard, 1973).

Aside from being influenced by current conditions, the sex ratio at birth can also be affected by the repercussions of adverse exposures in a woman's early life through selection in terms of survival to adulthood and entry into motherhood, through scarring in terms of possible damage to organs and systems of the body as well as through epigenetic inheritance. However, there are not many works that evaluate the impact of nutrition or exposure to disease during a woman's foetal stage and infancy on the sex ratio at birth of her offspring. An exception is a study based on historical French Canadian data, which finds that the sex ratio at birth is associated with the season of birth of the offspring and even more strongly with that of the mother (Nonaka et al., 1999).

Using data from the Scanian Economic Demographic Database (SEDD) for women born between 1813 and 1898, this work attempts to contribute to the literature by analysing the effects of early life exposures on the sex ratio at birth of a woman's offspring. We consider as exogenous indicators of the level of nutrition experienced during gestation and the disease load perceived in infancy whether the woman was conceived in a year with high grain prices or born in a year with a high infant mortality rate (IMR), respectively. Exposure to disease is measured generally as well as specifically to epidemics of whooping cough. These indicators had shown important patterns when their impact on mortality was evaluated. In Chapter 3, in fact, it was shown that from early adulthood, the women born in years with whooping cough epidemics had higher rates of mortality than those born in the years with a low-medium disease load, therefore indicating the dominance of scarring. Instead, during the childbearing and working ages, in Chapter 2 the

women who were conceived in years with high prices or born in years with measles or scarlet fever epidemics presented a relatively lower probability of dying than those conceived or born in more favourable years, hence showing the prevalence of selection.

4.3 Background

The early life literature defines 'selection' and 'scarring' as two pathways through which adverse exposures during the foetal stage and infancy can affect later life health (Preston, Hill, & Drevenstedt, 1998). Both of these pathways can explain possible associations between the conditions experienced during a woman's development and reproductive health, of which the offspring sex ratio at birth is an important measure.

When exposed to adverse early life conditions, only the strongest women may survive until reproductive ages. These selected women would therefore experience better health during these stages than their peers who faced more favourable situations in their growth. However, selection could also affect reproduction negatively. For example, the length of the reproductive lifespan can be shortened by diseases developed during adulthood, which may have their origin in early life (Lummaa & Tremblay, 2003). Furthermore, adverse experiences could impact educational outcomes, SES, the probability of marriage, partner selection, entry to motherhood and total fertility, which are all factors that are important determinants of the reproductive health of a couple.

However, direct damaging effects on the individuals' health, or scarring, may result from malnutrition during gestation, as is stated by the 'foetal origins hypothesis' (Barker, 1994; 1995a; 1995b; 1997; 2001), or may result from exposure to disease in the first year of life, as is claimed by the 'infancy inflammation hypothesis' (for inflammation see for example: Bengtsson & Lindström, 2000; 2003; Finch & Crimmins, 2004; Liuba, 2003). The foetal stage and the first year of life are the periods with the most rapid development of organs and cells. According to the 'critical period model' introduced by Ben-Shlomo and Kuh (2002; 2004), exposures during these stages leave permanent damage to the body that cannot be reversed by later experiences and that lead to the development of chronic disease later in life.

The foetal origins hypothesis states that the 'disproportionate' retardation in growth caused by the lack of sufficient nutrition in the second and third trimesters of gestation results in low birth weight, increasing systolic blood pressure at the

adult ages and the risk of heart disease later in life (Barker, 1994; 1995b). As an adaptive mechanism to an insufficient supply of nutrients or oxygen, the rate of cell division may be lowered, disturbing the tissues which are undergoing 'critical' development (Barker, 1995a). Changes in the distribution and number of cells and in the organ structure and the resetting of hormonal feedback and metabolic activity permanently affect the structure, physiology and metabolism of the body (McCance & Widdowson, 1974).

Exposure to disease in the first years of life could affect later life health through different mechanisms. Some types of infections can cause direct damage to organs. Some examples include streptococcal infections, which can cause rheumatic heart disease (Jones, 1956), or respiratory infections, which have been associated with lung impairments at older ages (Barker et al., 1991; Bengtsson & Lindström, 2003; Shaheen et al., 1994). According to Fridlizius, infection in the first years of life can reduce general immunity to disease across the life course (Fridlizius, 1984; 1989). In addition, through inflammatory mechanisms, short-term adaptive responses to infections or injury may become maladaptive in the long run, leading to chronic diseases such as cancer, diabetes, and cardiovascular or respiratory diseases in older ages (Finch & Crimmins, 2004).

The reproductive and hormonal systems are some of the many organs that could be damaged as a result of adverse exposures in early life. The development of the reproductive system occurs through stages, beginning with prenatal sex-specific organogenesis and continuing with further maturation in the perinatal period and at puberty (Lemasters et al., 2000). Reproduction can therefore be negatively affected if unfavourable conditions are experienced in any of these stages. For example, girls born small-for-gestational-age have a smaller uterus and reduced ovarian volumes (Ibanez et al., 2000). Moreover, malformations of the uterus can compromise a woman's ability to carry a pregnancy to term (Lumey & Stein, 1997). In fact, they can cause infertility, recurrent spontaneous abortions, or other complications such as prematurity and a positioning of the baby that is difficult for the birth process, both of which raise the risk of perinatal morbidity and mortality (Acién, 1993).

The inadequate growth of specific organs in early life can, moreover, lead to hormonal deregulation (Barker, 1995b). Development, reproduction and ageing in humans are regulated by the hypothalamus-pituitary-gonadal axis, which in women connects the brain, the gonad (an endocrine hormone producing gland) and the ovaries. A correct functioning of this axis is necessary to achieve regular ovulatory cycles (Elias et al., 2005). Hormones have a crucial role in female fecundity, determining the size of the ovum (Apter et al., 1987), its fertlisability (Yoshimura & Wallach, 1987), the likely success of implantation and the maintenance of the pregnancy (Ellison, 1996). Aside from affecting reproduction,

a woman's endogenous hormonal environment can also influence the long-term risk of the development of chronic diseases such as cancer, cardiovascular diseases and osteoporosis (Harlow & Ephross, 1995).

Exposure to adverse early life conditions could also damage other organs and body systems, which could indirectly affect a woman's ability to conceive or carry a pregnancy to term or the health of the foetus. Different studies have, for example, shown that individuals exposed to adverse early life conditions are more likely to develop type 1 (Montgomery et al., 2002) or type 2 diabetes (Barker, 2004; Sotomayor, 2012), and these conditions could have negative impacts on reproductive health. Women with type 1 diabetes can, in fact, have lower fertility, and they are also at greater risk of giving birth to offspring with congenital malformations (Jonasson et al., 2007), of experiencing complications such as preeclampsia and infections or of requiring delivery through caesarean section (Department of Health and Human Services, 2001). Compromised reproductive health could also be the result of reduced lung function or cardiovascular disease, which are also caused by adverse early life exposures. Lung function is, in fact, altered during pregnancy, and the health of the foetus is also dependent on the mother's lungs, which affect its oxygenation (Bhatia & Bhatia, 2000). Pathological respiratory or cardiovascular diseases existing before conception can worsen during gestation because the increases in oxygen consumption that are necessary for foetal growth cause physiological respiratory and hormonal changes (Felten, Mercier, & Benhamou, 1999). Associations have also been found between acute respiratory infectious diseases and preterm births (Bánhidy et al., 2008) and between severe maternal asthma and a lower offspring birth weight (Greenberger & Patterson, 1988). Moreover, women with congenital heart disease have a higher incidence of miscarriages, premature births, and low birth weights, and their foetuses are more likely to also develop congenital heart disease (Presbitero et al., 1994).

Based on these theories and findings, the exposure to high prices or to epidemics in early life is expected to have a damaging effect on the reproductive and hormonal systems of a woman or an indirect impact on reproduction through the development of diseases or damage to other organs unless selection dominates over scarring. Using the same data and similar methods to those employed here, Chapters 2 and 3 analysed how exposure to these adverse conditions affected the probability of dying at different stages of the life course. The results obtained in these chapters help to make the distinction between selection and scarring. It has been shown that in Scania, exposure to epidemics during infancy significantly influenced mortality at different ages, with variations in these effects by the type of disease environment experienced. More specifically, whereas for women born in years with epidemics of measles and scarlet fever, selection dominated during the childbearing and working ages, from around age 25, those who were exposed to whooping cough in

infancy presented higher probabilities of dying (Chapter 3). Between ages 25 and 70, the women who were exposed to whooping cough lived 1.7 years less, which corresponded to a 4.3% reduction in their life expectancies. The women born into landless families who were exposed to high prices during their foetal stage had lower mortality during the childbearing and working ages, indicating a dominance of selection (Chapter 2). Based on these findings, it is hypothesised that women born in a year with epidemics of whooping cough will experience worse reproductive health after age 25, while the impact for those conceived in years with high prices is expected to be either null or positive. Due to the dominance of selection observed during the childbearing and working ages for women born in years with measles or scarlet fever, we expect the effect of exposure to a high IMR to be less marked than the effect of specific exposure to whooping cough.

4.3.1 The sex ratio at birth

One of the outcomes of a pregnancy that can be affected by an incorrect functioning of the reproductive and hormonal systems or of the other organs is the offspring sex ratio at birth. The sex ratio at birth is determined by the sex ratio at conception and by sex-specific foetal mortality; in other words, it is determined by processes that occur both before and after fertilisation. Whether a female or a male offspring is conceived is dependent on the characteristics and conditions of both parents. The sperm carries the genetic material that defines the sex of the zygote (Magnuson, Bodin, & Montgomery, 2007). Male gametes are, in fact, heterogametic and contain one of the two types of sex chromosomes, X or Y, while the female gametes are homogametic and contain only the X sex chromosome. Previous research has shown that paternal exposures to environmental toxins may damage the quality of the sperm or its production (Fukuda et al., 1996; Fukuda et al., 1998) and that sperm carrying male material is more vulnerable to these exposures (Magnuson et al., 2007), thus causing reductions in the sex ratio at birth. Environmental toxins can also deteriorate male reproductive health if these exposures take place during the foetal stage and childhood (Toppari et al., 1996). These experiences have also been suggested as the underlying cause of the declining trends in sex ratios that have characterised several countries over the last decades (Allan et al., 1997). In Sweden, as well as in much of Scandinavia, the sex ratios showed an increasing trend up to the 1950s, and thereafter a decreasing trend (Fellman & Eriksson, 2011; Grech, 2012).

Even if the health of the prospective fathers, through influences in the quality of semen, has an important role in determining the sex of the conceptus, maternal conditions can affect whether X- or Y-bearing sperm remain viable in the cervical

mucus, reach the fallopian tube and penetrate the egg to fertilise it. In fact, although Y-bearing sperm is faster than X-bearing sperm, it is less resilient to unfavourable conditions in the reproductive system of the mother than X-bearing sperm, which survive longer (Byrne & Warburton, 1987; Hingorani & Shroff, 1995).

We therefore expect that in the mothers exposed to less favourable conditions, the fertilisation of an X-bearing sperm would be more common, resulting in lower sex ratios at birth. Although this work has the aim of studying the possible effects on offspring sex ratio at birth related to maternal early life exposures, the impacts originating from the conditions experienced by fathers during their development will also be considered so that different hypotheses can be distinguished. We expect that men with adverse exposures will father less male offspring due to a weaker semen quality.

According to the theories introduced by James, parental hormonal levels at the time of conception influence which sperm are selected to engage in fertilisation. More specifically, this author states that the proportion of male conceptions is higher when the levels of testosterone and oestrogen are greater in either parent and are lower with high levels of gonadotrophin and progesterone (James, 1996). For this reason, the sex of the human zygote could be dependent on the time during the woman's menstrual cycle when it is formed (Guerrero, 1974; Harlap, 1979). James argues that there is a U-shaped relationship between the sex ratio and the time of successful insemination within the woman's fertile interval, with a higher proportion of girls for conceptions that occur in the middle of the menstrual cycle and of boys for those that take place earlier or later (James, 2008). He also states that this relationship is dependent on the frequency of intercourse, because when the frequency is higher, it is more likely that conception takes place early in the menstrual cycle and therefore that a boy is produced (James, 1980). For adverse early life conditions to result in reductions in the sex ratio at birth of women's offspring through mechanisms related to their hormonal levels at the time of conception, the exposed women would have to have intercourse with lower frequency and with a timing concentrated around ovulation. This link cannot be excluded, but if it exists, it cannot be very strong.

Aside from depending on mechanisms that take place during insemination and fertilisation, another crucial determinant of the sex ratio at birth is foetal mortality. Approximately 10% of fertilised ova fail to be implanted, and around 50% of those that are implanted and become embryos are aborted spontaneously, even if many of these losses are not recognised by the mother (Tanner, 1989). Sporadic miscarriages are the most common type of pregnancy complications (Arck et al., 2008), the majority of which occur within the first 3 weeks after conception (Nepomnaschy et al., 2006). As the number of previous miscarriages rises, the risk of experiencing a further foetal loss increases cumulatively (Knudsen

et al., 1991; Regan, Braude, & Trembath, 1989), yet recurrent miscarriages are less common (Arck et al., 2008). Most spontaneous abortions are due to abnormalities in the development of the embryo or of the protective and nutritive structures that surround it (Tanner, 1989), and the factors affecting the likelihood of experiencing sporadic miscarriages include low body mass index, stress, low levels of progesterone (Arck et al., 2008), and exposure to organic solvents, cigarette smoking, cocaine use and the consumption of alcohol or of excessive quantities of coffee (Regan & Rai, 2000). The risk of miscarriage also rises with maternal age, often due to a greater incidence of foetal chromosomal abnormalities and neural tube defects (Regan & Rai, 2000). Foetal chromosome abnormalities account for approximately 50% of the pregnancy losses that occur within the first trimester (Goddijn & Leschot, 2000). The primary recognised medical causes of recurrent miscarriage are, instead, endocrine, autoimmune and thrombotic abnormalities (Regan & Rai, 2000). Although recent evidence has challenged some of these concepts, endocrine deficiencies include hormonal problems, the short length of the luteal phase of the menstrual cycle and polycystic ovaries (Regan & Rai, 2000). Furthermore, women with congenital uterine malformations are at greater risk of experiencing adverse pregnancy outcomes, including early and late foetal losses as well as preterm labour (Woelfer et al., 2001).

Women who experience worse health as a result of adverse early life exposures could face a greater incidence of spontaneous abortions. It has been widely recognised that there are sex-specific differences in foetal deaths, and consequently, these impacts are expected to cause reductions in the sex ratios at birth. The primary sex ratio – or sex ratio at conception – is, as a matter of fact, estimated to be at least 120 males per 100 females (McMillen, 1979), and the reductions of this ratio throughout pregnancy are the result of the excess mortality of male embryos (Byrne & Warburton, 1987; Hassold, Quillen, & Yamane, 1983; Mizuno, 2000), in particular, during the phase of organogenesis in early gestation (Kellokumpu-Lehtinen & Pelliniemi, 1984). This excess mortality may be caused by the faster growth rates of males, which makes them more vulnerable to abnormalities (Forchhammer, 2000). Females are less susceptible to infections not only *in-utero* but also during infancy, childhood and later life stages (Magnuson et al., 2007).

Factors related to the timing of births within the woman's life course and to parity can also generate changes in the sex ratio. The sex ratio at birth is lower for higher birth orders (James & Rostron, 1985; James, 1987b; Ruder, 1985) or multiple births (Bulmer, 1970; James, 1975). This higher ratio could in part be caused by variations in the rates of foetal death by parity in relation to the week of gestation. For example, within the first 12 weeks, foetal mortality is lower for gravida one than for gravida two, while the opposite is true after 20 weeks (Shapiro, Jones, & Densen, 1962). Younger women are more likely to give birth

to sons than older women (Almond & Edlund, 2007; James & Rostron, 1985; James, 1987b; Ruder, 1985), perhaps as a result of their more vascularised uteri, which allows them to produce infants with higher birth weights (Braza, 2004), but also, as discussed above, due to differences in foetal mortality.

Other mechanisms linking early life exposures to the sex ratio at birth of an individual's offspring could be related to epigenetics and epigenetic inheritance. When environmental experiences are altered, one same genotype can give rise to different phenotypes through developmental plasticity and subsequently be expressed in diverse physiological or morphological states without modifications to the DNA sequence (Bateson et al., 2004; Jablonka & Raz, 2009). Such epigenetic changes can programme disease in later life (Lucas, 2007); therefore, adverse early life conditions could result in worse reproductive health. Epigenetic inheritance can also occur, in which case any alterations on the parents' gene expressions that originated from conditions experienced during their development may be transferred to the next generation (Jablonka & Raz, 2009; Lummaa & Clutton-Brock, 2002). Consequently, we expect that adverse early life exposures experienced by an individual can be reflected in negative repercussions on the health, patterns of growth and likelihood of survival until the end of gestation of the foetuses conceived by these men and women. Through these transfers, weak parents would conceive unhealthy foetuses, and weak male foetuses would experience higher mortality during gestation, resulting in lower sex ratios at birth.

Summarising the mechanisms outlined in this section, we expect that men and women who faced adverse early life conditions will give birth to a lower proportion of boys. In fathers, this reduction could be caused by a deterioration in the quality of their semen or by the epigenetic transfer of poor health conditions, resulting in the greater attrition of male foetuses during gestation. For mothers, instead, these patterns could result from a higher selection of X-bearing sperm at the time of fertilisation, from a lower frequency of intercourse and a concentration of coitus around the time of ovulation or, more likely, from a greater incidence of male foetal losses due to the epigenetic transfers of defective genes or to pregnancy complications and impoverished conditions in the womb.

4.3.2 Later life effect modifiers: the possible effects of occupation

Within their framework of conceptual models in life course epidemiology, Ben-Shlomo and Kuh (2004) have introduced an extension to their 'critical period model', which they defined as the 'critical period model with later effect modifiers'. According to these theories, later life exposures can interact with the effects of experiences sustained in early life, enhancing or diminishing their negative impact

on health (Kuh & Ben-Shlomo, 2004). When studying how early life conditions affect reproductive health, it is important to consider whether contemporary exposures and behaviours can modify these effects. In the paragraphs above, it has been described how the sex ratio at birth is determined by the sex ratio at conception and by sex-specific foetal mortality. Such mechanisms could be affected by individual circumstances and behaviour in the period strictly before conception or during gestation. Not only could such patterns directly influence the sex ratio at birth, but they could also interact with the conditions experienced by women in early life, enhancing or diminishing their negative impact on reproductive health.

SES and other determinants of class, such as poverty or income inequality, can serve as good indicators of individual exposures and behaviours (Kramer et al., 2000), and SES may be captured by considering occupation. Several studies that used contemporary data have found associations between class or occupation and pregnancy outcomes (Cnattingius & Haglund, 1992; Joseph et al., 2007; Kramer et al., 2000; Magnuson et al., 2007; Morrison et al., 1989). According to the authors of these works, the possible mediators of this relationship are the demographic and anthropometric characteristics of the mother (e.g., marital status, parity, age, height and pregnancy weight gain), risk factors related to lifestyle (e.g., quantity and nutritional value of food consumption, smoking and alcohol consumption), and environmental and individual exposures (e.g., a physically demanding work load during pregnancy, stress and other psychosocial factors, education, housing conditions and overcrowding, poverty and early prenatal care) (Cnattingius & Haglund, 1992; Joseph et al., 2007; Kramer et al., 2000; Morrison et al., 1989). Fluctuations in the economy (Catalano et al., 2005; Catalano, 2003; Catalano & Bruckner, 2005), stress (Catalano et al., 2005; R. Catalano et al., 2005; R. Catalano et al., 2006), food availability and maternal nutrition (Andersson & Bergstrom, 1998; Gibson & Mace, 2003; Williams & Gloster, 1992) have been shown to influence the sex ratio at birth by affecting the risk of experiencing spontaneous abortions. For example, studies conducted on rodents have demonstrated that when mothers are exposed to stress, the production of the progesterone hormone is reduced, which compromises the equilibrium between the endocrine and immune systems, lowers maternal immune tolerance and often results in foetal rejection (Blois et al., 2004).

When studying reproduction, one of the most important factors that could be related to SES is childbearing patterns. The spacing between births, maternal age and parity have a very strong role in determining the outcomes of pregnancies, and they are also known to vary by SES. In Sweden, marital fertility started to decline around 1880 (Dribe, 2009), and in Scania, this drop began slightly later, around 1890 (Bengtsson & Dribe, 2009). Even though SES differences in mortality in this region started to manifest only in the 20th century, (Bengtsson & Dribe,

2011), the variances in fertility according to class were observed both before as well as during the fertility transition (Bengtsson & Dribe, 2009). Prior to the transition, the wealthier groups had higher fertility than the lower classes; during the transition, they showed earlier and more consistent control, whilst during the 20th century, SES differences in fertility diminished (Bengtsson & Dribe, 2009). Moreover, in this population, signs of non-parity-specific control were also observed prior to the fertility transition, and these patterns were dependent on class. As a response to short-term economic stress, in fact, landless and semi-landless families, but not landed families, adopted measures of deliberate non-parity-specific control when high prices were foreseen (Bengtsson & Dribe, 2006). Differences in the childbearing patterns of the various SES groups could also be related to the seasonality of conceptions, which could influence the outcome of pregnancies through the diverse risks of infection. For example, due to the need for both men and women to work on the land, farmers could have had a different seasonality than the high SES groups. Possibly due to differences in nutrition, quality of housing, the women's workload or childbearing patterns, we expect occupation to be a modifier in the impact of early life conditions on the sex ratio at birth, and we anticipate stronger negative effects for low SES women.

4.4 Data and methods

4.4.1 Source material

The data used for this work are from the SEDD[24], which comprises births, deaths, marriages and migrations occurring in the years 1813 to 1968 in the parishes of Halmstad, Hög, Kävlinge, Kågeröd and Sireköpinge, located in the southern Swedish region of Scania. This database was constructed using register type data from catechetical examination registers (*husförhörslängder*) and updated with information on births, marriages and deaths from church books maintained by the clergy. Individuals are therefore followed from birth or immigration until death or outmigration. The material used is of high quality, and the gaps in births, deaths

24 The SEDD was created in a collaborative project between the Regional Archives in Lund and the Centre for Economic Demography at Lund University (Bengtsson, Dribe, & Svensson, 2012), and it has been structured to follow the format suggested by the Intermediate Data Structure (Alter, Mandemakers, & Gutmann, 2009). This work uses the SEDD version 3 beta. The data was converted into spells using the code developed by Quaranta (2012).

and marriages are limited (Bengtsson & Lindström, 2000)[25]. The five parishes are located near one another, and they presented variations that were common in peasant societies with regards to topography, size, and socio-economic conditions (Bengtsson & Broström, 2009). The entire area was open farmland except for the northern part of Halmstad, which was more wooded. The southern localities became industrialised and urbanised in the last decades of the nineteenth century. The major population growth among these parishes occurred in Kävlinge, which changed from being a rural village to a small industrial town that had several railroad connections and factories (Bengtsson & Dribe, 2009). The current study is limited to women born between 1813 and 1898 and giving birth in the period 1828 to 1948, a sample that includes 4,026 women and 10,541 births.

Occupational information from poll-tax (*mantalslängder*) and income (*inkomslängder*) registers is also employed. All occupations in the database were coded into HISCO (van Leeuwen, Maas, & Miles, 2002) and later classified according to SOCPO (van de Putte & Miles, 2005), which is a classification scheme that comprises five categories based on level of skills, degree of supervision, and whether self-employed or not, as well as on pure status. Because SOCPO is highly correlated with education and income, it is a good classification scheme to adopt to capture possible differences in living conditions and childbearing patterns. SOCPO 5 indicates the highest status, and 1 indicates the lowest.

Data on the price of rye is also used. This grain is used because it was the most common grain in this part of the country (Bengtsson & Dribe, 1997). We use prices of the *födgeri* of Landskrona (Bengtsson & Dribe, 1997). A *födgeri* is a rural level below the county and prices were reported shortly after the harvest in the fall. It was not possible to use quarterly or monthly data because it is only available for shorter periods. Nevertheless, seasonal fluctuations were rather limited, and the variations in prices were dominated by year-to-year changes.

When evaluating the impact of exposure to high prices during the foetal stage, the models are estimated specifically for the full sample of women but also specifically for those born into landless families. High food prices, in fact, represent a measure of nutrition only for net consumers. Information relating to the sizes of farms, obtained from poll-tax registers, was used to identify families that could not cover their subsistence from the land[26].

25 Calculations made showed that for all occupational groups, at least 40% of all infant deaths occurred within the first month of the babies' life.

26 *Mantal* information on land tenure is used to consider whether the woman's family of origin was landless. Previous works have shown that in the early decades of the 19th century, a *mantal* of 1/16 was sufficient for subsistence (Bengtsson & Dribe, 2006; Dribe, 2000). For the latter part of the century, there are no studies measuring farm productivity in this area. We consider landless families to be those with a mantal below 1/16 if they were born between 1813 and

4.4.2 Measures of early life conditions

The impact of nutrition during the foetal stage and of exposure to disease during infancy on the sex ratio at birth of a woman's offspring is measured using the rye prices from the year prior to her birth and the IMR of her year of birth as indicators; the latter is calculated directly from the data. These contextual variables are exogenous indicators of early life conditions and have the advantage of being unrelated to the life course and, therefore, of being free from sources of confounding. Because the literature shows that nutrition during the second and third trimesters of a pregnancy is the most influential on later life health, instead of considering the prices of the harvest year[27] prior to the birth year, each woman is linked to the prices of the harvest year when at least half of the last two trimesters of pregnancy occurred.

The series of local IMR and of the logarithms of rye prices were decomposed into a trend and a cycle component using the Hodrick Prescott filter with a filtering factor of 6.25, which is the value usually selected for yearly series. Because the IMR was highly correlated with its cyclical component, relative rather than absolute deviations were used to select the years with a high disease load, calculated by dividing the short-term component of the IMR by its long-term trend. In the case of prices, actual deviations from the trend were used because logarithms already represent relative values. The years with a positive relative deviation from the IMR trend of at least 0.20 were considered to be years with a high disease load, and years with a positive deviation from the trend of the logarithm rye prices of at least 0.12 were considered to be years with low food availability[28].

For each disease year, the most common cause of these deaths was identified to define the years with distinct epidemics. Due to small numbers, the causes of death of all children deceased between ages 0-10 rather than only infants were taken into account. As a result of these steps, 1821 and 1846 were considered to be years with epidemics of measles, 1838 of smallpox, 1860, 1869 and 1877 of scarlet fever, 1816, 1826, 1831, 1832, 1835, 1853, 1859, 1874 and 1894 of whooping cough and 1842, 1881 and 1886 of other diseases (dropsy, pain, etc.), while the years with a low relative deviation from the trend in the IMR were defined as

1839, 1/32 if they were born between 1840 and 1869 and 1/64 if they were born between 1870 and 1898.

27 A harvest year is the period between October 1st and September 30th of the successive year.

28 These threshold levels correspond to roughly the eightieth percentile in the distribution of relative deviations from the trend in the IMR and of deviations from the trend of the logarithm of rye prices. A sensitivity analysis is also conducted, where the estimations are repeated using different threshold levels to define the high price or high disease years. The years with a high IMR are 1816, 1821, 1826, 1831, 1832, 1835, 1838, 1842, 1846, 1853, 1859, 1860, 1869, 1874, 1877, 1881, 1886 and 1894, while those of high prices are 1818, 1819, 1826, 1831, 1837, 1841, 1842, 1846, 1847, 1853, 1855, 1861, 1867, 1868, 1873, 1880, 1881 and 1891.

having a low-medium disease load. Although the threshold level to indicate a high IMR was not exceeded in 1877, it was considered to be an epidemic year because nearly 60% of all deaths of children resulted from scarlet fever. This work evaluates first the impact of exposure to a high IMR and then specifically to epidemics of whooping cough. By concentrating only on whooping cough, it is possible to determine whether an exposure that previously showed a damaging effect on health when considering mortality as an outcome (Chapter 3) also proves to have a detrimental impact on reproductive health. We do not conduct specific analyses on the effect of exposure to measles, scarlet fever, smallpox, or other diseases due to small numbers. Furthermore, when focusing on mortality in Chapter 3, women born in years with measles or scarlet fever presented a dominance of net selection during their childbearing and working ages, and it is therefore anticipated that the impact of these diseases on the offspring sex ratio at birth will be less defined than that of whooping cough.

4.4.3 Statistical models

The impact of a woman's early life conditions on the sex ratio at birth of her offspring is analysed by first constructing contingency tables and conducting likelihood ratio tests (Chi-squared) that compare the number of occurrences for groups with different early life exposures. At a second stage, nominal logistic regressions are used to introduce controls for the current SES (considering the five SOCPO occupational groups as well as a category for unknown occupation[29]), parish of residence, age of mother (continuous variable) and its squared term, an indicator of whether the mother was born in one of the studied parishes or outside, birth order of the child (first, 2-4, 5-7, 8+) and year of birth of the child (continuous variable). Descriptive statistics showing the distributions of birth for

29 The occupations considered refer to the current occupation (i.e., at the time of the child's birth) of the head of family. Therefore, for married women, the husband's occupation is used; for single women living in their parental homes, that of their fathers; and for single women forming their own household and for life-cycle servants, their own occupation is considered. Daughters and unmarried servants are, however, a minority (0.2 and 1.3%, respectively). Several steps were taken to replace missing occupations using other available data. When there were gaps in occupation from the census records, these gaps were filled in for cases where the occupation of the years preceding the gap was the same as that of years that followed it. For widows, instead, occupation was filled down for the first nine months after the death of the husband. In the next step, all occupations that were still missing were replaced by 'farmers' (SOCPO 4) if the family owned land, information that was obtained from the poll-tax registers. Successively, for recently formed families with still unknown occupations, we assigned the occupation which was first declared if less than two years had elapsed between the date of entry and the date when the occupation was declared. Finally, the remaining missing occupations were replaced by 'crofter' (SOCPO 2) if, according to the poll-tax registers, the family lived in croft land or in a house.

Table 1: Descriptive statistics

	Percentages of births / means
Prices in year of conception[a] (%)	
Low-medium prices	78.10
High prices[b]	21.90
IMR in year of birth[c] (%)	
Low-medium disease load	80.79
High IMR[d]	19.21
Whooping cough in year of birth (%)	
Low-medium disease load	89.58
Whooping cough epidemics [e]	10.42
SES (%)	
SOCPO 1	31.08
SOCPO 2	18.07
SOCPO 3	20.98
SOCPO 4	25.39
SOCPO 5	3.73
N/A	0.75
Parish of residence (%)	
Hög	8.83
Kävlinge	23.25
Halmstad	15.75
Sireköpinge	23.62
Kågeröd	28.55
Age of mother (n years)	31.70
Mother ´s birth parish (%)	
Studied parishes	25.75
Outside studied parishes	74.25
Child´s birth order (%)	
1	34.27
2 to 4	38.32
5 to 7	20.33
8 +	7.09
Child´s birth year (n years)	1886.50
Number of women	4026
Number of births	10541

Notes: a – determined from deviations from the trend in the logarithm of rye prices, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25. b – years with deviations from the trend in logarithm of rye prices greater than or equal to 0.12. c – determined from relative deviations from the trend in IMR, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25. d – years with relative deviations from the trend in IMR greater than or equal to 0.2. e – years with relative deviations from the trend in IMR greater than or equal to 0.2 and where whooping cough was the most diffused cause of death among children (years with high IMR but where whooping cough was not the main epidemic were excluded).

each category and the means for the continuous variables are presented in Table 1. Between 10 and 22% of births correspond to mothers exposed to adverse early life conditions. A total of 74% of births relate to mothers who were born outside of the studied parishes; however, the majority of these women were born within a

17 km radius of the studied localities, and they therefore shared the same early life environments. Estimations only considering the women born within this radius are shown in the sensitivity analysis.

To account for the shared characteristics of the mother for all of her births, a random effects component was included in all models. The first general models estimated are summarised as

$$logit(male\ offspring_{ij}) = \gamma_{0j} + \gamma_1 early\ life\ condition_j + \beta X_j$$

$$\gamma_{0j} = \gamma\beta_0 + u_{0j}\ ,\quad u_{0j} \sim N(0, \sigma_u^2)$$

where *i* represents the child, *j* the mother, X_j is the vector of control variables, and $var(u_{0j})$ is the frailty variance component.

SES is initially introduced as a control in the models, and later separate estimations are made for women from low (SOCPO categories 1-2) and medium-high (SOCPO categories 3-5) social status, each group representing approximately half of all births (Table 1). This step allows possible differences in the effects of early life exposures according to the living conditions and the availability of families to be measured. The impact of exposure to high prices during the foetal stage is evaluated for all women but also specifically only for those born into landless families. High food prices, in fact, represent a measure of nutrition only for net consumers. All analyses are conducted using the STATA 12 statistical software.

Separate estimations are made to evaluate the impact of exposure to high prices during a woman's foetal stage and to a high IMR or to whooping cough epidemics during infancy. In each of the studies, the mothers conceived during years with high prices or born in a year with a high IMR or with whooping cough epidemics are compared to those conceived or born in more favourable years. The impact of exposure to disease is therefore evaluated both generally, by considering an indicator of high disease load years, and also specifically, by only selecting those years where whooping cough was identified as the primary disease. In both cases, individuals born in these periods were compared to those born in years with a low-medium disease load. The years with whooping cough were widely spread across the studied period (four out of nine epidemic years occur after 1850); therefore, comparing the years with these epidemics to all years with a low-medium disease load should not lead to biased estimations. Moreover, in Chapter 3, the pattern of the results remained constant when comparing the risk of dying at later ages for the individuals born in one of the specific years with this epidemic to those born some years before or after. Because Chapter 3 also showed that for women who were exposed to whooping cough, scarring effects started to dominate from approximately age 25 while net selection prevailed when they were younger, separate studies are conducted for all women and only for those aged 25 or older. This division allows us to concentrate on a group of individuals for whom we had already observed a dominance of net scarring when considering a different

outcome; we will therefore be able to attest whether similar effects can also be found when focusing on the offspring sex ratio at birth.

This work also evaluates whether there are variations in the impact of early life conditions on the sex ratio at birth across different cohorts, which can capture possible changes in the relative magnitude of early life conditions as well as different disease environments and price levels. Separate models are estimated for women born in 1813-1849 and in 1850-1898. These two cohorts may have experienced different early life disease environments. In fact, aside from whooping cough, measles and smallpox epidemics were observed in the first group of years, and for the second group, scarlet fever was observed. Moreover, the IMR was much higher for the first cohort than for the second, meaning that in relative terms, the impact of epidemics is expected to be stronger for the second cohort, who were born during a time when competing disease environments were weaker. Finally, during adulthood, the two groups could have experienced different morbidity, the first more linked to infectious diseases and the second to chronic diseases. In Chapter 3, the negative impact of exposure to whooping cough on mortality was more severe for the second cohort. Instead, the relative impact of high prices is expected to be stronger for the first cohort, due to a general increase in prices as well as declining dependence on grain as a source of food. Moreover, the women from these cohorts would have reached age 15 before or after 1865; this age not only marked the initial stage of their reproductive lives but was also a common age to commence working. The year 1865 was an important dividing point in the history of this region. The years up to 1864 include the agricultural transformation, the early stages of industrialisation and the first phase of the demographic transition, with declining infant and child mortality. The second period was characterised by the breakthrough of industrialisation as well as by declines in adult mortality and, later, by continued industrial expansion and the decline of the rural sector (Bengtsson & Dribe, 2011).

In relation to the indicators of early life conditions for which significant results are found, further models are also estimated with the purpose of determining possible causal mechanisms for the differences in the offspring sex ratio at birth for women who had faced diverse early life exposures. The first model concerns calculations of the probability that a woman's offspring died in the early neonatal stage, introducing an interaction between the child's gender and the indicator of early life exposures for the woman. These results allow us to determine whether male or female offspring experienced different selective mechanisms during gestation. More specifically, if weaker mothers were less capable of conceiving males and if they had a greater probability of experiencing male foetal wastage, then it is expected that males born to mothers who had faced adverse early life conditions would have lower rates of neonatal mortality relative to female

offspring born to these women. Also, with the purpose of testing the validity of different hypothesised causal mechanisms, we measure the impact of the early life exposure of fathers. If the offspring born to men who experienced adverse early life conditions show lower sex ratios at birth, it would provide evidence of effects that relate to the sex ratio at conception via the quality of the semen and/or of epigenetic transfers. If, instead, no differences were observed, then it could be concluded that the results found for women are more likely to be caused by the conditions experienced by the foetus in the mother's womb. Caution needs to be taken when making these types of conclusions, however, because the patterns of conception for men and women are not influenced by the same exact factors.

In the final stage, a sensitivity analysis is conducted to determine whether the results obtained are dependent on the methodological choices adopted. In particular, logistic regressions are also estimated by considering the actual values of the IMR and prices, as well as their trend and cyclical components. Different threshold levels are also used to define years with epidemics or high prices. Furthermore, the impact of nutrition during gestation is also measured by linking each woman to the price level (deviation of 0.12 from the trend) of the harvest year preceding her birth. Each of these variables is introduced in a separate regression, except for cycle and trend, which are evaluated within the same model. In the interest of space, the sensitivity analysis is only conducted for mothers aged 25 or older of low or medium-high SES, with separate estimations for the two groups, and all cohorts and periods are considered within the same model. Furthermore, no distinction is made here for women born into landless families. The same control variables considered before are also introduced in these models.

A sensitivity analysis is also made to measure the possible variations in the results when different control variables are included in the models or when the age of the mother and the trend component (year) are considered in a different form. The same models are therefore re-estimated excluding one control variable at a time, considering the age of the mother and the decade of birth of the child as categorical variables, including the squared and cubed term of the year of birth of the child and excluding all controls.

4.5 Results

4.5.1 Sex ratio at birth

A higher proportion of male births is seen for women conceived in years with high prices than for those conceived in years with low-medium prices, while lower proportions are observed for those women born in years with a high IMR or, specifically, with whooping cough epidemics (Table 2). Except in relation to high prices for the landless, the differences between the exposed and the not exposed mothers are wider when only considering births occurring for women aged 25 or older. However, Chi-squared tests do not show any statistical significance for any of these comparisons. Significant differences appear when the estimations are made separately by SES (Table 3). For all women of high-medium SES, the difference in the proportion of male births was positive (2.9%) and slightly significant for those exposed to high prices, while it was not significant for those exposed to high prices and born into landless families or for all women exposed to whooping cough. The low SES women show no significant differences in connection to the impact of prices, but a 4.9% reduction in the proportion of male births if they were born in a year with whooping cough, a result that was statistically significant.

The patterns of the results do not change when the probability of having a male birth is estimated using logistic regressions that introduce different control variables. An exposure to high prices during the foetal stage does not impose significant impacts when all women are studied together (Table 4), although when distinguishing different SES groups (Table 5), high-medium SES women

Table 2: Contingency tables and Chi-squared tests showing the percentage of male births for women of all age groups or aged 25+ exposed in early life to high prices, high IMR or whooping cough epidemics – Scania cohorts 1813-1898

	Not exposed	Exposed	p-value
High prices			
All ages	51.92	52.84	0.44
Age 25+	52.20	53.44	0.33
All ages (landless at birth)	52.02	53.51	0.65
Age 25+ (landless at birth)	52.02	52.44	0.91
High IMR			
All ages	52.34	51.21	0.36
Age 25+	52.75	51.35	0.30
Whooping cough			
All ages	52.34	51.36	0.56
Age 25+	52.75	50.58	0.23

Note: see Table 1 for explanations on the early life conditions indicators.

Table 3: Contingency tables and Chi-squared tests showing the percentage of male births for women aged 25+ of low or high-medium current SES, exposed in early life to high prices, high IMR or whooping cough epidemics – Scania cohorts 1813-1898

	Not exposed	Exposed	p-value
High prices			
Low SES	52.85	52.00	0.645
High SES	51.70	54.61	0.096
Low SES (landless at birth)	53.56	51.53	0.65
High SES (landless at birth)	49.85	54.22	0.476
High IMR			
Low SES	53.11	51.03	0.262
High SES	52.44	52.1	0.861
Whooping cough			
Low SES	53.11	48.25	0.051
High SES	52.44	54.06	0.539

Note: see Table 1 for explanations on the early life conditions indicators.

exposed to high prices present higher odds of a male birth (O.R. = 1.12, C.I. = 0.98-1.29), even if this result was slightly above the threshold for statistical significance (p.value 0.101). High SES women born into landless families and exposed to high prices in their foetal stage also present higher probabilities of a male birth, although this result lacks statistical significance.

No strong or significant differences by SES are seen in the sex ratio at birth (Table 4). Statistical significance is found for SOCPO 2 in the models of women of all ages born into landless families or in the estimations that compare women exposed to whooping cough or to a low-medium disease load, although only at the 10% level.

Concerning the impact of exposure to disease, reduced odds ratios are observed both when considering all epidemics and specifically whooping cough epidemics, although statistical significance is not obtained for the models that consider all SES groups together (Table 4). Instead, when considering different groups (Table 5) of women aged 25 or older, the women of low SES present statistically significant reduced odds of a male birth if they were born in a year with whooping cough (O.R.= 0.82, C.I. = 0.67-1.00, p-value = 0.046)[30]. If a model is estimated for births occurring earlier than the age of 25 (results not shown), women of low SES exposed to whooping cough present an odds ratio of a male birth of 1.22 (C.I. = 0.75-

30 This result remains unchanged when also including the indicator of price levels during the woman's foetal stage in the model. If the model is estimated only for mothers conceived in years with low-medium prices, an odds ratio of 0.86 is obtained for exposure to whooping cough in infancy, while the odds ratio is 0.79 when estimating the models only for the women conceived in years with high prices. This result indicates that exposure to whooping cough in infancy results in reductions in the sex ratio at birth irrespective of the price level experienced during the foetal stage and that this effect becomes stronger if the woman was also exposed to high prices.

Table 4: Odds ratio of a male birth for women of all age groups or aged 25+ exposed in early life to high prices, high IMR or whooping cough epidemics – Scania cohorts 1813-1898

	High prices - all		High prices - landless [a]	
	all ages	age 25+	all ages	age 25+
Exposure to high prices				
Low-medium prices	ref.	ref.	ref.	ref.
High prices	1.03	1.05	1.04	1.01
	[0.94,1.13]	[0.95,1.16]	[0.80,1.36]	[0.76,1.35]
Exposure to high IMR				
Low-medium IMR				
High IMR				
Exposure to whooping cough				
Low-medium IMR				
Whooping cough epidemic				
Current SES				
Socpo 1	1.00	1.00	1.00	1.00
Socpo 2	1.08	1.04	1.32*	1.26
	[0.96,1.21]	[0.92,1.18]	[0.98,1.76]	[0.91,1.73]
Socpo 3	1.01	1.01	0.96	0.91
	[0.90,1.13]	[0.90,1.14]	[0.69,1.33]	[0.64,1.31]
Socpo 4	1.01	1.01	1.05	1.13
	[0.91,1.12]	[0.90,1.13]	[0.77,1.42]	[0.81,1.58]
Socpo 5	0.94	0.93	0.78	0.87
	[0.76,1.16]	[0.74,1.17]	[0.30,2.03]	[0.30,2.49]
Unknown	0.74	0.75	0.59	0.73
	[0.47,1.16]	[0.44,1.28]	[0.19,1.84]	[0.16,3.31]
Frailty variance	0.000	0.000	0.000	0.000
Number of mothers	4026	3504	408	350
Number of births	10541	8945	1341	1113

Notes: a = landless at birth. See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child's birth order. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

1.99, p-value = 0.406), which indicates, as was shown in Chapter 3, that selection effects dominated prior to this age. In Table 5, the odds ratio of a male birth is not statistically significant for the low SES women exposed in infancy to high IMR, but in the sensitivity analysis section, statistical significance is obtained when threshold levels below 0.2 are considered to define the years with a high disease load. No significant effects are observed in Table 5 for women of medium-high SES exposed to whooping cough during infancy, although they display an odds ratio that is slightly over one.

continuation of **Table 4**

	All epidemics		Whooping cough	
	all ages	age 25+	all ages	age 25+
Exposure to high prices				
Low-medium prices				
High prices				
Exposure to high IMR				
Low-medium IMR	ref.	ref.		
High IMR	0.95	0.95		
	[0.87,1.05]	[0.85,1.05]		
Exposure to whooping cough				
Low-medium IMR			ref.	ref.
Whooping cough epidemic			0.95	0.91
			[0.84,1.09]	[0.79,1.05]
Current SES				
Socpo 1	1.00	1.00	1.00	1.00
Socpo 2	1.08	1.04	1.12*	1.08
	[0.96,1.21]	[0.92,1.18]	[0.99,1.27]	[0.95,1.24]
Socpo 3	1.01	1.01	1.03	1.04
	[0.90,1.13]	[0.90,1.14]	[0.92,1.15]	[0.92,1.18]
Socpo 4	1.01	1.01	1.04	1.04
	[0.91,1.12]	[0.90,1.13]	[0.93,1.16]	[0.93,1.18]
Socpo 5	0.94	0.93	0.91	0.92
	[0.76,1.16]	[0.74,1.17]	[0.73,1.14]	[0.72,1.16]
Unknown	0.74	0.74	0.76	0.75
	[0.47,1.16]	[0.43,1.27]	[0.48,1.21]	[0.43,1.31]
Frailty variance	0.000	0.000	0.000	0.000
Number of mothers	4026	3504	3616	3148
Number of births	10541	8945	9507	8062

Notes: a = landless at birth. See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child's birth order. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

4.5.2 Cohort changes in the sex ratio at birth

The sex ratio at birth is lower for the second cohort. For women of all SES groups and for births taking place at all ages, the percentage of male births is 52.46 (S.R. = 110.36) for those born in 1813-1849 and 51.86 (S.R.= 107.71) for those born in 1850-1898. Variations in the impact of exposure to adverse early life conditions are also observed. However, because the number of women and births are small

Table 5: Odds ratio of a male birth for women aged 25+ of low or high-medium current SES, exposed in early life to high prices, high IMR or whooping cough epidemics – Scania cohorts 1813-1898

PRICES	All individuals		Landless [a]	
	low SES	high SES	low SES	high SES
Exposure to high prices				
Low-medium prices	ref.	ref.	ref.	ref.
High prices	0.97	1.12	0.95	1.28
	[0.83,1.12]	[0.98,1.29]	[0.66,1.36]	[0.78,2.13]
Frailty variance	0.000	0.000	0.000	0.000
Number of mothers	1970	1737	249	145
Number of births	4306	4584	682	424

DISEASE	All epidemics		Whooping cough	
	low SES	high SES	low SES	high SES
Exposure to high IMR				
Low-medium IMR	ref.	ref.		
High IMR	0.92	0.99		
	[0.80,1.07]	[0.85,1.15]		
Exposure to whooping cough				
Low-medium IMR			ref.	ref.
Whooping cough epidemic			0.82**	1.06
			[0.67,1.00]	[0.86,1.31]
Frailty variance	0.000	0.000	0.000	0.000
Number of mothers	1970	1737	1756	1573
Number of births	4306	4584	3843	4168

Notes: a = landless at birth. See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child's birth order. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

in many cases, these models can be used to capture changes in the pattern of the effects but not for making profound conclusions about their magnitude.

No statistically significant results in connection to exposure to high prices are observed when studying separate cohorts (Table 6). All of the women born in 1813-1849 present higher odds of giving birth to a boy if they were conceived in years with high prices. Instead, for those born in 1850-1898, the odds ratio is below one for those with low SES and above 1 for those with high SES. When looking at those born into landless families, the odds are below one for those born in 1814-1849, while those born in 1850-1898 with high SES in adulthood show higher odds of giving birth to a boy. However, these results also lack statistical significance and relate to a small number of women and births.

Table 6: Cohort changes in the odds ratio of a male birth for women aged 25+ of low or high-medium current SES, exposed in early life to high prices, high IMR or whooping cough epidemics

EXPOSURE TO HIGH PRICES				
	Cohort 1813-1849		Cohort 1850-1898	
	Low SES	High SES	Low SES	High SES
High prices	1.09	1.14	0.86	1.09
	[0.88,1.34]	[0.94,1.39]	[0.70,1.06]	[0.90,1.33]
Frailty variance	0.002	0.002	0.001	0.135
Number of mothers	768	659	1202	1078
Number of births	2007	2054	2299	2530
EXPOSURE TO HIGH PRICES - LANDLESS AT BIRTH				
	Cohort 1813-1849		Cohort 1850-1898	
	Low SES	High SES	Low SES	High SES
High prices	0.92	0.75	0.97	1.67
	[0.58,1.46]	[0.33,1.70]	[0.51,1.84]	[0.83,3.41]
Frailty variance	0.000	0.000	0.000	0.087
Number of mothers	146	67	103	78
Number of births	435	207	247	217
EXPOSURE TO HIGH IMR				
	Cohort 1813-1849		Cohort 1850-1898	
	Low SES	High SES	Low SES	High SES
High IMR	0.94	1.17	0.92	0.86
	[0.76,1.16]	[0.94,1.47]	[0.75,1.13]	[0.70,1.06]
Frailty variance	0.000	0.000	0.000	0.020
Number of mothers	768	659	1202	1078
Number of births	2007	2054	2299	2530
EXPOSURE TO WHOOPING COUGH				
	Cohort 1813-1849		Cohort 1850-1898	
	Low SES	High SES	Low SES	High SES
Whooping cough epidemic	0.90	1.35*	0.75*	0.86
	[0.70,1.17]	[0.99,1.84]	[0.55,1.03]	[0.65,1.16]
Frailty variance	0.002	0.003	0.002	0.177
Number of mothers	694	595	1062	978
Number of births	1824	1861	2019	2307

Notes: See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child's birth order. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

In relation to the impact of exposure to whooping cough on the year of birth, declines in the odds ratios of giving birth to a boy are observed across cohorts for the two SES groups. Low SES women of both cohorts present reduced odds of a male birth (Table 6), with significant results only for the women born in

Table 7: Odds ratio of neonatal mortality for the offspring of women aged 25+ of current low SES according to their early life disease exposures

	Neonatal mortality
Exposure to whooping cough in y.o.b	
Low-medium disease load	ref.
Whooping cough epidemic	2.45**
	[1.21,5.00]
Child gender	
Female	ref.
Male	1.75**
	[1.13,2.70]
Child gender & exposure to whooping cough in y.o.b	
Male & whooping cough epidemic	0.39*
	[0.14,1.10]
Frailty variance	0.452
Number of mothers	1712
Number of children	3714
Number of neonatal deaths	118

Notes: See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child's birth order. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

1850-1898 (O.R. = 0.75, C.I. = 0.55-1.03, p-value = 0.072). Among those of high SES, the odds of a having male birth are higher for the exposed women born in 1813-1849 and lower for those born in 1850-1898 (Table 6), the first of these results being statistically significant (O.R. = 1.35, C.I. = 0.99-1.84, p-value = 0.058). When looking at exposure to all epidemics (high IMR), the impacts are rather similar for those of low SES within the two cohorts, but among those of high SES, the proportion of males was lower for the second cohort.

4.5.3 Possible mechanisms causing the association between a woman's early life conditions and her offspring sex ratio at birth

Table 7 presents the results of logistic regressions that analyse, for low SES women, the odds that a newborn child will die in the neonatal stage, introducing an interaction between the disease exposure of the mother in her year of birth and the gender of the child. It can be observed that male offspring face relatively higher risks of dying in the first 28 days of life than female offspring if their mothers were born in years with a low-medium disease load (O.R. = 1.75; C.I. = 1.13-2.70; p-value = 0.012). Instead, newborn males born to mothers exposed to whooping cough in their infancy have relatively lower probabilities of dying in the

Table 8: Odds ratio of a male birth or of offspring neonatal mortality according to the disease exposure of fathers of current low SES

	Male birth		Neonatal mortality	
	All	Mothers not wc	All	Mothers not wc
Exposure to whooping cough in y.o.b of the father				
Low-medium disease load	ref.	ref.	ref.	ref.
Whooping cough	0.95	0.96	2.34**	2.25
	[0.77,1.18]	[0.76,1.22]	[1.07,5.11]	[0.80,6.31]
Child gender				
Female			ref.	ref.
Male			2.10***	2.60***
			[1.32,3.36]	[1.46,4.63]
Child gender & exposure to whooping cough in y.o.b of the father				
Male & whooping cough			0.39*	0.350
			[0.13,1.16]	[0.09,1.42]
Frailty variance	0.000	0.000	0.000	0.021
Number of mothers	1575	1263	1575	1263
Number of births	3425	2715	3425	2715
Number of male births	1799	1445		
Number of neonatal deaths			104	73

Notes: See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child's birth order. The sample is restricted to cases where the mother was aged 25+ and was born in 1813-1898. Mothers not wc = cases where the mother was born in a year with low-medium disease load. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

neonatal stage (1.75 x 0.39 = 0.6825; p-value of interaction term = 0.074). This result indicates that male foetuses conceived by mothers who had been exposed to whooping cough in infancy faced more intense selection during their foetal stage (i.e., more male foetuses were aborted spontaneously), and consequently those that were born alive had relatively better health.

When evaluating the impact of the fathers' exposures to whooping cough on their reproductive outcomes (Table 8), patterns similar to those found for women are obtained, although the magnitude as well as the statistical significance of these effects is smaller. Among the low SES families, the sex ratios at birth were 106.19 for fathers born in years with whooping cough epidemics and 111.24 for those born in years with a low-medium disease load, while, as is shown in Table 8, the odds ratio of giving birth to a boy estimated through logistic regressions that introduced the same control variables as in the previous models is 0.95 (C.I. = 0.77-1.18; p-value 0.666). The results for estimations that consider neonatal mortality as the outcome are also similar to those of the mothers. In fact, female

Table 9: Sensitivity analysis – different formulations of early life condition indicators

	Low SES	Medium-high SES
DISEASE		
IMR	0.999	1.000
IMR deviation and trend		
Deviation	0.999	1.001
Trend	1.001	0.997
IMR deviation [a]		
0.05	0.829 ***	1.021
0.10	0.827 ***	1.038
0.15	0.837 **	1.030
0.20	0.921	0.988
0.25	0.897	0.946
0.30	0.909	0.916
0.40	0.891	0.896
PRICES		
Ln rye prices	0.892	1.223*
Ln rye deviation and trend		
Deviation	0.838	1.208
Trend	0.939	1.237
Ln rye prices deviation		
0.03	0.922	1.049
0.06	0.935	1.086
0.09	0.942	1.108
0.12	0.965	1.123
0.15	0.968	1.094
0.18	0.945	1.128
0.21	0.945	1.096
Ln rye prices deviation of 0.12 year prior to birth	0.967	1.123

Notes: see Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child´s birth order. Each result shown in the tables relates to a separate estimation model, except for trend and deviation, which are included in the same model. a – all years with a high relative deviation from the trend, regardless of whether whooping cough or other diseases were the main epidemic. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

offspring born to fathers exposed to whopping cough in their infancy are more likely to die in the first 28 days of life (O.R. = 2.34; C.I. = 1.07-5.11; p-value = 0.033). Furthermore, the newborn male offspring of fathers born in years with a low-medium disease load have higher mortality than the female offspring (O.R. = 2.10; C.I. = 1.32-3.36; p-value = 0.002), while the opposite patterns are found for the offspring whose fathers had been exposed to whooping cough (2.10 x 0.39 = 0.819; p-value of interaction term = 0.090). The statistical significance of these effects, however, disappears when restricting the studies to cases where the

mother was not exposed to whooping cough, although the direction of the results remains unchanged.

4.5.4 Sensitivity analysis

The patterns shown above are confirmed if the models are estimated with indicators that consider different threshold levels to define years with high prices or a high disease load (Table 9) or when introducing different control variables (Table 10), thus showing that the results are not dependent on the methodological choices adopted. In the interest of space, only the models that take into account all cohorts are shown, and when measuring the effect of exposure to high prices in the foetal stage, all women are included, regardless of whether they were landed or landless at birth.

When considering different formulations of the indicators of early life conditions (Table 9), women of low SES always present lower odds of a male birth if they were exposed to a high disease load in their first year of life, with significant effects for threshold levels below 0.2. The thresholds of deviation from the trend in IMR here relate to all high disease years, regardless of whether the most diffused disease in that year was whooping cough or another epidemic. The magnitude of the odds ratios as well as their statistical significance are stronger when the thresholds that define the years with a high disease load are lower (5, 10 and 15%). This result shows that even if the excess over the trend in infant mortality rates is small, these exposures negatively affect reproductive health. However, as the threshold level increases, so does the disease load in the reference category, which explains the reductions in the magnitude and significance of the relative impacts of these exposures on the sex ratio at birth. Reduced odds of a male birth are also observed when considering the actual value of the IMR as well as the deviation from the trend. However, neither of these is statistically significant, although they are not very far from it (p-value of 0.167 for the IMR and 0.120 for the deviation component). Effects of a similar magnitude and statistical significance to those seen in previous sections are also obtained when considering the indicator of exposure to whooping cough epidemics but changing the control variables that are included in the models (Table 10). There is only a small decrease of statistical significance in two of the models, although both are very slightly below the 5% threshold. As was shown earlier, no clear patterns are observed in Tables 9 and 10 in connection to the impact of whooping cough on women of medium-high SES.

Concerning the effect of exposure to high prices during the foetal stage, low SES mothers always present odds of having a male birth that are slightly under

Table 10: Sensitivity analysis – different control variables

	Mod. 1	Mod. 2	Mod. 3	Mod. 4	Mod. 5	Mod. 6	Mod. 7	Mod. 8	Mod. 9	Mod. 10	Mod. 11
Whooping cough / low SES	0.82**	0.82*	0.83**	0.83**	0.83**	0.83**	0.83**	0.82**	0.82**	0.81**	0.82*
Whooping cough / medium-high SES	1.06	1.07	1.06	1.06	1.07	1.07	1.06	1.07	1.07	1.08	1.07
High prices / low SES	0.97	0.97	0.97	0.97	0.97	0.96	0.97	0.97	0.97	0.97	0.97
High prices / medium-high SES	1.12	1.13*	1.12	1.12	1.12	1.12*	1.12	1.12	1.12	1.12	1.12*
Controls											
Parish of residence	x	x	x	x		x	x	x	x	x	
Birth of mother in studied parishes		x	x	x	x	x	x	x	x	x	
Mother's age	x	x	x		x	x		x	x	x	
Mother's age squared	x	x			x	x		x	x	x	
Mother's age as categorical variable							x				
Child's birth order	x	x	x	x	x		x	x	x	x	
Year	x		x	x	x	x	x	x	x		
Year squared								x	x		
Year cubed									x		
Decade										x	

Notes: See Table 1 for explanations on the early life conditions indicators. All models control for parish of residence, an indicator of whether the mother was born in one of the studied parishes or outside, year of birth of the child, maternal age and age squared and child´s birth order. Each result shown in the tables relates to a separate estimation model (for example, the first row represents the odds ratio of a male birth for mothers of current low SES exposed in infancy to whooping cough relative to those born in a year with low-medium disease load). * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

1 if they were conceived during years with high prices, while the odds are always slightly higher than 1 for high SES women (Tables 9 and 10). When considering different formulations for the indicators of high prices, all of the coefficients lack statistical significance except for the actual value of the logarithm of rye prices in the model of women of medium-high SES (Table 10). The results also remain constant when the price level for the year prior to birth is taken into account rather than linking the data in the method described earlier. When a 0.12 threshold is used to define high price years and the control variables are changed (Table 10), statistical significance is observed for the medium-high SES in three of the models, although they are always slightly below the 10% threshold.

Models were also estimated that introduced an interaction between the indicators of early life conditions and whether the mother was born in the studied parishes or migrated to them; the interaction term was not statistically significant for any of the three indicators considered (results not shown). Moreover, when running the same analysis as that considered in Table 5, but selecting only women born in the same parish as their current residence or in another parish within a 17-km radius of them, the patterns of the results remained very stable. In fact, the current low SES women exposed in infancy to whooping cough still present statistically significant reduced odds of a male birth (O.R. = 0.80; C.I. = 0.63-1.00; p-value = 0.055), while no significant differences are observed in relation to the same exposure for the current medium-high SES women (O.R. = 1.13; C.I. = 0.88-1.45; p-value = 0.324) or for women exposed to high prices in their foetal stage who were currently low SES (O.R. = 1.02; C.I. = 0.86-1.22; p-value = 0.809) or medium-high SES (O.R. = 1.07; C.I. = 0.90-1.26; p-value = 0.445).

4.6 Discussion

Using data from the SEDD for women born between 1813 and 1898, this work aimed to analyse the effects of early life exposures on the sex ratio at birth of a woman's offspring. Early life conditions were considered by whether the woman was conceived in a year with high prices or born in a year with a high IMR, representing exogenous indicators of the level of nutrition experienced during gestation and the disease load perceived in infancy, respectively. The impact of exposure to disease was evaluated generally as well as specifically to the impact of epidemics of whooping cough.

We have shown that at age 25 or older, women of low SES gave birth to a lower proportion of male offspring if they had been born in a year with a

whooping cough epidemic, an effect that was observed irrespective of the price level experienced by the woman during her foetal stage. The mothers of medium-high SES, instead, did not present variations in the sex ratio at birth of their offspring according to the level of disease that they had experienced in infancy. No significant effects were observed in relation to the impact of high prices during the foetal stage, although for mothers of medium-high SES, weak signs of higher sex ratios were seen. These results were obtained when constructing contingency tables and conducting Chi-squared tests as well as when estimating logistic regressions that introduced several control variables. A sensitivity analysis confirmed that the findings of this work are not dependent on the methodological choices adopted. When measuring the cohort changes on the impact of exposure to whooping cough in infancy, women born after 1850 showed a greater relative reduction in their offspring sex ratio at birth.

The results obtained here confirm that the impacts shown in Chapter 2 and 3 when considering mortality as an outcome during different stages of the life course are also present when focusing on offspring sex ratio at birth. The somewhat positive direction of the association between exposure to high prices *in-utero* and offspring sex ratio at birth relates to the dominance of selection, or health advantage, observed in previous chapters during the childbearing and working ages. Under selection, women born into landless families who were exposed to high prices *in-utero* had a reduced risk of death (Chapter 2). Similarly, the lower sex ratios at birth obtained for women of low SES who were born in years with whooping cough epidemics confirms the dominance of net scarring found earlier, when from approximately age 25, women exposed to this disease presented higher mortality relative to those born in years with a low-medium disease load (Chapter 3). Instead, when considering exposure to all epidemics (high IMR), the lack of statistically significant results observed here could be explained by the fact that, as was shown in Chapter 3 when focusing on mortality, women who had been exposed to measles or scarlet fever in their infancy presented a dominance of net selection during their childbearing and working ages. Nevertheless, in the sensitivity analysis section of this work, statistically significant lower sex ratios at birth were shown for low SES women when threshold levels below 0.2 were considered to define the years with a high IMR, and the effects of exposure to a high IMR always showed the same pattern as when considering specific exposure to whooping cough. Epidemics of whooping cough were well distributed across the studied period; therefore, comparing women born in these years to those born in years with a low-medium disease load does not represent a bias.

Stronger damaging effects on health from exposure to whooping cough were observed for women born after 1850 when focusing on mortality as well as on the offspring sex ratio at birth (Chapter 3 and this study). Such patterns could be

explained by the fact that the IMR was higher before 1850; therefore, individuals of the first cohort born in years considered to have a low-medium disease load could have faced unfavourable conditions that damaged their bodies and resulted in compromised health in later life. Instead, the impact of whooping cough was more severe in relative terms during epochs when the competing disease environments were weaker. These patterns could also be related to different morbidity during the adult ages because the first cohort was more exposed to infectious diseases and the second was more exposed to chronic diseases.

Although no associations in this work were found between SES and offspring sex ratio at birth, we showed that the relationship between exposure to disease in infancy and the proportion of male births was class dependent. It was therefore demonstrated that SES is an important later life modifier in this relationship. For women of low SES, the effects of adverse early life conditions could have interacted with those of miserable housing characteristics, impoverished quality and quantity of nutrition or high maternal workload, augmenting the propensity to experience spontaneous abortions. Instead, effects of these kinds may not have been encountered by high SES women due to better environmental circumstances and nutrition, lower workload and lower levels of perceived stress. The different impacts observed could also be related to distinct childbearing patterns.

With the aim of describing mechanisms that could possibly determine the results observed, the impact of the fathers' early life exposure to whooping cough on the sex ratio at birth of their offspring and the impact of the exposure of either parent to this disease on offspring neonatal mortality were also measured. The models focusing on fathers displayed similar results to those estimated for mothers, although the impacts were weaker. Nevertheless, this result shows that men's early life conditions could also affect foetal health and, therefore, that further research focusing specifically on men is required. It was also observed that the risk of dying in the first 28 days of life for the offspring of mothers with different early life disease experiences depended on the gender of the child. Male offspring born to mothers who were exposed to a low-medium disease load faced relatively higher odds of dying than the female offspring, confirming patterns generally observed in the literature, as males are more vulnerable to early life stress. Instead, boys born to mothers exposed to whooping cough in their infancy had lower probabilities of experiencing neonatal mortality than girls. Among female offspring, neonatal mortality was relatively higher for those born to exposed mothers, while for males, relatively lower mortality was found. Because the risk of spontaneous abortions is higher for male foetuses, this health selective advantage of newborn boys over girls is likely to indicate that women exposed to whooping cough experienced a higher incidence of spontaneous abortions of male foetuses. Possible mechanisms causing these patterns could have been

epigenetic transfers to the foetus of defective genes or pregnancy complications and impoverished conditions in the womb, occurring because of direct damage to the reproductive organs and hormonal systems or indirectly through developed diseases, for example, cardiovascular diseases or diabetes, or damage to other organs, for instance, the lungs.

Miscarriages not only cause the loss of the foetus, but they can also have multiple negative consequences for the health and wellbeing of women and their families. For example, the tissues from the placenta or the foetus might not be completely expelled from the uterus after a spontaneous abortion, often leading to haemorrhages and/or infection (World Health Organization, 2003). Today, women suffering these problems are treated with antibiotics and often require surgery to evacuate the uterus, but before the diffusion of penicillin, these risks might have been widely connected with future infertility and even could have been lethal. Spontaneous abortions could also be linked with mental distress and psychological morbidity, including grief, depression and anxiety (Lok & Neugebauer, 2007). These symptoms can be harmful to the health of women, negatively affecting the function of their immune systems, and they can also interfere with their personal relationships, especially the ability to care for other children (Ney et al., 1994). Single or recurrent miscarriages as well as reduced fecundity also result in a higher number of pregnancies taking place at advanced ages, which may lead to further health problems for the mother and the child, as well as the inability to attain the desired family size.

4.7 Conclusions

In recent decades, many works have shown associations between exposure to insufficient nutrition during gestation or to disease in infancy and later life health. The majority of these studies, however, concentrate on the elderly, and not much is known about the effects of these early life conditions on health during the childbearing and working ages. In particular, the literature looking at the impact of early life conditions on reproductive health is scant and inconclusive. The richness of the Scanian Economic Demographic database has allowed us to follow 86 cohorts from birth until old age and therefore to identify the stages of the life course where selection or scarring effects on individual health dominated in relation to exposures to adverse early life conditions. In this work, we also show that for the same age groups where net scarring had prevailed, women exposed in infancy to epidemics of whooping cough gave birth to a lower proportion

of boys than those experiencing more favourable early life conditions, possibly as a result of a greater incidence of miscarriages. Although the impact of early life conditions on mortality was constant across different SES groups, the effects on the sex ratio at birth were only found for the low SES women. Moreover, we demonstrate that exposure in infancy to whooping cough epidemics is more detrimental to later life reproductive health than exposure to high grain prices during the foetal stage and that the negative repercussions of this epidemic are not limited to exposed women but are also transferred across generations. These findings are new to the literature and provide scope for further research as well as having policy implications. Women who were exposed to infectious diseases in their infancy should, in fact, receive additional and/or specialised screening during their pregnancies, especially those belonging to lower socioeconomic groups.

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Chapter 5

The impact of early life conditions on socioeconomic status in adulthood, fertility and offspring neonatal mortality among 19th and 20th century women in Southern Sweden

5.1 Abstract

A growing body of literature has shown that early life conditions affect health and wellbeing later in life. The vast majority of these studies, however, have concentrated on the elderly. To understand the implications of these effects, the full life course needs to be considered, and other outcomes must be evaluated in addition to mortality. Using data on women born in Southern Sweden between 1813 and 1898, this study analyses the impact of exposure to high grain prices during the foetal stage or to a high disease load during infancy on socioeconomic status attainment, fertility and offspring neonatal mortality. No direct effects were found on fertility. Instead, females born into low SES families in a year with a high infant mortality rate or a year with a whooping cough epidemic showed a lower probability of attaining a high SES in adulthood. Similarly, in the period preceding the fertility decline, higher neonatal mortality was observed for offspring born to mothers who were exposed to a high disease load in infancy. No significant effects were found for women who were exposed to high prices during the foetal stage for any of the outcomes considered.

5.2 Introduction

In recent decades, a large body of literature has shown that later life health and wellbeing are strongly influenced by conditions experienced in early life. According to the foetal origins hypothesis introduced by Barker and co-authors (1994; 1995a; 1995b; 1997; 2001), chronic disease develops due to insufficient nutrition during the foetal stage (for more recent reviews see e.g., Almond & Currie, 2011; Currie & Vogl, 2012; Gluckman et al., 2008). Alternatively, the infancy inflammation hypothesis focuses on the role of the disease load experienced in the first years of life (e.g., Bengtsson & Lindström, 2000; 2003; Finch & Crimmins, 2004; Liuba, 2003). Stressful conditions in early life can permanently damage the body in a process that Preston and co-authors dub scarring (Preston, Hill, & Drevenstedt, 1998). Selection can also occur, as those individuals who resist adverse early life conditions may be genetically or congenitally stronger.

Conditions experienced in early life can affect health and wellbeing over the full life course. Much of the existing literature, however, focuses on demonstrating the relationships between these types of exposures and the development of chronic disease in old age, whereas the possible impacts during early and mid-adulthood have not been analysed in depth, particularly for women. Impoverished health and wellbeing during these stages of the life course have other consequences than morbidity and death, particularly because mortality is low at these ages. Other measures of health must therefore be considered if we hope to better understand the potential impacts of early life conditions. The candidate outcomes for such an analysis include socioeconomic status (SES) attainment and markers of reproductive health such as offspring neonatal mortality, sex ratio at birth and birthweight.

Using data from Southern Sweden for women born between 1813 and 1898, this work evaluates the impacts of adverse early life conditions on SES attainment in adulthood, fertility and offspring neonatal mortality. As early life conditions, we consider grain prices in the year of conception and the local infant mortality rate (IMR) in the individual's birth year, respectively, as indicators of the level of nutrition experienced during gestation and of the disease load perceived in infancy. Exposure to disease is measured generally and specifically using whooping cough epidemics. In the previous chapters of this thesis, which were based on the same data and used methodologies similar to those employed here, significant impacts on health were observed with respect to these exogenous indicators of early life exposures, and this work aims to determine whether similar patterns will also be found when other measures of health are used. Chapters 2 and 3 demonstrated that the effect of exposure to epidemics during the first year of life on mortality

varied according to the type of disease environment. More specifically, whereas net selection dominated during early adulthood for women who had been born in years with epidemics of measles and scarlet fever, beginning at approximately age 25, the probability of dying was relatively higher for females exposed to whooping cough in infancy. This dominance of net scarring was also observed in Chapter 4, in which women of low SES who were born in a year with a high disease load exhibited lower proportions of male births, likely as a result of a greater incidence of miscarriages of male foetuses. In addition, women exposed to high prices during their foetal stage had lower mortality during their childbearing and working years, which indicated the dominance of selection (Chapter 2), although no significant effects were found with respect to this variable when the offspring sex ratio at birth was the outcome of interest (Chapter 4). This work also seeks to determine whether similar effects are also found when different measures of health are considered.

5.3 Background

Inadequate nutrition in early life can permanently damage the body. According to the foetal origins hypothesis, the 'disproportionate' retardation in growth caused by insufficient nutrition during the second and third trimesters of pregnancy leads to low birth weight, increasing systolic blood pressure in adulthood and the risk of heart disease later in life (Barker, 1994; 1995b). If the supply of nutrients or oxygen is insufficient, the rate of cellular division declines as an adaptive mechanism, negatively affecting tissues that are undergoing 'critical' development (Barker, 1995b). Changes in the distribution and number of cells and in organ structure and the resetting of hormonal feedback and metabolic activity permanently affect the structure, physiology and metabolism of the body (McCance & Widdowson, 1974). These permanent changes in the body's structure and function 'program' disease that manifests later in life.

The body may also be permanently affected by exposure to disease in early life. Some types of infections can directly damage organs. For example, streptococcal infections can cause rheumatic heart disease (Jones, 1956), and respiratory infections in early life have been associated with lung impairments at later ages (Barker et al., 1991; Bengtsson & Lindström, 2003). Infection in the first years of life can also reduce general immunity to disease throughout the life course (Fridlizius, 1984; 1989). Finch and Crimmins claim that cancer, diabetes, cardiovascular, respiratory and other chronic diseases in old age are the result of chronic inflammatory mechanisms; short-term adaptive responses to infections

or injuries in early life become maladaptive in the long run (Crimmins & Finch, 2006; Finch & Crimmins, 2004).

The hypotheses of inflammatory infection and nutrition are not necessarily competing or contradictory; rather, they may be complementary (Finch & Crimmins, 2004). Exposure to disease, in fact, can also have an effect on net nutrition. The 'nutritional status' of an individual is a net measure of the energy that can be used for growth after that required for body maintenance, disease resistance and work has been subtracted (Floud et al., 2011). Infections can influence nutritional status by reducing appetite, worsening the quality of the ingested diet, increasing the metabolic loss of nutrients and the metabolic needs of the body and decreasing the absorption of nutrients (Bellagio conference authors, 1983).

5.3.1 Possible impacts of early life conditions on SES attainment

Occupations are good indicators of social position in historical populations. Van Leeuwen and Maas (2010) wrote a review article that discusses factors that may potentially affect social mobility and stratification within industrialising societies. They argue that occupations are determined by intergenerational mobility, through marriage mobility or by mobility within an individual's career. Indicators of economic and social change such as industrialisation and urbanisation, geographical mobility and educational expansion can affect intergenerational mobility. Moreover, social mobility during the life course, or career mobility, can be influenced by formal hierarchical structures, the development of internal labour markets, increased education, migration patterns and discrimination related to race, religion or sex. These authors outline the existing theories stating that individuals tend to marry within their own social groups because of personal preferences, culture, pressure from others or constraints imposed by the marriage market. Nevertheless, marital mobility does exist, and it is affected by the longevity of the individual's parents and the person's economic dependency on them, the availability of social security (which reduces dependency), migration, educational development and the degree to which transportation systems have expanded the individual's networks.

Dribe, Lundh and Svensson studied partner selection and social mobility in 19th century Scania. Social attainment was shown not only to depend on individual factors and network availability but also to depend strongly on inheritance and partner selection, and the social origin of both the individual and the spouse were important determinants (Dribe & Svensson, 2008). Men and women who were born into higher-status families were more likely to form homogamous unions, which helped them to maintain or increase their income, wealth and social status,

while for those originating in lower-status families, having a partner from a higher class increased the chances of experiencing upward mobility (Dribe & Lundh, 2009). Both men and women experienced greater upward SES mobility if they married a spouse from a higher SES background, whereas those who married someone from a lower class were less able to experience upward SES mobility and experienced a greater risk of downward mobility (Dribe & Lundh, 2010). Access to land was one of the most important determinants of socioeconomic status in rural societies; in pre-industrial Sweden, land could be acquired through inheritance, becoming a tenant, purchasing land on the market, or marrying (Dribe & Svensson, 2008).

In examining the various possible determinants of SES attainment, the current research exclusively focuses on those that originate in early life. The exposures experienced during development may influence SES at older ages through individual capabilities. Fogel and Costa (1997) and Floud et al. (2011) claim that the economic growth experienced during the last three centuries in much of Europe and the United States is largely the result of improvements in nutritional status, which have allowed greater labour force participation and work intensity. Early life exposures also affect individual capabilities through cognitive ability (Case, Fertig, & Paxson, 2005; Case & Paxson, 2008)

Several studies have shown associations between early life conditions and SES attainment in adulthood. Using data for the period from 1813 to 1894 for the parishes studied in this work, Bengtsson and Broström observed that exposure to disease in infancy influenced an individual's probability of belonging to the landed class at age 50 but that socioeconomic position at age 50 did not have an effect on old age mortality (Bengtsson & Broström, 2009). Palloni and co-authors showed, for the 1958 British Cohort, that early childhood health has an influential role in adult SES through cognitive ability (Palloni et al., 2009). Moreover, they indicated that early childhood health also influences the socioeconomic gradient in health in adulthood. Based on data from the United States and the United Kingdom, Case and Paxson concluded that cognitive ability explains the existing association between earnings and height; cognitive ability is related to the timing of adolescent growth spurts and therefore to early life conditions (Case & Paxson, 2008). Other studies conducted using contemporary or historical data from developed and developing countries have shown that health and nutrition in early life influence cognitive development, health and educational attainment in childhood as well as height, SES attainment, earnings, economic productivity and labour supply decisions in adulthood (Johnson & Schoeni, 2011; Lundberg, 1991; Smith, 2009; Victora et al., 2008).

In historical studies, the SES of females is primarily measured through the husband's occupation and is therefore substantially influenced by marriage

mobility. In addition to SES attainment itself, marriage partner selection can be influenced by conditions experienced in early life. Individuals choose their partners to improve their life chances as well as because of romantic considerations, socioeconomic and cultural factors, and this selection process can also be influenced by health (van de Putte, Matthijs, & Vlietinck, 2008). Three types of health characteristics may be influential: health conditions (physical or mental illnesses), physical qualities that relate to past or current health (e.g., weight and height) and behaviours connected with health (e.g., smoking and drinking) (Fu & Goldman, 1996). In preindustrial populations, marriage partner selection has been shown to be affected by physical attributes such as strength, weight, height and previous health experiences (Baten & Murray, 1998; Fu & Goldman, 1996; Sköld, 2003).

In a study of marriage partner selection in a Flemish Village between the 18th and 20th centuries, Van de Putte and co-authors found that the probability of marriage was generally greater for individuals whose families of origin had low infant and child mortality (van de Putte et al., 2008). Spouses who were born in families with high mortality were more likely to marry a partner who was also born into a high mortality family, which indicated a tendency toward homogamy. Among men, homogamy was greater for the sons of farmers than for elite sons or men whose fathers were lower class. Another study conducted on 19th century Bavaria showed strong evidence that women of short stature were less likely to marry than women of average height (Baten & Murray, 1998). A similar finding was also obtained for males in an analysis based on two Italian populations at the turn of the 20th century; when SES was controlled for, short men presented a lower probability of marrying (Manfredini et al., In Press).

In this study, SES attainment for females in adulthood is measured using the highest registered occupation for the family head. We hypothesise that early life conditions may affect SES attainment by influencing intergenerational mobility, the probability of marriage and partner selection, and the ability to experience career mobility. One of the underlying hypotheses considered here is therefore that the potential associations between early life conditions and a woman's SES attainment in adulthood may be caused by her capacity to accumulate wealth prior to marrying and her attractiveness in the marriage market. The latter could be related to wealth, current health and physical characteristics. To avoid prolonged or permanent celibacy, women exposed to adverse early life conditions and born into low SES families may accept not marrying upward. For the same reasons, those born into high SES families might need to marry downward, although this is less likely. We also hypothesise that another channel through which adverse early life conditions may influence SES attainment is limitations on the individual's or the couple's capacity for upward career mobility.

5.3.2 Possible impacts of early life conditions on fertility and offspring neonatal mortality

Fertility results from a mixture of biological and behavioural factors, as described in Bongaarts' framework of proximate determinants (Bongaarts, 1978; 1993). Behavioural factors include age at marriage, duration of post-partum infecundability due to breastfeeding and/or abstinence, frequency of intercourse and, in post-decline populations, contraception. Biological factors influence the age of the onset of sterility, intra-uterine mortality and the biological risk of conception failure (Bongaarts, 1978; 1993). Approximately 50% of embryos are aborted spontaneously, usually due to abnormalities in their development or that of the surrounding protective and nutritive structures (Tanner, 1989). Fecundity also varies by age (Wilson, Oeppen, & Pardoe, 1988).

An important variable that can affect fertility is the death of previous children. Fertility responses to the death of an infant or child can be voluntary or involuntary, as discussed by Tsuya, Campbell and Feng (2010). Women who experience the premature death of an infant are more likely to conceive, as lactation has a restraining effect on ovulation, and therefore, the interruption of breastfeeding shortens the duration of postpartum amenorrhea. Moreover, a couple may wish to replace a deceased child, and the likelihood of experiencing a successive birth may consequently be higher after a death. In addition to considering these two mechanisms, Preston (1978) also argues that parents who expect that some of their children will die may adopt an active and anticipatory strategy by having more children and thus may exhibit higher fertility than they would have if survival were more certain; he defines this as an insurance or 'hoarding' strategy. He also states that the link between mortality and fertility may be related to society, with institutional forces ensuring the maintenance of high fertility levels to overcome the effect of high levels of mortality. The relative importance of childhood mortality for fertility has changed over the course of the transition, with biological mechanisms related to the premature termination of breastfeeding dominating initially, followed by the prevalence of insurance behaviour and lastly by replacement (Montgomery & Cohen, 1998).

Another important determinant of fertility is SES. SES is a good measure not only of variations in wealth across individuals but also of other factors such as investments in education, household labour demand or the characteristics of work environments (Dribe, 2009). Research conducted by Bengtsson and Dribe revealed that in Scania, there were differences in fertility according to SES before the decline that also affected the timing of the decline. Before the transition, couples working in higher SES occupations and farmers had the highest fertility levels (Bengtsson & Dribe, 2009).

Childbearing patterns and the conditions experienced during gestation influence the likelihood that offspring will experience neonatal mortality. Neonatal mortality includes both early and late neonatal deaths, which occur, respectively, on days 0-6 and 7-27 of life. Early neonatal mortality is often related to maternal health and nutrition during gestation, pregnancy complications, obstetric problems during delivery, premature birth, low birth weight, malformations, the newborn child's lack of adaptation to the extrauterine environment and poor partum or post-birth hygiene (World Health Organization, 2006). In contrast, late neonatal deaths are more frequently linked to infections and poor after-birth care. Currently, approximately 1% of all newborn infants have a major congenital malformation, and approximately 15% weigh less than 2500 g; these complications are particularly common in developing countries (World Health Organization, 2006).

Fertility and the likelihood that newborn offspring will survive may be strongly influenced by the conditions that a woman experienced in her early life, which could hinder her biological ability to conceive or carry a pregnancy to term and which could have adverse effects on the health of her foetuses. The reproductive system begins to develop at the time of sex-specific organogenesis during gestation and continues to mature in the perinatal period and at puberty (Lemasters et al., 2000). This system is therefore sensitive to adverse exposures in any of these stages. For example, girls who are born small for their gestational age have smaller uteruses and reduced ovarian volume, (Ibanez et al., 2000) and malformations of the uterus can compromise a woman's ability to carry a pregnancy to term (Lumey & Stein, 1997). Moreover, inadequate growth of specific organs can lead to hormonal deregulation (Barker, 1995b). The hypothalamus-pituitary-gonadal axis, which in females connects the brain, the gonad (an endocrine hormone-producing gland) and the ovaries, regulates human development, reproduction and ageing. This axis must function correctly for ovulatory cycles to be regular (Elias et al., 2005). Female fecundity is strongly linked to hormones, which determine the size of the ovum (Apter et al., 1987), its fertilisability, (Yoshimura & Wallach, 1987) the success of implantation and the maintenance of the pregnancy (Ellison, 1996). All of these conditions also affect the health of the foetus and newborn offspring.

Inadequate nutrition or infections in early life may also cause damage to organs and cells that are not part of the reproductive or hormonal systems but that may indirectly affect a woman's ability to conceive or carry a pregnancy to term as well as the health of the foetus or new-born offspring. Such exposures may also lead to the development of diseases, which could have the same effects. For example, individuals who are exposed to adverse early life conditions are more likely to develop type 1 (Montgomery et al., 2002) or type 2 diabetes (Barker, 2004; Sotomayor, 2012). Females with type 1 diabetes may have lower fertility, and they are more likely to give birth to offspring with congenital malformations

(Jonasson et al., 2007) and to experience complications such as preeclampsia and infections or to need to deliver through caesarean section (Department of Health and Human Services, 2001). The survival of foetuses and newborn offspring may also be compromised if the mother has reduced lung function or experiences cardiovascular problems, two conditions that are often associated with adverse early life exposures. Lung function is altered during pregnancy, and the foetus is dependent on the mother's lungs for oxygenation (Bhatia & Bhatia, 2000). Pathological respiratory or cardiovascular diseases that exist before conception can worsen during gestation, as the increases in oxygen consumption that are necessary for foetal growth cause physiological respiratory and hormonal changes (Felten, Mercier, & Benhamou, 1999). Associations have also been found between acute respiratory infectious diseases and preterm births (Bánhidy et al., 2008) and between severe maternal asthma and lower offspring birth weight (Greenberger & Patterson, 1988). Moreover, women with congenital heart disease have a higher incidence of miscarriages, and their foetuses are more likely to be born prematurely and with lower weight. They are also more likely to develop congenital heart disease (Presbitero et al., 1994).

A connection between women's adverse early life exposures and their fertility or the health of their offspring may also exist through epigenetics and epigenetic inheritance. Under stressful environmental conditions, a given genotype can give rise to different phenotypes and can subsequently be expressed in diverse physiological or morphological states through developmental plasticity without modifications to the DNA sequence (Bateson et al., 2004; Jablonka & Raz, 2009). Epigenetic changes can programme disease in later life (Lucas, 2007) and, consequently, can also result in worse reproductive health. These alterations in a parent's genetic expression can be transferred to the next generation in a process called epigenetic inheritance (Jablonka & Raz, 2009; Lummaa & Clutton-Brock, 2002). Due to impoverished foetal health, exposed women may therefore be more likely to experience spontaneous abortions or neonatal mortality.

The previous literature focusing on the impact of early life conditions on reproduction and offspring viability is scant and inconclusive. Moreover, it only evaluates the role of exposure to inadequate nutrition, disregarding the possible effects of disease. Some studies have found associations between birth weight and age at first birth (Ekholm et al., 2005), time to achieve a pregnancy (Nohr et al., 2009) and fecundity (Ekholm et al., 2005). Short length at birth and reduced weight gain in the first year of life were also linked to the earlier onset of menopause (Cresswell et al., 1997). Another study demonstrated that being underweight/overweight is related to the age at menarche (Frisch, 1994) and to a woman's likelihood of experiencing menstrual problems (Lake, Power, & Cole, 1997). Furthermore, associations were found between the season of birth and the

probability of experiencing menstrual disorders, earlier menarche and early or late menopause, (Jongbloet et al., 1994) as well as with fecundability (Nonaka et al., 1990), length of reproductive lifespan, number of live births and the survival of offspring to adulthood (Lummaa & Tremblay, 2003).

The impacts of famines were also examined by different scholars, but the conclusions reached across different studies were not always identical. Women exposed to the Dutch Hunger Winter gave birth to low weight offspring that experienced higher perinatal mortality (Lumey & Stein, 1997). In one study, no impacts were observed on age at menarche, the proportion of women who remained childless, age at first birth, the total number of children or inter-birth intervals (Lumey & Stein, 1997), and in another, the exposed women actually exhibited greater reproductive success (Painter et al., 2008). However, a decreased probability of experiencing births was found in an analysis that considered women who were exposed to this famine during childhood and adolescence (Elias et al., 2005). Another study that examined the impact of crop yields during the birth year in 18th century Finland found associations between this factor and a woman's probability of marrying and giving birth to at least one child as well as the viability of offspring for men and women born into landless families (Rickard et al., 2010).

5.4 Expected findings

Expectations can be formulated based on the results presented in of the previous chapters of this thesis. Because females who were born in years with whooping cough epidemics presented a higher probability of dying in early adulthood and lower offspring sex ratios at birth, here we also expect to find a dominance of scarring effects, manifested in reduced probability of attaining high SES in adulthood, lower fertility and higher offspring neonatal mortality. However, the expected outcomes for females exposed to high IMR[31] in infancy or to high prices during their foetal stages are less clear, as selection effects dominated during reproductive ages, particularly for those conceived in years with high prices. It is anticipated that selection will also dominate to some extent for the outcomes considered here. We expect that if exposure to high prices during the foetal stage has significant effects, these effects will be more marked for women born into low SES families. Grain prices only represent a measure of nutrition for individuals

31 In Chapter 3, females exposed to epidemics of measles or scarlet fever in infancy presented a lower probability of dying during adulthood than did those born in years with a low-medium disease load; those exposed to whooping cough presented a prevalence of net scarring.

who are net consumers, particularly in earlier historical societies, where a large fraction of income was spent on food. In Scania during the 19th century a social gradient was in fact observed in the fertility and mortality response to short-term economic stress, showing that the landless and semi-landless were more vulnerable than individuals pertaining to other social groups (Bengtsson & Dribe, 2006; 2010; Bengtsson, 2000; 2004).

We expect the impacts of early life exposures on fertility to be stronger prior to the fertility decline, as after the decline, behavioural factors dominated biological effects in terms of importance. The decline in fertility was observed in this region beginning in the 1890s and continued uninterrupted until the 1930s (Bengtsson & Dribe, 2009). It began slightly later than in the country as a whole, where declines were observed beginning in the 1880s (Bengtsson & Dribe, 2009). As in Sweden as a whole, declines occurred across the entire reproductive span, not only due to the cessation of reproductive behaviour after the desired parities had been reached but also due to prolonged birth intervals (Bengtsson & Ohlsson, 1994; Bengtsson & Dribe, 2009; Dribe, 2009).

We also anticipate that the effects of early life conditions on SES attainment and the offspring's neonatal mortality will be more marked than their effects on fertility. Early life conditions may affect various proximate determinants of fertility, but each of these effects may also influence fertility in opposite directions. For example, these exposures could generate disturbances or changes in the patterns of breastfeeding, although the resulting effect on birth intervals might not necessarily be unidirectional. Mothers with compromised health, for instance, may be incapable of breastfeeding for prolonged periods or even at all; however, weak females may extend lactation to increase the survival prospects of their offspring. The length of time the last-born child is breastfed may also be shortened if the parents are seeking to replace recently deceased children. In couples with compromised health, the length of post-partum abstinence may also increase or decrease for the same reasons. The effects of early life conditions on access to or age at marriage could also affect fertility. Finally, even if adverse early life exposures have increased a woman's likelihood of having difficulty conceiving or of experiencing a spontaneous abortion, the parents may have adopted a hoarding strategy, increasing childbearing to guarantee that at least a certain number of their children survived.

We also anticipate that some of the effect of early life conditions on fertility may work through SES attainment and child mortality, but each in opposite directions, therefore reducing the total impact observed. Women who are exposed to whooping cough epidemics are likely to experience higher neonatal mortality among their offspring, which will lead to shorter successive birth intervals and therefore indirectly to increases in their fertility. However, women with the same

exposures are less likely to attain high SES in adulthood, and, especially prior to the fertility decline, this impact should have indirectly led to reductions in fertility.

5.5 Data and methods

The aim of this work is to evaluate the impacts of exposure to high prices in the year of conception, high IMR in the birth year and whooping cough epidemics in the birth year on SES attainment in adulthood, offspring neonatal mortality and fertility. We use data from the Scanian Economic Demographic Database (SEDD)[32], which provides information on births, deaths, marriages and migrations for the period from 1813 to 1968 in the parishes of Halmstad, Hög, Kävlinge, Kågeröd and Sireköpinge, which is located in the southern Swedish region of Scania. Register type data from catechetical examination registers (*husförhörslängder*), together with information on births, marriages and deaths from church books maintained by the clergy, were used to construct this database. Individuals are therefore followed from the time they are born or immigrate until they die or outmigrate. The material employed is of high quality, and the gaps in births, deaths and marriages are limited[33]. The five parishes were located near one another, and throughout the studied period, they presented variations in topography, size and socio-economic conditions that were common to peasant societies (Bengtsson & Broström, 2009). The area considered was open farmland except for the northern part of Halmstad, which was more wooded. The southern localities became industrialised and urbanised in the last decades of the nineteenth century. Throughout the studied period, the major population growth in these parishes occurred in Kävlinge, which was transformed from a rural village to a small industrial town with several railroad connections and factories (Bengtsson & Dribe, 2009).

The SEDD also contains information on occupations that was obtained from poll-tax (*manltaslängder*) and income (*inkomslängder*) registers. All occupations in the database were coded into HISCO (van Leeuwen, Maas, & Miles, 2002) and were later classified according to SOCPO (van de Putte & Miles, 2005), which is

32 The SEDD was created in a collaborative project between the Regional Archives in Lund and the Centre for Economic Demography at Lund University (Bengtsson, Dribe, & Svensson, 2012) and as structured using the format suggested by the Intermediate Data Structure (Alter, Mandemakers, & Gutmann, 2009). This study used SEDD version 3 beta. The data were converted into spells using the code developed by Quaranta (2012).

33 Calculations made showed that for all occupational groups, at least 40% of all infant deaths occurred within the first month of life.

a scheme that comprises five categories based on skill level, degree of supervision and whether one is self-employed as well as on pure status. SOCPO 5 represents the highest status and 1 the lowest. This classification scheme is considered in the analysis because it is highly correlated with education and income and can therefore capture potential differences in living conditions and childbearing patterns. The SES of the woman's family of origin and her current SES are considered in different parts of this study[34]. Because this area was characterised by very high migration rates (Dribe, 2000; 2003), where possible, married individuals were traced back to their birth parishes when the SEDD was constructed so that information about the occupation of their fathers at the time of their birth could be included.

Data on the price of rye are also employed. The reason that this cereal is considered is that it was the most common grain in this part of the country during the period under study (Bengtsson & Dribe, 1997). We use prices of the *födgeri* of Landskrona (Bengtsson & Dribe, 1997). A *födgeri* is a rural level below the county and prices were reported shortly after the harvest in the fall. Each year, prices were reported shortly after the fall harvest (Bengtsson & Dribe, 2006). It was not possible to use quarterly or monthly data because the data is only available for shorter periods. Nevertheless, seasonal fluctuations were rather limited, and the variations in prices were dominated by year-to-year changes.

In evaluating the impact of exposure to high prices during the foetal stage, we estimated the models for the full sample of women and specifically for those whose families of origin was of low SES (considered here as SOCPO 1-2). As mentioned above, in historical populations, grain prices only represent a measure of nutrition for net consumers. Net consumers could also have been identified using data on land size. However, whereas information on occupations is available for individuals migrating into the studied parishes, data concerning land size is only available for those born within them. Limiting the sample to this group of women would have

34 The estimations that consider current SES refer to the occupation of the head of household. Therefore, for married women, their husbands' occupations is used; for single women living in their parental homes, their fathers' occupations are used; and for single women forming their own households and for life-cycle servants, their own occupations are considered. Daughters and unmarried servants are, however, a minority. Several steps were taken to replace missing occupations using other available data. When there were gaps in the occupation data from the census records, these gaps were filled for cases in which the occupation in the years preceding the gap was identical to that of years that followed it. For widows, occupation was filled down for the first nine months after the death of their husbands. In the next step, all occupations that were still missing were replaced by 'farmer' (SOCPO 4) if the family owned land; this information was obtained from poll-tax registers. For recently formed families with still unknown occupations, occupational data were successively replaced with the first declared occupation if fewer than two years had elapsed between the two dates. Finally, the remaining missing occupations were replaced by 'crofter' (SOCPO 2) if the family lived in croft land or in a house according to the poll-tax registers.

yielded a small number of cases, particularly with regard to neonatal deaths[35], and therefore, we chose to consider the occupation of the birth family of each woman to obtain a subsample of individuals originating from families that were net consumers.

The current study is limited to women born between 1813 and 1898 who gave birth in the period from 1828 to 1948. In considering mortality as the outcome, Chapter 3 indicated that selection dominated until age 25 for females who had been exposed to whooping cough during their infancy and that scarring dominated after this age. Moreover, in Chapter 4, negative effects on offspring sex ratios at birth were only found after age 25 for women exposed to this disease. We therefore exclude from the current study all females who died before the age of 25. This change makes it possible to exclusively concentrate on women for whom the effect of net scarring was greater when considering different outcomes and therefore to determine whether similar effects can also be found when SES attainment, fertility and offspring survival are considered. The final sample includes 4,167 women.

Fertility is studied separately for the periods from 1828 to 1889 and from 1890 to 1948 to measure possible changes related to the fertility decline. Because offspring neonatal mortality can be largely dependent on childbearing patterns, different models are also estimated for the two periods for this outcome.

5.5.1 Measures of early life conditions

To measure the impact of nutrition during the foetal stage, we employ rye prices in the year prior to a woman's birth as indicators. We use local IMR, calculated directly from the data, to capture the effect of exposure to disease during the first year of life. Both of these are exogenous indicators of early life conditions. Because the literature shows that nutrition during the second and third trimesters of pregnancy is most influential to health later in life, instead of considering the prices for the harvest year[36] prior to birth, this study links each woman to the prices in the harvest year in which at least half of the last two trimesters of her pregnancy occurred.

The local IMR and the logarithm of rye prices were decomposed into trend and cycle components using the Hodrick Prescott filter with a filtering factor of 6.25, which is the value that is usually selected for yearly series. Relative rather than absolute deviations from the trend in IMR were considered because there is a high correlation between IMR and its cyclical component. Relative deviations

35 Only 38 neonatal deaths were observed among the offspring of women born in the studied parishes.

36 A harvest year is the period between October 1st and September 30th of the successive year.

in IMR were calculated by dividing the short-term component of IMR by its long-term trend. Logarithms already represent relative values, and therefore, the actual deviations from the price trend were used in the analyses. Years with a positive relative deviation from the IMR trend of at least 0.20 were considered years with a high disease load, and years with a positive deviation of at least 0.12 from the logarithm of the rye price trend were considered years with low food availability[37].

In addition to measuring the impact of infant exposure to a high general disease load on fertility, we also specifically evaluate the effects of exposure to whooping cough epidemics. As mentioned above, this step makes it possible to study whether exposure to an illness that was shown in previous chapters to result in higher mortality and reductions in the offspring sex ratio at birth also negatively influences fertility, SES attainment and offspring neonatal mortality. To define these epidemics, the major cause of death was identified for each year that had high deviations from the IMR trend. Due to the limited number of observations, the causes of death for all children who died at ages 0-10 were considered rather than only those of infants. Based on these data, 1821 and 1846 were identified as years with measles epidemics, 1838 as a year with a smallpox epidemic, 1860 and 1869 as years with scarlet fever epidemics, 1816, 1826, 1831, 1832, 1835, 1853, 1859, 1874 and 1894 as years with whooping cough epidemics and 1842 as years with epidemics of other diseases (dropsy, pain, etc.). Years with a low relative deviation from the IMR trend were considered to have a low-medium disease load. Although the threshold that indicates high IMR was not exceeded in 1877, 1877 was considered a high disease year because nearly 60% of all childhood deaths resulted from scarlet fever. We study the specific effect of exposure to whooping cough, but due to the small number of available observations, we do not separately analyse measles, smallpox or scarlet fever. Furthermore, in focusing on mortality, Chapter 3 revealed that net selection dominated during childbearing ages for females exposed to measles or scarlet fever in their first year of life and therefore that studying the impact of these exposures would likely show less defined effects on the outcomes considered here than exposure to whooping cough.

37 These threshold levels correspond to approximately the eightieth percentile in the distribution of relative deviations from the IMR trend and of deviations from the trend in the logarithm of rye prices; approximately one of every five years was characterised by high prices or high IMR. Years with high IMR are 1816, 1821, 1826, 1831, 1832, 1835, 1838, 1842, 1846, 1853, 1859, 1860, 1869, 1874, 1877, 1881, 1886 and 1894, whereas those with high prices are 1818, 1819, 1826, 1831, 1837, 1841, 1842, 1846, 1847, 1853, 1855, 1861, 1867, 1868, 1873, 1880, 1881 and 1891. When mortality and the offspring sex ratio at birth were considered as outcomes (Chapters 2 and 4), a sensitivity analysis showed that the results remained constant when different threshold levels were considered to define the years with a high disease load or high prices or the actual values of IMR and prices or of their deviations from the trend.

5.5.2 Statistical models

The effects of exposure to high prices during gestation or to a high IMR or a whooping cough epidemic in the year of birth are each analysed separately, comparing exposed women, respectively, to those conceived in years with low-medium prices or to those born in years with a low-medium disease load. SES attainment in adulthood is estimated by measuring the probability that the woman belonged to a medium-high SES (SOCPO 3-5) family in her adult years using logistic regressions. Adult SES is operationalised as the highest SES level observed from the woman's first observed birth until age 50 and, as mentioned above, is based on the occupation of the head of household. In each model, the indicator for early life conditions is interacted with SES at birth (low: SOCPO 1-2; medium-high: SOCPO 3-5), and females with unknown SES at birth are therefore excluded. This part of the study considers 2,937 women. Controls are also introduced for parish of residence and the woman's birth decade (a categorical variable) along with an indicator for whether she was born in one of the studied parishes or migrated into it. A sensitivity analysis is also conducted by re-estimating the same model while individually excluding each of these control variables and considering different formulations of the trend component (year of birth, year of birth squared and year of birth cubed). All estimations conducted in this study are made using STATA 12.

The probability of offspring neonatal mortality is estimated by considering whether a woman's last-born offspring died in the first 28 days of life. Due to the limited number of observations, we do not distinguish between early and late neonatal mortality. This outcome is also modelled using logistic regressions, in this case including a random effects component for the woman to account for shared characteristics. The models also control for parish of residence, the child's decade of birth (a categorical variable), the mother's age (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49) and an indicator for whether the mother was born in one of the studied parishes. Separate estimations are performed for the periods 1829-1889 and 1890-1948, and stillbirths are excluded from the study. In all, 10,226 children are considered, of whom 335 experienced neonatal deaths. A sensitivity analysis is also conducted for this case by including different control variables and diverse formulations of mother's age and the trend component.

The impact of early life exposures on fertility is measured by considering the time to childbirth. The analysis is limited to second and higher order births because first births are highly connected with marriage decisions. The overall effects of early life conditions on the probability of experiencing second and higher order births are estimated using piecewise constant hazard rate models that employ six-month periods for the baseline hazard. The duration is therefore the time elapsed

since the previous birth, and all of the models are truncated at eight years. Births occurring in 1829-1889 and 1890-1948 are studied separately, and all models control for parish of residence, decade (a categorical variable), the age of the woman (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49) and an indicator for whether she was born in one of the studied parishes. Moreover, a shared frailty component is used in these models to account for characteristics shared by the woman across all her births. The variance component is assumed to follow an inverse Gaussian distribution. Current SES and previous child survival are not included in the models because they could be correlated with the indicators for early life conditions and therefore would lead to biased estimates. Nevertheless, these factors are included as control variables in the sensitivity analysis, in which additional estimations are conducted excluding different control variables and employing various formulations of age and the trend component. Moreover, to avoid confounding, all females are considered regardless of their marital status. Tests based on the Shoenfeld residuals, obtained from Cox regressions, are conducted after each analysis to assess the proportionality of hazards assumption. No statistically significant violations of this assumption were observed in relation to the indicators of early life conditions.

The effects of current SES and previous child mortality on the probability of experiencing a second or higher order birth are each estimated in separate models without controls for early life conditions. Piecewise constant hazard rate models are used, and each estimation includes controls for parish of residence, decade (a categorical variable), the age of the woman (a categorical variable) and an indicator for whether she was born in one of the studied parishes. Due to a violation of the proportional hazards assumption, current SES and previous child survival are allowed to vary within the intervals of 0-2.5 and 2.5-8 years from the previous birth, and the baseline hazard also considers these time periods.

5.6 Results

5.6.1 SES attainment in adulthood

In their adult years, 53% of women have attained high SES, and 46% have the same SES at birth and in adulthood. Table 1 presents the distribution of women based on a combination of birth and current SES. Of those who were born into low SES families, 43% were medium-high SES in adulthood. Of the women born into medium-high SES families, 68% remain high SES in adulthood.

No significant differences in the odds of being of high SES in adulthood are observed for females conceived in years with high prices when the full sample of women is considered (Table 2). Similarly, no significant effects are observed when only women born into low SES families are considered, although they exhibit an odds ratio above unity.

Females born in years with high IMR and who had low SES at birth present relatively lower odds of attaining high SES in adulthood than those born in years with a low-medium disease load (O.R. 0.67, statistically significant at the 1% level). Those who had high SES at birth had a higher probability of also having high SES in adulthood (O.R. 2.55, statistically significant at the 1% level), but they did not present variations in these odds if they were exposed in infancy to high IMR (0.67 x 1.39 = 0.93; interaction term not statistically significant).

Females born in years with whooping cough epidemics exhibit effects that are very similar the effects observed for individuals exposed to high IMR in infancy (Table 2). Those who had low SES at birth and who were born in a year with these epidemics have reduced odds of attaining high SES in adulthood (O.R. 0.67, statistically significant at the 5% level). Moreover, in this case, no significant differences in the probability of attaining high SES are observed for those who had high SES at birth according to their early life disease exposures (1.68 x 0.67 = 1.13; interaction term statistically significant at the 10% level).

Table 1: Percentage of women with low or medium-high SES at birth who attained low or medium-high SES in adulthood

		SES attainment in adulthood	
		Low	Medium-high
Birth SES	Low	57.22	42.78
	Medium-high	32.44	67.56

Notes: SES attainment is operationalised as the highest SES from the woman's first observed birth until age 50.

Table 2: Odds ratio of attaining high SES in adulthood according to women's early life exposures and SES at birth

PRICES	High prices		High prices low SES at birth	
	Means	O.R.	Means	O.R.
Not exposed	77.87	ref.	76.23	ref.
Exposed [a]	22.13	1.08	23.77	1.10
		[0.85,1.37]		[0.86,1.41]
Low SES at birth	58.02	ref.		
High SES at birth	41.98	2.66***		
		[2.23,3.17]		
Exposed & high SES at birth		1.10		
		[0.76,1.60]		
Number of women		2937		1704

DISEASE	High IMR		Whooping cough	
	Means	O.R.	Means	O.R.
Not exposed	80.15	ref.	89.10	ref.
Exposed [b]	19.85	0.67***	10.90	0.67**
		[0.52,0.86]		[0.47,0.94]
Low SES at birth	58.02	ref.	58.02	ref.
High SES at birth	41.98	2.55***	41.98	2.57***
		[2.14,3.04]		[2.16,3.06]
Exposed & high SES at birth		1.39		1.68*
		[0.93,2.05]		[0.97,2.88]
Number of women		2937		2642

Notes: a – years with deviations from the trend in the logarithm of rye prices, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25, greater than or equal to 0.12. b – years with relative deviations from the trend in IMR, decomposed using a Hodrick Prescott filter with a filtering factor of 6.25, greater than or equal to 0.2 (for 'high IMR') and years with relative deviations from the trend in IMR greater than or equal to 0.2 and in which whooping cough was the most diffused cause of death among children (for 'whooping cough'. In these models the years with high IMR but where whooping cough was not the main epidemic were excluded). The means represent the percentage of women in each category. SES attainment is operationalised as the highest SES from the woman's first observed birth until age 50. The models also control for parish of residence, and the woman's birth decade and include an indicator for whether she was born in one of the studied parishes. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% C.I. shown in brackets.

Table 3: Sensitivity analysis of the odds ratio of attaining high SES in adulthood according to women's early life exposures and SES at birth

	Mod. 1	Mod. 2	Mod. 3	Mod. 4	Mod. 5	Mod. 6	Mod. 7
				HIGH PRICES			
Exposed	1.08	1.04	1.07	1.05	1.08	1.08	1.04
High SES at birth	2.68***	2.59***	2.75***	2.63***	2.65***	2.65***	2.69***
Exposed & high SES at birth	1.12	1.11	1.12	1.12	1.1	1.1	1.15
				HIGH PRICES - LOW SES AT BIRTH			
Exposed	1.10	1.04	1.10	1.05	1.08	1.08	1.04
				HIGH IMR			
Exposed	0.66***	0.68***	0.65***	0.68***	0.68***	0.68***	0.66***
High SES at birth	2.58***	2.50***	2.63***	2.53***	2.54***	2.54***	2.59***
Exposed & high SES at birth	1.40*	1.39*	1.44*	1.39	1.40*	1.40*	1.45*
				WHOOPING COUGH EPIDEMICS			
Exposed	0.66**	0.67**	0.65**	0.68**	0.68**	0.68**	0.64**
High SES at birth	2.60***	2.50***	2.65***	2.54***	2.55***	2.55***	2.59***
Exposed & high SES at birth	1.70*	1.75**	1.69*	1.73**	1.74**	1.74**	1.77**
Control variables							
Parish of residence	x	x		x	x	x	
Born in studied parishes		x	x	x	x	x	
Decade of birth	x		x				
Year of birth				x	x	x	
Year of birth squared					x	x	
Year of birth cubed						x	

Notes: See Table 2 for notes on indicators. SES attainment is operationalised as the highest SES during child-bearing years, considered from the first observed birth until age 50. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

All of the results concerning SES attainment remain relatively stable when different control variables are employed in the models (Table 3). Changes in the magnitude of the effects and in their statistical significance are minor. Moreover, the patterns of the results also remain constant if the model is estimated only for women born in the studied parishes or within a 17 km radius of them[38].

38 The model that examines the impact of exposure to high prices in the foetal stage (all women regardless of their SES at birth) yields an odds ratio of 0.98 (C.I. 0.73-1.31, not statistically significant) for exposed women and an odds ratio of 1.24 (C.I. 0.79-1.95, not statistically significant) for the interaction term for exposure and high SES at birth. The model that examines the impact of exposure to high IMR in infancy yields an odds ratio of 0.71 (C.I. 0.53-0.96, statistically significant at the 5% level) for exposed women and an odds ratio of 1.54 (C.I. 0.96-2.49, statistically significant at the 10% level) for the interaction term for exposure and high SES at birth. The model that examines the impact of exposure to whooping cough in infancy yields an odds ratio of 0.68 (C.I. 0.45-1.01, statistically significant at the 10% level) for exposed women and an odds ratio of 1.84 (C.I. 0.97-3.51, statistically significant at the 10% level) for the interaction term for exposure and high SES at birth.

5.6.2 Offspring neonatal mortality

Women who were exposed to high prices in their foetal stage do not present statistically significant differences in the probability that their offspring will die in the neonatal stage (Table 4). Odds ratios below 1 are obtained for 1829-1889, whereas these ratios were above 1 in 1890-1948. When only on those females who were born into low SES families are considered, the patterns of the results remain constant.

Females who were exposed to high IMR in their infancy exhibit a higher probability of their offspring experiencing neonatal mortality in 1829-1889 (O.R. 1.44, statistically significant at the 5% level). A very similar odds ratio is obtained during this period for those exposed to whooping cough in early life, but this result is slightly above the 10% threshold for statistical significance. If the same model is estimated exclusively for women who were had low SES at the time (results not shown), relatively higher odds of offspring neonatal mortality are observed for those exposed to whooping cough in infancy (O.R. 2.10, statistically significant at the 1% level). In 1890-1948, however, lower odds of offspring neonatal mortality were obtained for females exposed to high IMR or to whooping cough epidemics in their infancy, although neither of these effects was statistically significant.

The pattern of results obtained in this section remains constant when different control variables are included in the models (Table 5). There are only minor changes in the magnitude and statistical significance of these estimates. The pattern of the results also remains constant if the model is estimated exclusively for women born in the studied parishes or within a 17 km radius of them[39].

5.6.3 Probability of birth

When the full sample of women is considered, no statistically significant differences in the likelihood of experiencing a second or higher order birth are observed for females exposed to high prices during their foetal stage in either of the periods (Table 6). The same patterns are observed when a subsample of women born into low SES families is used.

39 The models that examine the impact of exposure to high prices in the foetal stage (all women regardless of their SES at birth) yield an odds ratio of 0.81 (C.I. 0.54-1.22, not statistically significant) in 1890-1948 and an odds ratio of 1.31 (C.I. 0.71-2.43, not statistically significant) in 1890-1948. The models that examine the impact of exposure to high IMR in infancy yield an odds ratio of 1.64 (C.I. 1.13-2.39, statistically significant at the 1% level) in 1829-1889 and an odds ratio of 0.77 (C.I. 0.39-1.54, not statistically significant) in 1890-1948. The models that examine the impact of exposure to whooping cough in infancy yield an odds ratio of 1.69 (C.I. 1.08-2.66, statistically significant at the 5% level) for 1829-1889 and an odds ratio of 1.03 (C.I. 0.39-2.71, not statistically significant) for 1890-1948.

Table 4: Odds ratio that a woman's offspring will die in the neonatal stage according to her early life exposures

	High prices				High prices - low SES at birth			
	1829-1889		1890-1948		1829-1889		1890-1948	
	Means	O.R.	Means	O.R.	Means	O.R.	Means	O.R.
Not exposed	76.01	ref.	80.78	1.00	77.22	ref.	79.96	ref.
Exposed	23.99	0.85	19.22	1.27	22.78	0.71	20.04	1.55
		[0.59,1.22]		[0.82,1.96]		[0.38,1.33]		[0.78,3.09]
Number of women		1815		2298		792		896
Number of children		5397		4829		2212		1916
Number of neonatal deaths		201		134		74		49
	High IMR				Whooping cough epidemics			
	1829-1889		1890-1948		1829-1889		1890-1948	
	Means	O.R.	Means	O.R.	Means	O.R.	Means	O.R.
Not exposed	80.43	ref.	81.36	ref.	87.48	ref.	91.80	ref.
Exposed	19.57	1.44**	18.64	0.68	12.52	1.40	8.20	0.76
		[1.02,2.03]		[0.40,1.14]		[0.91,2.16]		[0.35,1.65]
Number of women		1815		2298		1665		2044
Number of children		5397		4829		4962		4280
Number of neonatal deaths		201		134		180		123

Notes: See Table 2 for notes on indicators. The means represent the percentage of offspring with mothers in each category. Neonatal mortality is measured as death in the first 28 days of life; stillbirths are excluded. The models also control for parish of residence, the child's decade of birth and the mother's age (categorical) and include an indicator for whether the mother was born in one of the studied parishes. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

Table 5: Sensitivity analysis of the odds ratio that a woman's offspring will die in the neonatal stage according to her early life exposures

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10
High prices - 1829-1889										
Exposed	0.85	0.85	0.85	0.88	0.88	0.88	0.85	0.85	0.85	0.88
High prices - 1890-1948										
Exposed	1.27	1.25	1.27	1.32	1.26	1.26	1.26	1.27	1.27	1.32
High prices, low SES at birth - 1829-1889										
Exposed	0.71	0.70	0.70	0.73	0.74	0.74	0.71	0.70	0.70	0.72
High prices, low SES at birth - 1890-1948										
Exposed	1.55	1.42	1.62	1.73	1.58	1.58	1.57	1.62	1.58	1.64
High IMR - 1829-1889										
Exposed	1.43**	1.43**	1.44**	1.39*	1.39*	1.39*	1.42**	1.44**	1.43**	1.37*
High IMR - 1890-1948										
Exposed	0.68	0.69	0.68	0.71	0.69	0.69	0.68	0.68	0.67	0.71
Whooping cough - 1829-1889										
Exposed	1.41	1.41	1.41	1.37	1.34	1.34	1.38	1.41	1.4	1.35
Whooping cough - 1890-1948										
Exposed	0.77	0.74	0.76	0.76	0.74	0.74	0.75	0.76	0.75	0.76
Control variables										
Parish of residence	x		x	x	x	x	x	x	x	
Born in studied parishes		x	x	x	x	x	x	x	x	
Age (categorical)	x	x		x	x	x	x			
Decade of birth	x	x	x					x	x	
Year of birth					x	x	x			
Year of birth squared						x	x			
Year of birth cubed							x			
Age (continuous)								x	x	
Age squared									x	

Notes: See Table 2 for notes on indicators. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 6: Hazard of experiencing a second or higher order birth in 1829-1889 and 1890-1948 according to women's early life disease exposures

	High prices				High prices - low SES at birth			
	1829-1889		1890-1948		1829-1889		1890-1948	
	Means	O.R.	Means	O.R.	Means	O.R.	Means	O.R.
Not exposed	75.74	ref.	80.35	ref.	77.45	ref.	79.27	ref.
Exposed	24.26	1.01	19.65	1.08	22.55	0.90	20.73	1.08
		[0.90,1.14]		[0.95,1.22]		[0.75,1.08]		[0.91,1.29]
Number of women		1880		2557		831		1016
Number of births		3707		2848		1480		1159

	High IMR				Whooping cough epidemics			
	1829-1889		1890-1948		1829-1889		1890-1948	
	Means	O.R.	Means	O.R.	Means	O.R.	Means	O.R.
Not exposed	79.97	ref.	81.6	ref.	86.94	ref.	92.05	ref.
Exposed	20.03	0.99	18.4	1.04	13.06	0.9	7.95	1.02
		[0.87,1.12]		[0.92,1.18]		[0.76,1.06]		[0.84,1.23]
Number of women		1880		2557		1727		2261
Number of births		3707		2848		3407		2511

Notes: See Table 2 for notes on indicators. The means represent the percentage of person years in each category. The models also control for parish of residence, decade and age (categorical) and include an indicator for whether the woman was born in one of the studied parishes. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

No statistically significant differences in the probability of birth are observed in either period for females exposed to high IMR in infancy, and the hazard ratios are consistently close to unity (Table 6). Moreover, for women exposed to whooping cough in infancy, there are no large or statistically significant differences in hazard of birth (Table 6). In 1829-1889, somewhat lower probabilities of birth are observed (approximately 10%), and these results are statistically significant when controls for women's age or all variables are excluded from the models in the sensitivity analysis (Table 7). The pattern of the results concerning the impact of exposure to high prices, high IMR or whooping cough epidemics remained constant when the model was estimated including only women born in the studied parishes or within a 17 km radius of them[40].

Women with high current SES faced a greater hazard of experiencing a successive birth in 1829-1889 than did those with low SES, but there were no large differences of this nature in 1890-1948. These effects are observed over the 8-year birth interval, although the proportional hazard assumptions are violated. The impacts are therefore allowed to vary over the time periods. For 1829-1889, significantly higher relative hazard of birth is observed for high-medium SES women within 0-2.5 years since the previous birth (H.R. 1.55, statistically significant at the 1% level), but no large differences are observed in the succeeding interval (Table 8). However, in 1890-1948, the risk of birth is higher for high SES women within the interval 0-2.5 (H.R. 1.19, significant at the 1% level) but is lower in the succeeding interval (H.R. 0.73, significant at the 1% level).

Regarding the impact of child mortality on fertility, it is important to note that women whose last-born child had died in the first month of life had a greater risk of experiencing a successive birth in 1829-1889 and 1890-1948. Although this effect is observed across the 8-year interval, the proportional hazard assumption is violated. When the impact of this variable is allowed to vary over time, higher hazard is observed in the interval of 0-2.5 years since the previous birth, whereas the relative risk is lower after this interval (Table 9). The same patterns are observed over the two time periods.

40 The model that examines the impact of exposure to high prices in the foetal stage for the full sample of women yields an odds ratio of 0.98 (C.I. 0.87-1.12) for in 1829-1889 and an odds ratio of 1.08 (C.I. 0.91-1.27) in 1890-1948. The model that examines the impact of exposure to high IMR in infancy yields an odds ratio of 0.97 (C.I. 0.84-1.11) in 1829-1889 and an odds ratio of 1.05 (C.I. 0.89-1.25) in 1890-1948. The model that examines the impact of exposure to whooping cough in infancy yields an odds ratio of 0.90 (C.I. 0.75-1.07) in 1829-1889 and an odds ratio of 1.03 (C.I. 0.80-1.31) in 1890-1948. None of these results were statistically significant.

Table 7: Sensitivity analysis of the hazard of experiencing a second or higher order birth in 1829-1889 and 1890-1948 according to women's early life exposures

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
			High prices - 1829-1889			
Exposed	1.01	1.00	1.00	1.01	1.01	1.01
	[0.89,1.13]	[0.88,1.13]	[0.90,1.12]	[0.89,1.14]	[0.89,1.14]	[0.89,1.14]
			High prices - 1890-1948			
Exposed	1.08	1.07	0.97	1.17**	1.07	1.07
	[0.95,1.22]	[0.94,1.21]	[0.88,1.08]	[1.03,1.33]	[0.94,1.21]	[0.94,1.21]
			High prices, low SES at birth - 1829-1889			
Exposed	0.90	0.89	1.01	0.89	0.90	0.90
	[0.75,1.08]	[0.74,1.07]	[0.87,1.18]	[0.74,1.06]	[0.75,1.08]	[0.75,1.08]
			High prices, low SES at birth - 1890-1948			
Exposed	1.08	1.11	1.00	1.16	1.07	1.07
	[0.91,1.29]	[0.93,1.32]	[0.86,1.16]	[0.97,1.38]	[0.90,1.28]	[0.90,1.28]
			High IMR - 1829-1889			
Exposed	0.98	0.99	0.93	0.99	0.99	0.99
	[0.86,1.12]	[0.87,1.13]	[0.83,1.04]	[0.87,1.13]	[0.87,1.13]	[0.87,1.13]
			High IMR - 1890-1948			
Exposed	1.04	1.03	1.02	1.07	1.04	1.04
	[0.92,1.18]	[0.91,1.18]	[0.92,1.13]	[0.94,1.22]	[0.92,1.19]	[0.92,1.19]
			Whooping cough - 1829-1889			
Exposed	0.90	0.92	0.86**	0.91	0.90	0.90
	[0.76,1.06]	[0.78,1.09]	[0.74,0.99]	[0.77,1.07]	[0.76,1.06]	[0.76,1.06]
			Whooping cough - 1890-1948			
Exposed	1.02	1.04	1.02	1.04	1.01	1.01
	[0.84,1.24]	[0.85,1.26]	[0.87,1.19]	[0.85,1.26]	[0.84,1.23]	[0.84,1.23]
Control variables						
Parish number	x		x	x	x	x
Born in parishes		x	x	x	x	x
Decade	x	x	x		x	x
Year					x	x
Year squared						x
Year cubed						
Age (categorical)	x	x		x		
Age (continuous)						
Age squared						
Current SES						
Previous child died in first month						

Notes: See Table 2 for notes on indicators. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

continuation of **Table 7**

	Model 7	Model 8	Model 9	Model 10	Model 11	Model 12
			High prices - 1829-1889			
Exposed	1.01	1.03	1.02	0.99	1.01	1.01
	[0.89,1.14]	[0.91,1.17]	[0.90,1.15]	[0.88,1.12]	[0.89,1.14]	[0.92,1.10]
			High prices - 1890-1948			
Exposed	1.07	1.10	1.10	1.07	1.07	1.04
	[0.94,1.21]	[0.96,1.26]	[0.96,1.26]	[0.94,1.21]	[0.94,1.21]	[0.95,1.14]
			High prices, low SES at birth - 1829-1889			
Exposed	0.90	0.89	0.87	0.89	0.90	1.00
	[0.75,1.08]	[0.74,1.07]	[0.71,1.05]	[0.75,1.07]	[0.75,1.08]	[0.87,1.14]
			High prices, low SES at birth - 1890-1948			
Exposed	1.08	1.10	1.10	1.08	1.09	1.08
	[0.90,1.28]	[0.92,1.32]	[0.92,1.33]	[0.91,1.29]	[0.91,1.30]	[0.94,1.24]
			High IMR - 1829-1889			
Exposed	0.99	0.98	1.00	1.02	1.00	0.93
	[0.87,1.13]	[0.86,1.12]	[0.87,1.14]	[0.90,1.16]	[0.88,1.15]	[0.84,1.02]
			High IMR - 1890-1948			
Exposed	1.03	1.05	1.05	1.03	1.04	1.05
	[0.90,1.17]	[0.91,1.20]	[0.91,1.20]	[0.91,1.17]	[0.91,1.18]	[0.95,1.15]
			Whooping cough - 1829-1889			
Exposed	0.90	0.89	0.91	0.94	0.93	0.89*
	[0.76,1.06]	[0.75,1.06]	[0.77,1.08]	[0.80,1.11]	[0.79,1.10]	[0.79,1.01]
			Whooping cough - 1890-1948			
Exposed	1.02	1.04	1.03	1.00	1.01	1.05
	[0.84,1.24]	[0.85,1.27]	[0.84,1.26]	[0.83,1.21]	[0.84,1.23]	[0.90,1.21]
Control variables						
Parish number	x	x	x	x	x	
Born in parishes	x	x	x	x	x	
Decade	x	x	x	x	x	
Year	x					
Year squared	x					
Year cubed	x					
Age (categorical)				x	x	
Age (continuous)		x	x			
Age squared			x			
Current SES				x	x	
Previous child died in first month					x	

Notes: See Table 2 for notes on indicators. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. 95% confidence intervals shown in brackets.

Table 8: Hazard of experiencing a second or higher order birth in 1829-1889 and 1890-1948 for women of low or high-medium SES

	1829-1889		1890-1948	
	Means	H.R.	Means	H.R.
0-2.5 years since previous birth - Low current SES	48.73	ref.	45.98	ref.
0-2.5 years since previous birth - High-medium current SES	50.69	1.55*** [1.40,1.72]	53.38	1.19*** [1.07,1.32]
2.5-8 years since previous birth - Low current SES	49.91	ref.	38.58	ref.
2.5-8 years since previous birth - High-medium current SES	47.23	1.02 [0.91,1.14]	60.67	0.73*** [0.65,0.83]
Number of women		1880		2557
Number of births		3707		2848

Notes: * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. The means represent the percentage of person years in each category. Current SES unknown is not shown in the table.

Table 9: Hazard of experiencing a second or higher order birth in 1829-1889 and 1890-1948 for women whose last-born child died in the first month of life

	1829-1889		1890-1948	
	Means	H.R.	Means	H.R.
0-2.5 years since previous birth - Previous child survived 1 month	97.32	ref.	97.38	ref.
0-2.5 years since previous birth - Previous child died	2.68	3.06*** [2.56,3.65]	2.62	1.85*** [1.47,2.32]
2.5-8 years since previous birth - Previous child survived 1 month	98.01	ref.	97.46	ref.
2.5-8 years since previous birth - Previous child died	1.99	0.56* [0.30,1.04]	2.54	0.67* [0.43,1.06]
Number of women		1853		2517
Number of births		3615		2782

Notes: * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. The means represent the percentage of person years in each category. 'Previous child died' refers to the death of the child in the first month of life. Stillbirths were excluded because they exhibited different patterns than neonatal deaths.

Even if no large or significant effects of adverse early life exposures are observed on the hazard of birth, some indirect effects are found for 1829-1889. As the results in tables 2 and 8 indicate, women who were exposed to high IMR or whooping cough in infancy had lower fertility because they had a lower probability of attaining high SES in adulthood. However, based on the results in tables 4 and 9, it is clear that females who were exposed to a high disease load in infancy had shorter birth intervals and therefore had a higher probability of birth due to greater odds that their previous children had experienced neonatal mortality.

However, we cannot verify the existence of a causal relationship between early life exposures and fertility based on these indirect effects.

5.7 Discussion

The aim of this work was to study the impact of exposure to adverse early life conditions on the probability that a woman would attain high SES in adulthood, her likelihood of experiencing a birth and her offspring's neonatal mortality. Early life conditions were measured using three exogenous indicators: exposure to high prices during the foetal stage and to high IMR and whooping cough epidemics during infancy. The impact of exposure to high prices was evaluated for the full sample of women and specifically for those whose families of origin had low SES, as grain prices could only be employed as a measure of nutrition for net consumers.

No significant impacts of exposure to high grain prices during a woman's foetal stage were found for any of the outcomes considered, either when the full sample of women was used or when those whose families of origin had low SES were examined. Odds ratios above unity were obtained when the probability of attaining high SES in adulthood was measured, and for the period 1829-1889, reduced odds of experiencing offspring neonatal mortality were observed for exposed women. Although neither of these effects was strong or statistically significant, they remain consistent with the findings obtained in the previous chapters. Chapter 2 demonstrated that net selection dominated during the childbearing and working years for women who had been exposed to high grain prices during their foetal stage.

Females with low SES at birth had a lower probability of attaining high SES during their childbearing and working years if they had been exposed to a high IMR or specifically to a whooping cough epidemic in infancy. Those whose families of origin had high SES, however, did not present variations in their likelihood of attaining high SES in adulthood related to their early life disease exposure. We hypothesise that the first pattern may be related to worse health in adulthood, likely an effect of damages to the body or inflammatory mechanisms that were developed due to exposure to epidemics in infancy. As a result of impaired health and the lack of ability to accumulate wealth in their youth, these women might have been less attractive on the marriage market and might therefore have been less likely to marry a high SES spouse. Accepting not marrying upward could have been necessary for these women to avoid prolonged

or definite celibacy. Moreover, because of characteristics that also originated from adverse early life conditions, these women and their spouses could have been less capable of attaining upward mobility in adulthood. The results obtained in this study are consistent with those of Chapter 3, in which relatively higher mortality was observed beginning in early adulthood for women born in years with whooping cough epidemics. Both of these findings represent evidence of compromised health.

We also observed that in 1829-1889, offspring born to mothers who had experienced high IMR or whooping cough epidemics in infancy had higher probabilities of dying in the early neonatal stage, particularly those born to mothers who had low SES at the time. The number of surviving children of these women was therefore smaller. However, in 1890-1948 women with similar life exposures were less likely to experience the death of their offspring during the neonatal stage, although these effects lacked statistical significance. Chapter 4 indicated that, particularly among women born after 1850, those who had low SES at the time and had been exposed to a high disease load in infancy most likely experienced more spontaneous abortions (they had lower offspring sex ratios at birth). This high incidence of miscarriages could explain why, during their first month of life, offspring born to mothers with such exposures were healthier than children whose mothers had experienced more favourable early life conditions. A higher incidence of foetal and/or neonatal mortality indicates that these women had worse reproductive health, likely as a result of diseases of or damage to their reproductive organs that had originated from exposure to epidemics in infancy. This factor would have limited their ability to carry a pregnancy to term and would have reduced the health of the foetuses.

No significant impacts were observed regarding the hazard of experiencing second and higher order births for females born in years with a high disease load. Those exposed to whooping cough epidemics in infancy presented a somewhat reduced probability of births in 1829-1889, but this effect was only statistically significant when age controls were excluded from the models. The lack of strong findings regarding fertility could indicate that this outcome is not substantially influenced by disease exposure in early life or that such exposures may affect more than one of the determinants of fertility (for example, coital frequency, breastfeeding, or access to marriage), but each of these factors may work in opposite directions. Two of these mechanisms have been demonstrated here for the period preceding the fertility decline. Females born in years with epidemics have been observed to experience higher offspring neonatal mortality. We have also seen that mothers whose last-born child had died had higher probabilities of birth within short intervals. However, women with the same exposures were less likely to attain high SES in adulthood, and fertility was lower for low SES

women. Because these two indirect mechanisms have effects that work in opposite directions, they cancel each other out. The lack of significant findings relating to fertility could be partially explained by such patterns. Moreover, even if the high incidence of spontaneous abortions presumed from the results of Chapter 4 suggests longer birth intervals and reduced fertility, the greater rates of foetal and offspring mortality may have affected patterns of intercourse, leading couples to attempt more conceptions to guarantee a certain number of live births and children who survived infancy.

5.8 Conclusions

Previous research has shown that early life exposures have substantial implications for health and wellbeing later in life. The majority of these studies have focused on the elderly, and there is still a need to understand the potential implications during early and mid-adulthood, particularly for women. This study evaluated the impact of exposure to high grain prices during the foetal stage and that of disease in infancy on female health in adulthood by focusing on SES attainment, fertility and offspring neonatal mortality. Although no significant impacts were found for women conceived in years with high grain prices, exposure to a high disease load in infancy influenced SES attainment in adulthood for those who had low SES at birth and affected neonatal mortality among their offspring during the period preceding the fertility decline. No significant impacts on fertility were found, but somewhat lower probabilities of birth were observed before the fertility transition among those exposed to whooping cough epidemics in infancy.

The findings related to SES attainment are consistent with the results obtained for the same parishes considered here by Bengtsson and Broström, which showed that individuals who had been exposed to disease in infancy had lower probabilities of belonging to the landed class after age 50 (Bengtsson & Broström, 2009). That study only considered the 19th century and focused on old age, estimating the average effects for males and females. The current study adds to these results by also considering part of the 20th century and measuring the impact of exposure to adverse early life conditions, specifically for women during their reproductive years.

The results concerning offspring neonatal mortality, together with the findings presented in Chapter 4, show that the effects of exposure to disease in early life are not limited to the women facing such experiences but are also transferred across generations. The lack of substantial effects on fertility, however, indicates that

reproduction may be more robust to adverse early life exposures than mortality (Chapters 2 and 3) and that the nature of this relationship may be complex and may not be purely direct.

5.9 References

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